Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende eptinezumab til behandling af kronisk migræne

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. eptinezumab
2. Forhandlingsnotat fra Amgros vedr. eptinezumab
3. Ansøgers endelige ansøgning vedr. eptinezumab

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24 October 2022

Att. The Danish Medicines Council

Lundbeck would like to thank the Danish Medicines Council (DMC) for the assessment report on eptinezumab (Vyepti®) for the treatment of chronic migraine. In the following, you will find our comments on the assessment report.

Comments on the DMC's assessment of the populations included in the application

Overall, the DMC states in the assessment report that the populations included in the studies that have been used to compare the efficacy and safety of eptinezumab and the three marketed CGRP antibodies (aCGRP) are comparable in a way that allows the results of the analyses to be used in the assessment of eptinezumab. Furthermore, the DMC comments that potentially, the effect of eptinezumab could be overestimated, because the DELIVER trial includes patients with less severe disease compared to the three marketed aCGRPs. In the following, we would like to add some comments to the statements in the assessment report.

On page 16/39 in the assessment report, the DMC comments on the exclusion of patients with previous aCGRP failures in the DELIVER trial:

> '*DELIVER-studiet er imidlertid det eneste, som ekskluderer patienter, der tidligere har fået CGRP-antistoffer uden effekt. Dermed er nogle patienter sorteret fra, som ikke ville have gavn af CGRP-antistoffer, og resultaterne vedrørende effekt af eptinezumab kan være overestimerede*'.

Lundbeck would like to emphasise that the inclusion/exclusion criteria of both the FOCUS (1) and CONQUER (2) primary publications are presented in the supplementary appendix of the respective publications, where it is explicitly stated that previous exposure to aCGRP is an exclusion criterion. In addition, the erenumab phase 2 trial (Study 295) was completed before any aCGRPs were on the market (study 295 completed in 2016 (3) and the first aCGRP to obtain marketing authorisation, erenumab, obtained EMA marketing authorisation on 26 July 2018), and therefore, Lundbeck finds it reasonable to conclude that patients included in Study 295 had no previous aCGRP failures, even though this was not explicitly stated as an exclusion criterion in the trial.

Furthermore, the DMC states the following on page 16/39:

> '*Baselinedata viser også, at færre af disse patienter har dage med behov for akut medicin, sammenlignet med de øvrige studier'.*

In this comparison, DMC is comparing the baseline number of monthly migraine days (MMDs) with acute medication from the full DELIVER population with the erenumab phase 2 chronic migraine trial and the chronic subgroups of the CONQUER and REGAIN trials. It is important for Lundbeck to bring to the DMC's attention that the baseline number of MMDs with acute medication use in the chronic migraine subgroup from DELIVER (see below table with data from a post-hoc analysis on DELIVER data) are on par with that in the galcanezumab trials, i.e., the trials with higher MMDs with acute medication use compared to the full population from DELIVER.

Trial arm	N	Mean number of MMDs with acute medication at baseline	Standard error
Placebo	134	16.93	0.44
Eptinezumab 100mg	137	16.97	0.41
Eptinezumab 300mg	134	16.44	0.42

On page 16/39, the DMC states:

> '*Desuden ses generelt en lidt større effekt for placebogruppen i DELIVER, sammenlignet med de øvrige studier, hvilket også tyder på en lidt bedre stillet studiepopulation'.*

Lundbeck would like to cite the publication by Swerts et al. 2022 (4), where a meta-analysis was conducted aiming to analyse how different routes of administration may affect the placebo response in chronic migraine. Swerts et al. 2022 reports that the route of administration of placebo may contribute to the placebo effect size, as it influences patients' expectations of the treatment received (which is placebo in this case). Lundbeck regards this as highly relevant in terms of the statements from the DMC on the

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placebo response in the DELIVER trial, given that the placebo in DELIVER was administered intravenously and the placebo in the other aCGRP trials were administered subcutaneously.

Comments on the DMC's health economic assessment

On page 30/39, the DMC states:

> *'Endvidere vurderer Medicinrådet, at der ikke er taget højde for post-infusion monitorering af patienten i 30 minutter i forbindelse med IV-administration, hvorfor tidsforbruget for en sygeplejerske ved denne ydelse ændres fra 45 til 75 minutter'.*

The DMC does not explicitly state what the 30 minutes of additional nurse time associated with eptinezumab IV administration is based on. As we state in our application aligned with our SPC, no post-infusion observation time was included in our health economic analysis, and we would also like to emphasise that this was based on our interview with a Danish clinical expert. He stated that no anaphylactic reactions are known in connection to CGRP antibodies, and therefore, the clinical expert expected not to recommend that patients are observed for a specific period of time after the infusion.

Comments to the challenges eptinezumab will face given its mode of administration

On page 35/39, the DMC states:

> *'Den intravenøse administration af eptinezumab kræver mere tid for patienterne og flere personaleressourcer end de øvrige lægemidler, som administreres subkutant, ofte af patienten selv. Anvendelse af eptinezumab vil derfor potentielt presse kapacitets–udfordringerne på landets hovedpinecentre yderligere.'*

We acknowledge the capacity challenges hospitals might face with eptinezumab being IV. However, Lundbeck believes that an IV migraine treatment is a valuable supplement to the existing aCGRPs that could potentially rectify capacity challenges by reducing the burden on the Danish healthcare system caused by poor patient adherence and compliance. Lundbeck would like to cite the patient-focused publication by Ailani et al. 2022 (5) that investigated to which extent patients with episodic or chronic migraine value fast onset of migraine-preventative efficacy, on top of the improvement in the frequency of migraine. Most patients considered the time to onset of efficacy offered by eptinezumab (compared to placebo) to be as important as the clinically relevant reduction in the frequency of migraine; meaning having a fast onset of efficacy due to the IV route of administration could be an advantage of eptinezumab from a patient preference point of view.

Lundbeck thanks the DMC for a constructive dialogue during the validation and assessment of eptinezumab

Best regards,

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31. oktober 2022
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.11.2022
Leverandør	Lundbeck
Lægemiddel	Vyepti (eptinezumab)
Ansøgt indikation	Forebyggende behandling af migræne hos voksne patienter med mindst 4 migrænedage per måned

Forhandlingsresultat

Amgros har opnået følgende pris på Vyepti (eptinezumab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/form	Pakningsstørrelse	AIP	Forhandlet SAIP	Rabatprocent ift. AIP
Vyepti (eptinezumab)	100 mg/IV	1 stk.	9.252,28	[redacted]	[redacted]

[redacted]

Vyepti (eptinezumab) skal indplaceres sammen med de andre tre anti-CGRP-antistoffer til behandling af kronisk migræne; Aimovig (erenumab), Ajovy (fremanezumab) og Emgality (galcanezumab). Derfor skal der udarbejdes et kliniske sammenligningsgrundlag og en omkostningsanalyse. Omkostningsanalysen skal tydeliggøre forskelle i omkostninger mellem lægemidlerne, da der er forskel på lægemidlerne i

administrationsfrekvens, da Vyepti (eptinezumab) administreres IV hver 3. måned mens Aimovig (erenumab), Ajovy (fremanezumab) og Emgality (galcanezumab) gives SC en gang om måneden.

[redacted].

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt tre andre mulige behandlinger til patienter med kronisk migræne; Aimovig (erenumab), Ajovy (fremanezumab) og Emgality (galcanezumab). Følgende tabel viser prisen for behandling med lægemidlerne over en periode på 18 måneder.

Tabel 2: Sammenligning af lægemiddelpriser. Priser indtil d. 31.03.2023 samt de nye priser, som starter d. 01.04.2023. Udregningerne er lavet for 18 måneders behandling.

Lægemiddel	Dosis	Pakningsstørrelse	Pakninger i alt for perioden	Pakningspris SAIP (DKK) Indtil 31.03.2023	Pris 18 måneder SAIP (DKK) Indtil 31.03.2023	Pakningspris SAIP (DKK) Fra 01.04.2023	Pris 18 måneder SAIP (DKK) Fra 01.04.2023
Vyepti (eptinezumab)	100 mg hver 3. måned	1 stk.	6	[redacted]	[redacted]	[redacted]	[redacted]
Aimovig (erenumab)	140 mg en gang om måneden	1 stk.	1 startpakn. + 15	[redacted]	[redacted]	[redacted]	[redacted]
Ajovy (fremanezumab)	225 mg én gang om måneden eller 675 mg hver 3. måned	1 stk.	18	[redacted]	[redacted]	[redacted]	[redacted]
Emgality (galcanezumab)	240 mg støddosis efterfulgt af 120 mg én gang om måneden	1 stk.	1 startpakn. + 17	[redacted]	[redacted]	[redacted]	[redacted]

Amgros har indhentet nye priser på Aimovig (erenumab), Ajovy (fremanezumab) og Emgality (galcanezumab) i et udbud og priserne vil være gældende pr. 01.04.2023.

[redacted]

Status fra andre lande

Norge: Under vurdering[1].
England: Under vurdering[2].

[1] https://nyemetoder.no/metoder/eptinezumab
[2] https://www.nice.org.uk/guidance/indevelopment/gid-ta10677

Konklusion

Det er Amgros vurdering, at vi har fået den bedst mulige pris på Vyepti (eptinezumab),

[redacted]

Application for the assessment of eptinezumab (Vyepti®) for the treatment of chronic migraine

Text and numbers highlighted with yellow are confidential.

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Vyepti®
Generic name	Eptinezumab
Marketing authorisation holder in Denmark	H. Lundbeck A/S
ATC code	N02CD05
Pharmacotherapeutic group	Analgesics, calcitonin gene-related peptide (CGRP) antagonists (1)
Active substance(s)	The recombinant humanised immunoglobulin G1 (IgG1) antibody eptinezumab
Pharmaceutical form(s)	Concentrate for solution for injection (1)
Mechanism of action	Eptinezumab is a recombinant humanized IgG1 antibody that binds to α- and β- forms of human CGRP ligand with low picomolar affinity (4 and 3 pM Kd, respectively). Eptinezumab prevents the activation of the CGRP receptors and hence the downstream cascade of physiological events linked to initiation of a migraine attack. Eptinezumab inhibits α and β- CGRP-mediated neurogenic inflammation and vasodilation. Eptinezumab is highly selective (>100,000-fold vs related neuropeptides amylin, calcitonin, adrenomedullin and intermedin) (1). The intravenous route of administration of eptinezumab confers 100% bioavailability and a maximum concentration of the agent directly after infusion, resulting in an immediate migraine-preventive effect and fast relief from ongoing migraine pain.

Overview of the pharmaceutical	
Dosage regimen	The recommended dose is 100 mg administered by intravenous (IV) infusion every 12 weeks. Some patients may benefit from a dosage of 300 mg administered by IV infusion every 12 weeks. The need for dose escalation should be assessed within 12 weeks after initiation of the treatment. When switching dosage, the first dose of the new regimen should be given on the next scheduled dosing date. Overall benefit and continuation of treatment should be assessed six months after initiation of the treatment. Any further decision to continue the treatment should be made on an individual patient basis (1).
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Prophylaxis of migraine in adult patients with at least four migraine days per month
Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	None required
Packaging – types, sizes/number of units, and concentrations	Eptinezumab comes in packages of 1 x 100 mg vial
Orphan drug designation	No

2. Abbreviations

DMC	Danish Medicines Council
CGRP	Calcitonin gene-related peptide
CrI	Credibility intervals
CSR	Cortical spreading depression
QoL	Quality of life
CM	Chronic migraine
EM	Episodic migraine
MMD	Monthly migraine days
MHD	Monthly headache days
SPC	Summary of product characteristics
NMA	Network meta-analysis
MRR	Migraine response rate
HRQoL	Health-related Quality of life
IV	Intravenous
SC	Subcutaneous
AE	Adverse events

RCTs	Randomised clinical trials
CSR	Clinical study report
EPAR	European public assessment report
ITT	Intention-to-treat
APRS	All-patients-randomised set
APTS	All-patients-treated set
FAS	Full-analysis set
MSQ-RFR	Role Function-Restrictive domain score of the Migraine-Specific Quality of Life Questionnaire
ROA	Route of administration
ICHD	International Classification of Headache Disorders
N	Sample size
NR	Not reported
SD	Standard deviation
SAE	Serious adverse event
CfB	Change from baseline
mITT	Modified intention-to-treat
RF-R	Role Function-Restrictive
RF-P	Role Function Preventive
EF	Emotional Function
OR	Odds ratio
RR	Relative risk
CI	Confidence interval
PPP	Pharmacy purchasing price
HCP	Healthcare personnel
PSA	Probabilistic sensitivity analyses
MOH	Medication overuse headache
MeSH	Medical Subject Headings
MIDAS	Migraine Disability Assessment
HIT-6	Headache impact test
MSQ	Migraine-specific quality-of-life questionnaire
MSMD	Acute migraine-specific medication days
GLM	Generalised linear model
MCMC	Markov chain Monte Carlo
PICO	Population, Intervention, Comparison, Outcomes
WPAI	Work productivity and activity impairment

3. List of tables and figures

4. Summary of the application

Migraine is a widespread neurologic condition that is highly prevalent in Denmark and present in all age groups. Migraine causes decreased functional ability and reductions in health-related quality of life (HRQoL), as the pain and associated symptoms of migraine negatively impact all aspects of daily life, including home, work, school and social activities (2–8). Migraine is one of the diseases in Denmark that causes the highest amount of absences from work, and studies show that 24-32% of all Danish females and 5-17% of all Danish males experience migraine at least once in their lives (9). The migraine is diagnosed as chronic (CM) if a patient experiences 15 or more monthly headache days (MHDs), of which at least eight are monthly migraine days (MMDs), for more than three months. Remaining patients are considered to have episodic migraine (EM).

Migraine preventive care is dominated by oral drugs that either lack efficacy or have unfavourable adverse event profiles (10). Later treatment lines, such as Botox® (onabotulinumtoxin A), are characterised by inconvenient intramuscular injections. In addition, Botox® has only demonstrated efficacy among patients with CM (10). As a new drug class for preventive migraine therapy, CGRP antibodies offer multiple advantages compared with agents indicated for earlier lines of treatment, such as improved tolerability and a significantly improved adverse event profile (10). Currently, three other CGRP antibodies have been evaluated by the Danish Medicines Counsel (DMC); erenumab, fremanezumab and galcanezumab. All three drugs are recommended as standard treatment for patients with CM who have failed at least two different previous migraine treatments (antihypertensives and antiepileptics). In addition, all three drugs are administered subcutaneously every month (fremanezumab also has a quarterly administration option). These three drugs are clinically equivalent and ranked in a drug recommendation by the DMC, in which the cheapest of them is recommended as first choice. Despite the available CGRP antibodies, there is still a need for additional CGRP antibody treatments that offer powerful, fast and sustained efficacy as defined by high response rates as well as reductions in migraine days and headache severity (10).

Eptinezumab is a new CGRP antibody. Eptinezumab has been extensively studied in four randomised, double-blind, placebo-controlled trials conducted among patients eligible for migraine prevention: PROMISE-1, PROMISE-2, DELIVER and RELIEF. The pivotal PROMISE-1 and -2 trials were conducted among patients with EM and CM, respectively. DELIVER evaluated patients with EM and CM who had tried at least two previous unsuccessful preventive treatments in the last 10 years. RELIEF was conducted in EM and CM patients and assessed eptinezumab's efficacy and safety when initiated during an ongoing migraine attack. In addition, PREVAIL, an open-label, single-arm long-term trial with safety as primary objective, was conducted with the high dose of 300 mg in patients with CM to show that eptinezumab is safe and efficacious over a two-year period. Eptinezumab is also undergoing clinical trials among patients with medication overuse headache
(MOH).

Eptinezumab is a humanised monoclonal antibody, and is, like the three marketed CGRP antibodies, indicated for the prophylaxis of migraine in adults who have at least four migraine days per month. Eptinezumab offers a new route of administration (ROA) and a milder administration burden due to less frequent administrations, as eptinezumab is administered intravenously every 12 weeks according to the summary of product characteristics (SPC). The novel administration of eptinezumab confers 100% bioavailability and a maximum concentration of the agent directly after end of the 30 minutes infusion, resulting in an immediate migraine preventive effect and fast relief from ongoing migraine pain. In addition, eptinezumab has a long half-life, which supports a sustained effect between 12-week administration intervals.

In both PROMISE-1 and PROMISE-2, eptinezumab demonstrated a fast onset of action due to its intravenous route of administration. In both pivotal trials, the proportion of patients experiencing migraine on the first day following the infusion of eptinezumab halved compared with the average on any given day during the screening period (11,12).

In the current application, we compared the efficacy and safety of eptinezumab with the three marketed CGRP antibodies erenumab, fremanezumab and galcanezumab. In addition, we estimated the cost per patient of treating patients with each of these drugs and the budget impact of recommending eptinezumab in Denmark. The patient population of interest in the current application is patients with CM who have failed at least two different previous migraine treatments. We conducted a literature search to identify relevant evidence to apply in the application. The efficacy and safety of eptinezumab, erenumab, fremanezumab and galcanezumab were compared in a network meta-analysis (NMA) including trials on the relevant patient population. The purpose of the NMA was to demonstrate that eptinezumab is at least as effective and safe as the three marketed CGRP antibodies to justify a placement of eptinezumab into the existing drug recommendation as equal to the three marketed CGRP antibodies. The NMA included the following outcomes: Primary endpoint in pivotal trials; change from baseline (CfB) in MMD , 50% migraine response rate (MRR), Headache impact test (HIT-6), Migraine-Specific Quality of Life Questionnaire (MSQ) and MMD with acute medication use, which are all outcomes frequently used in migraine trials and also outcomes used in the previous DMC evaluations. The NMA provided strong evidence that eptinezumab is at least as effective as marketed CGRP antibodies in a variety of efficacy, HRQoL and safety outcomes in third-line treatment (2+ treatment failures) for migraine prevention in patients with chronic migraine.

The health economic analysis conducted in the current application was a cost-minimisation analysis, which was chosen based on the result of the NMA which showed that eptinezumab is as effective and safe as the marketed CGRP antibodies. We constructed a cost-minimisation model in Excel and interviewed relevant clinical experts to inform the model. To inform the marketed CGRP antibodies, we applied the DMC national criteria for treating patients with CGRP antibodies where the DMC has outlined the treatment course for erenumab, fremanezumab and galcanezumab.

The cost-minimisation analysis had a time horizon of 21 months in the base case and resulted in an incremental cost per patient of treating patients with eptinezumab compared to erenumab of DKK 5,123. The incremental cost per patient of eptinezumab compared to fremanezumab was DKK -4,232, and compared to galcanezumab, the incremental cost per patient was DKK -1,208. The budget impact of recommending eptinezumab in Denmark was DKK -0.16 million in the first year and DKK -0.14 million in year 5. Over all five years, the budget impact of recommending eptinezumab is DKK -0.33 million i.e., a reduced budget impact at a pharmacy purchasing price (PPP) level. The main cost driver in both the cost per patient analysis and the budget impact analysis is drug costs. However, the analyses in the current application are conducted with PPPs and does not reflect confidential rebates on eptinezumab and the marketed CGRP antibodies.

The documentation provided in the current application shows that eptinezumab offers a new CGRP antibody that is as effective and safe as the marketed antibodies. In addition, eptinezumab offers benefits in terms of reducing the administration burden, as eptinezumab is administrated quarterly instead of monthly and can help patients with adherence problems because patients are treated at the hospital instead of managing their treatment themselves at home. Furthermore, the intravenous route of administration of eptinezumab confers 100% bioavailability and a maximum concentration of the agent directly after infusion, resulting in an immediate migraine-preventive effect and fast relief from ongoing migraine pain.

5. The patient population, the intervention and choice of comparator(s)

5.1 Migraine and patients with migraine

Migraine is a widespread neurologic condition that causes decreased functional ability, reductions in QoL and is one of the diseases in Denmark that causes the highest amount of absences from work (9). Migraine involves both nerves and blood vessels in the head, where CGRP signalling is considered an essential possible factor in the disease mechanism, but the actual causes of migraine are not fully known (13,14).

Clinical presentation and symptoms of migraine

In clinical practice, migraine is categorised as with or without aura. Aura is a term that covers transient neurological disturbances such as disturbances of the vision and tactile sense for up to 60 minutes before the migraine headache starts (9,13,14). Migraine headache is characterised by a pulsating unilateral headache of moderate to severe intensity that gets worse with normal physical activity. A migraine attack lasts 4-72 hours (if not treated) and is often associated with nausea, vomiting and hypersensitivity to light and sounds.
In clinical studies, migraine is typically categorised as EM or CM. EM is defined as <15 migraine days per month and CM is defined as ≥15 days in a month, of which at least eight days are with migraine and the rest involve other types of headaches, e.g., tension headache. The categorisation is continuous, as patients can go from being categorised as episodic to chronic and vice versa. A migraine day is defined as a calendar day with at least four consecutive hours with migraine or headache (independent of duration) that are treated with migraine-specific acute treatments (triptans or ergotamines). A headache day is defined as a calendar day where the patient experiences migraine headache or non-migraine headache with a duration of at least four consecutive hours, or a headache (independent of duration) where the patient needs acute treatment (triptans, ergotamine or other pain-relieving medication). This means that a migraine day per definition is also a headache day, but not the other way around.

Migraine pathophysiology

The pathophysiology of migraine is complex and involves multiple areas of the brain (15). One hypothesis in terms of the pathophysiology involves the trigeminovascular system, which transmits nociceptive impulses from the meningeal blood vessels to the central nervous system (16,17). Imaging studies have pointed to a role for the hypothalamus in the generation of migraine, although most of its involvement remains unknown (15). The anterior hypothalamus may be involved in migraine initiation and the posterior part may be involved in migraine pain. Oscillations in hypothalamic activity alter connections with other regions of the brain, which have been implicated in changing the susceptibility threshold to sensory stimuli and are also believed to play a role in the migraine initiation and termination (15). Cortical spreading depression (CSD) is a wave of depolarisation followed by supressed brain activity, which has also been postulated as playing a role in migraine initiation, generated as part of the process of cortical excitability noted with migraine. However, this remains an area of ongoing research and debate (15,17,18).

Epidemiology of migraine

Migraine is highly prevalent in Denmark and present in all age groups. It often debuts before the age of 40 and sometimes even in childhood or adolescence (9,13,14). More females than males have migraine, and studies show that 24-32% of all Danish females and 5-17% of all Danish males experience migraine at least once in their lives (9). Most patients are treated in the primary healthcare sector, but patients can be referred to a headache clinic at the hospital if the patient has unsatisfactory treatment effect. In the Global Burden of Disease Study, the 2017 total migraine prevalence was estimated to be over 1.3 billion people, making migraine the third most prevalent disorder in the world (19).
In previous migraine evaluations in DMC, the migraine expert committee has estimated that approximately 5,000-6,000 migraine patients per year are treated at Danish hospitals, but no actual estimation of the total patient number

connected to the headache clinics in Denmark exists. A global age-standardised point migraine prevalence rate of 14,107 per 100,000 individuals and a migraine incidence rate of 1,142 per 100,000 individuals were estimated by the Institute for Health Metrics and Evaluation in 2019 (20). In addition, an increase of 1% in the prevalence rate and an increase of 0.8% in the incidence rate from 2010 to 2019 were reported (20). Based on these estimates, and the fact that approximately 10% of the total migraine population has CM, a Danish prevalence and incidence of CM were estimated (see Table 1) (2). Since the increase in the prevalence and incidence rates of migraine from 2010 to 2019 were very small, a constant prevalence and incidence was assumed in Table 1.

Table 1: Incidence and prevalence of chronic migraine in Denmark over the past five years

Year	2017	2018	2019	2020	2021
Incidence in Denmark	6,624	6,624	6,624	6,624	6,624
Prevalence in Denmark	81,820	81,820	81,820	81,820	81,820

Note: calculated based on a prevalence rate and incidence rate from 2019 and a Danish population of 5.8 mil. Inhabitants

In a previous DMC evaluation of a CGRP antibody for treating patients with CM who have failed at least two different previous migraine treatments, the expert committee estimated that 1,200 new patients are candidates to CGRP antibody treatment each year. The number of new patients with CM who are eligible for treatment with eptinezumab in the coming five years are presented in Table 2.

Table 2: Estimated number of chronic migraine patients eligible for treatment with eptinezumab in Denmark. Source: DMC evaluation of galcanezumab (21).

Year	2022	2023	2024	2025	2026
Number of new patients expected to use eptinezumab in the coming years	1,200	1,200	1,200	1,200	1,200

5.1.1 Patient populations relevant to this application

Eptinezumab is indicated for the prophylaxis of migraine in adults who have at least four migraine days per month. The Danish patient population relevant to this application comprises patients with CM who have failed at least two different previous migraine treatments. It was assumed that this subpopulation of patients with CM does not differ from the overall patient population with CM. This assumption was based on the baseline characteristics of the study populations in PROMISE-2 and DELIVER (12,22). The mean age at first migraine diagnosis was 22.5 years in PROMISE-2 and 26.1 years in DELIVER. The mean number of years since first migraine diagnosis was 18.1 years in PROMISE-2 and [redacted] years in DELIVER and the mean duration of CM was 11.8 years in PROMISE-2 and [redacted] years in DELIVER. In PROMISE-2, the mean number of MHDs was 20.5 and in DELIVER, [redacted] had ≤14 MHDs and [redacted] had more than 14 MHDs. The only characteristic where the two study populations were slightly different was in relation to the diagnosis of MOH, where 40.2% in PROMISE-2 and [redacted] in DELIVER had this diagnosis. Based on this, it was deemed reasonable to assume that the patients with CM who have previously failed at least two different migraine treatments does not differ considerably from the overall patient population with CM. Thus, a description of the patient population can be found in section 5.1.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

Medical treatment of migraine is categorised as acute treatment of attacks (pain-relieving and nausea-relieving treatment) and preventive treatment. Preventive treatment is offered to patients with at least two migraine days per month with insufficient effect of acute treatments and reduced QoL as a consequence (13). The goal of preventive treatment is to reduce the severity and frequency of headaches. Preventive treatment is successful if the patient experiences improved QoL and a reduction in the frequency and severity of their migraine. Many patients experience spontaneous improvement over time; therefore, it is individual how long patients need preventive treatment, and in Denmark, it is clinical practice to assess if treatment can be stopped every 6 to 12 months to ensure that the patient still needs the medication (13).

Antihypertensives, antiepileptics and antidepressant drugs are used as preventive migraine treatments. These are: metoprolol/propranolol (betablockers), flunarizine (calcium antagonist), topiramate (antiepileptic), pizotifen (amin antagonist), clonidine (alfa-2-receptor and imidazoline receptor agonist) and amitriptyline (tricyclic antidepressant). Recently, anti-CGRP monoclonal antibodies have entered the market for preventive migraine treatment. Erenumab, fremanezumab and galcanezumab are all approved for preventive treatment of adult patients with at least four migraine days per month. Botulinum type-A toxin is also approved for patients with CM. Not all drugs mentioned in Danish treatment guidelines are approved as preventive treatment for migraine and are used off-label. There is no national or international consensus regarding the relative placement of these drugs in the treatment algorithm for preventive migraine treatment. Furthermore, the effect and adverse events (AE) of these drugs vary between patients. Therefore, the choice of drug is dependent on an individual assessment of the patient's risk profile, comorbidities and previous experience. In general, there is consensus regarding metoprolol/propranolol being the first choice. According to the expert committee in migraine, topiramate and the anti-hypertensive drugs candesartan and lisinopril (used off label) are widely used due to the favourable safety profile. Together with the beta blockers, they should be considered as first choices for migraine prevention.
If patients experience treatment failure (e.g., due to lack of effect or lack of an adequate response or unacceptable AEs) or contraindications, patients typically receive amitriptyline/nortriptyline or valproate as second line treatment. For patients with CM, botulinum type A toxin is also an option as second choice. For patients with CM, who have failed at least one anti-epileptic drug and one anti-hypertensive drug, the anti-CGRP antibodies erenumab, fremanezumab and galcanezumab are treatment alternatives.

Anti-CGRP antibodies offer a new drug class with multiple advantages as preventive migraine treatment compared to earlier treatment lines, e.g., improved tolerability and a significantly reduced AE profile. However, the current options within anti-CGRP antibodies are limited and there is still a need for additional anti-CGRP antibodies that offer powerful, fast and sustained efficacy in terms of reducing migraine days, high response rates and reducing headache severity.

5.2.2 Choice of comparators

At the time of the development of the current application, three other CGRP antibodies have been recommended by the DMC for the patient population specified in section 5.1.1. These include: erenumab (sold under the brand name Aimovig), fremanezumab (sold under the brand name Ajovy) and galcanezumab (sold under the brand name Emgality). Eptinezumab is an alternative to all three marketed alternatives; therefore, we include all three drugs as comparators in the current application. In the following tables, we describe each comparator in detail.

5.2.3 Description of erenumab (Aimovig)

Erenumab is a fully human IgG2 monoclonal antibody indicated for prophylaxis of migraine in adults who have at least four migraine days per month. The recommendation from the SPC is 70 mg erenumab every four weeks, administered subcutaneously, and patients can self-administer erenumab. Some patients may benefit from a dose of 140 mg every four weeks. Erenumab binds to the CGRP receptor. The CGRP receptor is located at sites that are relevant to migraine pathophysiology, such as the trigeminal ganglion. Erenumab potently and specifically competes with the binding of CGRP and inhibits its function at the CGRP receptor, and it has no significant activity against other calcitonin families of receptors. CGRP is a neuropeptide that modulates nociceptive signalling and a vasodilator that has been associated with migraine pathophysiology. In contrast to other neuropeptides, CGRP levels have been shown to increase significantly during migraine and return to normal with headache relief (23). Additional information on erenumab is provided in Table 3.

Table 3: Description of the comparator erenumab. Source: SPC on erenumab (23) and DMC document (24).

Description of erenumab	
Proprietary name	Aimovig
Generic name	Erenumab
ATC code	N02CX07
Pharmaceutical form(s)	Solution for injection
Packaging	70 mg solution for injection in pre-filled syringe or pre-filled pen. 140 mg solution for injection in pre-filled syringe or pre-filled pen. The pre-filled syringe is supplied as 1 ml, Type 1 glass with a stainless steel needle and a needle cover (rubber containing latex). The pre-filled pen is supplied as 1 ml, Type 1 glass with a stainless steel needle and a needle cover (rubber containing latex). Erenumab is available in packs containing one pre-filled syringe and in packs containing one pre-filled pen and in multipacks containing three (3x1) pre-filled pens. The shelf life is two years.
Mode of action	Erenumab is a human monoclonal antibody that binds to the CGRP receptor. The CGRP receptor is located at sites that are relevant to migraine pathophysiology, such as the trigeminal ganglion. Erenumab competes with the binding of CGRP and inhibits its function at the CGRP receptor, and has no significant activity against other calcitonin receptor families. CGRP is a neuropeptide that modulates nociceptive signalling and a vasodilator that has been associated with migraine pathophysiology. In contrast to other neuropeptides, CGRP levels have been shown to increase significantly during migraine and return to normal with headache relief.
Dosage regimen/posology	Erenumab is indicated for patients with at least four migraine days per month when initiating treatment. The recommended erenumab dose is 70 mg subcutaneous (SC) every four weeks. Some patients may benefit from 140 mg SC every four weeks. Each 140 mg dose is administrated as either one SC injection or two SC injections of 70 mg. Erenumab is intended for patient self-administration after proper training.

Description of erenumab	
Combination therapy and/or co-medication	None required
Treatment duration/criteria for end of treatment	According to the SPC for erenumab, consideration should be given to discontinuing treatment in patients who have shown no response after three months of treatment. Evaluation of the need to continue treatment is recommended regularly thereafter (23). In Danish clinical practice, the DMC has developed national criteria for treating patients with CGRP antibodies. In this document, it is stated that treatment with CGRP antibodies should be paused for one month after 17 months of treatment. If treatment is continued hereafter, treatment should be paused again for one month after 35 months of treatment (24).
Necessary monitoring, both during administration and during the treatment period	According to the SPC, there is no necessary monitoring during administration of erenumab or the treatment period (23).
Need for diagnostics or other tests (i.e. companion diagnostics)	None

5.2.4 Description of fremanezumab (Ajovy)

Fremanezumab is a humanised monoclonal antibody indicated for prophylaxis of migraine in adults who have at least four migraine days per month. Two dosing options are available: 225 mg once monthly (monthly dosing) or 675 mg every three months (quarterly dosing), and patients can self-administer fremanezumab subcutaneously. Fremanezumab is a humanised IgG2Δa/kappa monoclonal antibody derived from a murine precursor. Fremanezumab selectively binds the CGRP ligand and blocks both CGRP isoforms (α-and β-CGRP) from binding to the CGRP receptor. While the precise mechanism of action by which fremanezumab prevents migraine attacks is unknown, it is believed that prevention of migraine is obtained by its effect modulating the trigeminal system. CGRP levels have been shown to increase significantly during migraine and return to normal with headache relief. Fremanezumab is highly specific to CGRP and does not bind to closely related family members (e.g., amylin, calcitonin, intermedin and adrenomedullin) (25). Additional information on fremanezumab is provided in Table 4.

Table 4: Description of the comparator fremanezumab (Ajovy). Source: SPC on fremanezumab (25) and DMC document (24).

Description of fremanezumab	
Proprietary name	Ajovy
Generic name	Fremanezumab
ATC code	N02CD03
Pharmaceutical form(s)	Solution for injection

Description of fremanezumab	
Packaging	225 mg fremanezumab solution for injection in pre-filled syringe or pre-filled pen. The pre-filled syringe pack contains 1.5 mL solution in a 2.25 mL type I glass syringe with plunger stopper (bromobutyl rubber) and needle. The pre-filled pen pack contains 1.5 mL solution in a 2.25 mL type I glass syringe with plunger stopper (bromobutyl rubber) and needle. The pre-filled pen and pre-filled syringe come in packages of 1 or 3 pre-filled pens or pre-filled syringes. The shelf life is two years.
Mode of action	Fremanezumab is a humanised IgG2Δa/kappa monoclonal antibody derived from a murine precursor. Fremanezumab selectively binds the CGRP ligand and blocks both CGRP isoforms (α-and β-CGRP) from binding to the CGRP receptor. While the precise mechanism of action by which fremanezumab prevents migraine attacks is unknown, it is believed that prevention of migraine is obtained by its effect in modulating the trigeminal system. CGRP levels have been shown to increase significantly during migraine and return to normal with headache relief. Fremanezumab is highly specific to CGRP and does not bind to closely related family members (e.g., amylin, calcitonin, intermedin and adrenomedullin).
Dosage regimen/posology	Fremanezumab is indicated for patients with at least four migraine days per month when initiating treatment. Two dosing options are available: 225 mg SC once monthly (monthly dosing) or 675 mg SC every three months (quarterly dosing).
Combination therapy and/or co-medication	None required
Treatment duration/criteria for end of treatment	According to the SPC for fremanezumab, consideration should be given to discontinuing treatment in patients who have shown no response after three months of treatment. Evaluation of the need to continue treatment is recommended regularly thereafter (25). In Danish clinical practice, the DMC has developed national criteria for treating patients with CGRP antibodies. In this document, it is stated that treatment with CGRP antibodies should be paused for one month after 17 months of treatment. If treatment is continued hereafter, treatment should be paused again for one month after 35 months of treatment (24).
Necessary monitoring, both during administration and during the treatment period	According to the SPC, there is no necessary monitoring during administration of fremanezumab or the treatment period (25).
Need for diagnostics or other tests (i.e. companion diagnostics)	None

5.2.5 Description of galcanezumab (Emgality)

Galcanezumab is a recombinant humanised monoclonal antibody indicated for the prophylaxis of migraine in adults who have at least four migraine days per month. The recommended dose in the SPC is 120 mg galcanezumab injected SC once monthly, with a 240 mg loading dose as the initial dose. Patients can self-administer the 120 mg SC administrations. Galcanezumab is a humanised IgG4 monoclonal antibody that binds CGRP, thus preventing its biological activity (26). Additional information on galcanezumab is provided in Table 5.

Table 5: Description of the comparator galcanezumab (Emgality). Source: SPC on galcanezumab (26) and DMC document (24).

Description of galcanezumab	
Proprietary name	Emgality
Generic name	Galcanezumab
ATC code	N02CD02
Pharmaceutical form(s)	Solution for injection
Packaging	Galcanezumab comes in a pre-filled pen containing 120 mg of galcanezumab in 1 mL. The package contains 1 mL solution in a type I clear glass syringe. The syringe is encased in a disposable single-dose pen. Galcanezumab comes in packs of 1 and 2 pre-filled pens.
Mode of action	Galcanezumab is a humanised IgG4 monoclonal antibody that binds CGRP; thus preventing its biological activity.
Dosage regimen/posology	Galcanezumab is indicated for patients with at least four migraine days per month when initiating treatment. The recommended dose is 120 mg galcanezumab SC once monthly, with a 240 mg SC loading dose as the initial dose.
Combination therapy and/or co-medication	None required
Treatment duration/criteria for end of treatment	According to the SPC for galcanezumab, consideration should be given to discontinuing treatment in patients who have shown no response after three months of treatment. Evaluation of the need to continue treatment is recommended regularly thereafter (26). In Danish clinical practice, the DMC has developed national criteria for treating patients with CGRP antibodies. In this document, it is stated that treatment with CGRP antibodies should be paused for one month after 17 months of treatment. If treatment is continued hereafter, treatment should be paused again for one month after 35 months of treatment (24).
Necessary monitoring, both during administration and during the treatment period	According to the SPC, there is no necessary monitoring during administration of galcanezumab or the treatment period (26).

Description of galcanezumab	
Need for diagnostics or other tests (i.e. companion diagnostics)	None

5.3 The intervention: Eptinezumab (Vyepti®)

Eptinezumab is a humanised monoclonal antibody indicated for the prophylaxis of migraine in adults who have at least four migraine days per month. The recommended dose in the SPC is 100 mg administered IV every 12 weeks. Some patients may benefit from a dosage of 300 mg administered IV every 12 weeks; however, it is not established who these patients are. Eptinezumab is a recombinant humanised IgG1 antibody that binds to α- and β- forms of human CGRP ligand with low picomolar affinity (4 and 3 pM Kd, respectively). Eptinezumab prevents the activation of the CGRP receptors and hence the downstream cascade of physiological events linked to initiation of migraine attacks.

Eptinezumab is an alternative to the three marketed CGRP antibodies erenumab, fremanezumab and galcanezumab but offers a new mode of administration, as eptinezumab is administered IV. Some patient groups might benefit from an IV treatment, e.g., due to adherence difficulties. Thus, eptinezumab is a valuable alternative to the three marketed SC CGRP antibodies. Additional information on eptinezumab is provided in Table 6.

Table 6: Description of the intervention eptinezumab. Source: SPC on eptinezumab and clinical expert input.

Description of eptinezumab	
Proprietary name	Vyepti®
Generic name	Eptinezumab
ATC code	N02CD05
Pharmaceutical form(s)	Concentrate for solution for infusion
Packaging	Eptinezumab comes in vials of 100 mg. Each vial of concentrate contains 100 mg eptinezumab per mL.
Mode of action	Eptinezumab is a recombinant humanised IgG1 antibody that binds to α- and β- forms of human CGRP ligand with low picomolar affinity (4 and 3 pM Kd, respectively). Eptinezumab prevents the activation of the CGRP receptors and hence the downstream cascade of physiological events linked to initiation of migraine attacks.

Description of eptinezumab	
Dosage regimen/posology	Eptinezumab is indicated for patients with at least four migraine days per month when initiating treatment. The recommended dose is 100 mg administered IV every 12 weeks. Some patients may benefit from a dosage of 300 mg administered IV every 12 weeks. The need for dose escalation should be assessed within 12 weeks after initiation of the treatment. When switching dosage, the first dose of the new regimen should be given on the next scheduled dosing date. Overall benefit and continuation of treatment should be assessed six months after initiation of the treatment. Any further decision to continue the treatment should be made on an individual patient basis.
Combination therapy and/or co-medication	None required
Treatment duration/criteria for end of treatment	In Denmark, the SC anti-CGRP antibodies are paused after month 17 for one month to check if patients still benefit from the treatment. Eptinezumab cannot be paused after 17 months due to the dose regimen with administrations every three months. Instead, eptinezumab can be paused after 18 months of treatment (last administration in month 15).
Necessary monitoring, both during administration and during the treatment period	According to the SPC, there is no necessary monitoring during administration of eptinezumab or during the treatment period.
Need for diagnostics or other tests (i.e. companion diagnostics)	None

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

A systematic literature search was conducted, applying relevant search terms for the condition (migraine), the intervention and comparators as well as a filter to identify randomised controlled trials (RCTs) and a filter to exclude irrelevant publication types and study designs. Literature was searched for in the databases Medline (via PubMed) and CENTRAL (via Cochrane Library) on 24 January 2022. The specific search terms and number of hits in Medline and CENTRAL can be found in Table 68 and Table 69, respectively, in Appendix A.

PICO

Studies with patients (≥18 years) with CM who had failed at least two different previous migraine treatments were included to make sure that the patient population in the studies matches the Danish patient population that the expert committee have found relevant for CGRP antibody treatment in previous DMC migraine evaluations. We searched for head-to-head trials between eptinezumab and any of the comparators as well as studies including the intervention or one or more of the comparators, with the possibility of applying the studies in indirect comparisons. Additionally, we only included articles reporting results on one or more of the prespecified relevant outcomes, i.e., MMD, 50% MRR, HIT-6, MSQ, MMD with acute medication use and safety. Furthermore, only RCTs published in full-text publications were included and case reports, comments, editorials, guidelines, letters, reviews, meta-analyses and trial registrations were excluded. All English-language literature published before the literature search on 24 January 2022 were searched and no other time limits were applied.

6.2 List of relevant studies

64 records were identified using Medline and 416 records in CENTRAL. A total of 345 records were identified after duplicates were removed. All references were screened based on title and abstract, and 323 records were excluded at this screening. 22 articles were screened based on full-text review and 15 articles were excluded. In total, seven articles from the literature search were included in the assessment (see PRISMA diagram in Figure 24). In addition, the publication on the STRIVE trial by Goadsby et al. 2017 was included in the analysis and the subgroup analysis published in Lanteri-Minet et al. 2018 (27,28). The Goadsby et al. 2017 publication was not identified in the search due to the population exclusion criterion excluding studies within EM. The Goadsby et al. 2017 article, as well as the article by Reuters et al. 2018 on the LIBERTY trial, was included for the comparative analysis of eptinezumab and erenumab on discontinuation, since only a few discontinuation events were reported in the studies, and pooled EM and CM analyses were applied for this outcome. In addition, DELIVER, which is not yet published, was included. In total, seven trials were included based on nine articles. Information on DELIVER came from a Lundbeck data on file subgroup analysis, the clinical study report (CSR), the European public assessment report (EPAR) and the publication by Ashina et al. 2022 (29), which will be published in 2022. The articles are listed in Table 7. For detailed information on included studies, see Appendix B and Appendix C.

Table 7: Relevant studies included in the assessment

Reference	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Ashina et al. 2022: Safety and efficacy of eptinezumab for migraine prevention in patients with two-to-four previous preventive treatment failures (DELIVER): a multi-arm, randomised, double-blind, placebo-controlled, phase 3b trial. Lancet Neurol, 2022; 21: 597–607 (29)	DELIVER	NCT04418765	Start and completion date from clinicaltrials.gov: June 2020 and September 2022. Data cut-off date was October 7 2021.	• Eptinezumab compared to erenumab • Eptinezumab compared to fremanezumab • Eptinezumab compared to galcanezumab
Ashina et al. 2018: Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study. Cephalalgia, 2018 Sep;38(10):1611-1621 (30)	NCT02066415	NCT02066415	Start and completion date from clinicaltrials.gov: March 2014 and April 2016	Eptinezumab compared to erenumab
Ferrari et al. 2019: Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. The Lancet, 2019 Sep;394(10203):1030-1040 (31)	FOCUS	NCT03308968	Start and completion date from clinicaltrials.gov: October 2017 and May 2019	Eptinezumab versus fremanezumab
Pazdera et al. 2021: Fremanezumab for the Preventive Treatment of Migraine: Subgroup Analysis by Number of Prior Preventive Treatments with Inadequate Response. Cephalalgia, 2021 May;41(10): 1075-1088 (32)	FOCUS	NCT03308968	Start and completion date from clinicaltrials.gov: October 2017 and May 2019	Used to describe some baseline characteristics of patients in the FOCUS study

Reference	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Mulleners et al. 2020: Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial. The Lancet Neurology, 2020 Oct;19(10): 814-825 (33)	CONQUER	NCT03559257	Start and completion date from clinicaltrials.gov: July 2018 and September 2019	Eptinezumab versus galcanezumab
Ruff et al. 2019: Efficacy of galcanezumab in patients with chronic migraine and a history of preventive treatment failure. Cephalalgia, 2019 May;39(8): 931-944 (34)	REGAIN	NCT02614261	Start and completion date from clinicaltrials.gov: November 2015 and July 2021	Eptinezumab versus galcanezumab
Goadsby et al. 2017: A Controlled Trial of Erenumab for Episodic Migraine. New England Medicine, 2017 Nov;377(22): 2123-2132 (27)	STRIVE	NCT02456740	Start and completion date from clinicaltrials.gov: July 2015 and June 2017	Comparative analysis of discontinuation due to AEs between eptinezumab and erenumab (EM study included due to very low discontinuation events)
Reuter et al. 2018: Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. Lancet, 2018 Nov;392(10161): 2280-2287 (35).	LIBERTY	NCT03096834	Start and completion date from clinicaltrials.gov: March 2020 and January 2021	Comparative analysis of all-cause discontinuation between eptinezumab and erenumab (EM study included due to very low discontinuation events)
Lanteri-Minet et al. 2018: Patient-reported outcomes in chronic migraine patients with prior prophylactic treatment failure receiving placebo or erenumab: subgroup analysis of a	NCT02066415	NCT02066415	Start and completion date from clinicaltrials.gov: March 2014 and April 2016	Subgroup analysis of NCT02066415 used in the comparison of erenumab and eptinezumab in HIT-6

Reference	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
pivotal randomised study. Cephalalgia, 2018. Issue 38 (supplementary) page: 124-26 (28).				
Tepper et al. 2022: Effects of Galcanezumab on Health-Related Quality of Life and Disability in Patients with Previous Failure of 2-4 Migraine Preventive Medication Categories: Results from a Phase IIIb Randomized, Placebo-Controlled, Multicenter Clinical Trial (CONQUER).. Clinical Drug Investigation, 2022;42: 263-275(36).	CONQUER	NCT03559257	Start and completion date from clinicaltrials.gov: July 2018 and September 2019	Analysis of MSQ-RF-P and MSQ-RF-R in galcanezumab arm

7. Efficacy and safety

The efficacy and safety of eptinezumab compared to the three marketed CGRP antibodies was assessed in an NMA. The NMA was conducted by Costello Medical for Lundbeck based on a systematic literature review (SLR) conducted for the NMA. The literature search conducted in the current application was based on the SLR but adjusted to fit the PICO of interest in the current application. RCTs were included in the NMA if they investigated interventions that were preventive CGRP antibodies in CM, and if they reported results for patients who have failed at least two different previous treatments (either as subgroup results or as intention-to-treat (ITT) populations). In the following, we describe each study used to inform the NMA on the included CGRP antibodies. Hereafter, results per study are presented and comparative analyses for each outcome included in the assessment. A more thorough description of the methodology of the NMA is presented in section 7.3. The full NMA has also been submitted to the DMC along with this application. Eptinezumab 300 mg was also included in the NMA: thus, eptinezumab 300 mg is also included in section 7.2, 7.3 and 7.4. However, eptinezumab 100 mg is the standard recommended dose of eptinezumab and the main focus of the current application.

7.1 Relevant studies

A brief description of each study included in the NMA is presented in the following. Additional information on main characteristics from the studies and baseline characteristics on patients included in the studies can be found in Appendix B and Appendix C, respectively. The comparability and differences between the studies are addressed in Appendix C and section 7.1.8.

7.1.1 The DELIVER trial

Information on the DELIVER trial came from the CSR on the trial and the EPAR, as no publication was available at the time of preparing the current application. Lundbeck expects results from the trial to be published in the second quarter of 2022.

The DELIVER trial is a phase 3b, interventional, prospective, randomised, double-blinded, parallel-group placebo-controlled trial assessing the efficacy and safety of eptinezumab as preventive treatment for patients with migraine with unsuccessful prior preventive treatments. The study includes two eptinezumab doses: eptinezumab 100 mg and eptinezumab 300 mg, both administered IV. The comparator arm in the study is placebo administrated to match the intervention. The study design is presented in Figure 1.

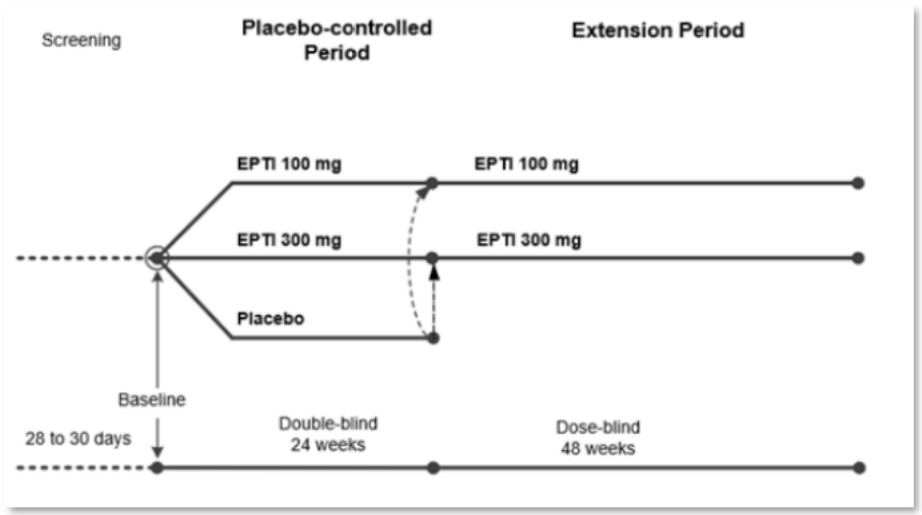

Figure 1: Study design of the DELIVER trial (22)

As presented in Figure 1, the study consisted of a screening period of 28-30 days from screening to randomisation and a 24-week double blinded placebo-controlled treatment period where patients were randomised to either placebo or eptinezumab. The study also included a dose-blinded extension period with eptinezumab of 48 weeks after completion of the placebo-controlled period, making the total study duration from the screening visit to the completion visit 76 weeks. The study included three analysis sets:

- All-patients-randomised set (APRS) that included all randomised patients
- All-patients-treated set (APTS) that included all patients in the APRS who received at least one infusion of the randomised treatment
- Full-analysis set (FAS) that included all patients in the APTS who had a valid post-baseline 4-week assessment of MMDs in weeks 1 to 12

Efficacy analyses were done on the FAS that included 299 patients treated with 100 mg eptinezumab, 298 patients treated with placebo and 293 treated with 300 mg eptinezumab. Safety analyses were done on the APTS that included the same number of patients for placebo and 100 mg eptinezumab, but 294 instead of 293 patients in 300 mg eptinezumab.

Patients were randomised 1:1:1 to 24 weeks of double-blinded treatment with eptinezumab 100 mg or 300 mg or placebo. Randomisation was stratified by country and by number of MHDs at baseline (≤14 MHDs/>14 MHDs). Patients received treatment by IV infusion over 30 minutes (up to 45 minutes), starting from the baseline visit; hereafter, the patients were dosed every 12 weeks (i.e., a total of two doses). The majority (62%) of the patients had two previous treatment failures; 31% of the patients had three previous treatment failures, and 6.7% of the patients had four previous treatment failures. 6.7% and 80% of patients in the eptinezumab 100 mg arm had failed an antihypertensive drug and an antiepileptic drug, respectively. In the eptinezumab 300 mg arm, 6.1% had failed an antihypertensive drug and 83% had failed an antiepileptic drug. In the placebo arm, 6.4% had failed an antihypertensive drug and 79% had failed an antiepileptic drug. The most common types of treatment failures were lack of efficacy (100%) and safety/tolerability issues (56%).

7.1.2 NCT02066415

NCT02066415 (also called Study 295) was a phase 2, multicentre, randomised, double-blinded, placebo-controlled parallel-group trial assessing the efficacy and safety of erenumab in patients aged 18–65 years with CM. The study included two erenumab arms: erenumab 70 mg and erenumab 140 mg. Both doses were administered SC on day 1, at week 4 and week 8 in the double-blinded treatment phase (37).

Patients in NCT02066415 were randomised 3:2:2 to placebo, erenumab 70 mg or erenumab 140 mg monthly for three months (12 weeks) via interactive response technology. Randomisation was stratified by region (North America vs Europe) and medication overuse (presence vs absence) and the investigators, patients and sponsor were masked to treatment assignment. Patients who completed the 12-week double-blind treatment phase of the study were eligible to enrol in an open-label extension study. The study is completed.

667 patients were randomly assigned, and the efficacy analysis included 656 patients (281 in the placebo arm, 188 in the erenumab 70 mg arm and 187 patients in the erenumab 140 mg arm). 609 patients continued in the follow-up study, where all patients received erenumab by SC injections.

A subgroup analysis on NCT02066415 was conducted (published in Ashina et al. 2018 (30)) among patients with CM who have failed ≥1 or ≥2 prior treatments and patients who had never failed. Subgroups were defined on the basis of prior migraine preventive treatment failure (either for lack of efficacy and/or unacceptable tolerability, as recorded by the investigator). The number of prior preventive treatment failures for any given patient was based on medication categories. The group with patients that had not failed previous treatments included treatment-naïve patients and patients who had been exposed to a preventive treatment but did not fail it due to lack of efficacy and/or unacceptable tolerability. The following were classified as migraine preventive treatment categories: topiramate; beta blockers (e.g., propranolol or metoprolol); tricyclic antidepressants (e.g. amitriptyline or nortriptyline); divalproex sodium or sodium valproate; calcium channel blockers (e.g. flunarizine or verapamil); serotonin-norepinephrine reuptake inhibitors; botulinum toxin; antihypertensives (lisinopril or candesartan); or other medications. The analyses were conducted on CfB in MMDs, achievement of ≥50% and ≥75% reduction in MMDs, and change in monthly acute migraine-specific medication days and AEs. In the comparative analysis of eptinezumab and erenumab, we applied results from the subgroup of patients who have failed ≥2 prior treatments.

7.1.3 The FOCUS study

The FOCUS study was an international, multicentre, randomised, double-blinded, placebo-controlled, parallel-group phase 3b trial assessing the efficacy and tolerability of fremanezumab in patients with difficult-to-treat EM or CM with

documented inadequate response to two to four pharmacological classes of migraine preventive medications (31). The study design is presented in Figure 2.

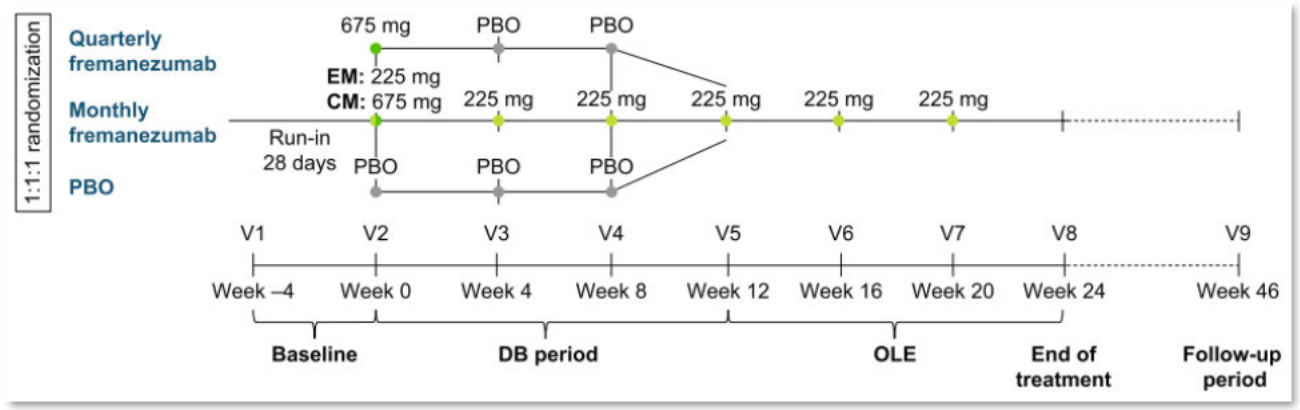

Figure 2: Study design of the FOCUS study. Source: Ashina et al. 2021 (38).

As presented in Figure 2, the study consisted of an initial screening period of 28 days, a 12-week double-blinded, placebo-controlled treatment period where the patients were randomised to either placebo or one of the fremanezumab treatments, a 12-week open-label extension period and a follow-up period of six months after the last dose of fremanezumab: thus, the total study duration from the screening period to end of the follow-up period was 50 weeks (31).

The study participants were randomly assigned (1:1:1) to 12 weeks of treatment with either SC administered monthly fremanezumab, SC administered quarterly fremanezumab or SC administered placebo to match the intervention by an electronic interactive response technology. The randomisation assigned the patients to the different treatment categories as follows: 279 patients receiving placebo, 283 patients receiving monthly fremanezumab and 276 patients receiving quarterly fremanezumab. Randomisation was stratified by migraine classification (episodic or chronic), sex, country and failure to migraine preventive medication classes, and valproic acid or valproate (31).

For patients who received quarterly fremanezumab, the treatment consisted of 675 mg fremanezumab as the first dose (loading dose), followed by two matched monthly placebo injections for two months. For patients with EM who received monthly fremanezumab, the treatment consisted of 225 mg and two matching placebo injections as the first dose, followed by 225 mg monthly fremanezumab for two months, and for patients with CM who received monthly fremanezumab, the treatment consisted of 675 mg fremanezumab as the first dose, followed by 225 mg monthly fremanezumab for two months. The patients who were randomised to the placebo treatment received three placebo injections over the 12 weeks. The majority of the patients (50%) had two previous preventive medication classes failures, 32% of the patients had three previous failures, and 18% of the patients had four previous failures (31).

7.1.4 The CONQUER study

The CONQUER study was a multicentre, randomised, double-blinded, parallel, placebo-controlled phase 3b study assessing the efficacy and safety of galcanezumab in patients with EM or CM for whom previous migraine preventive medication from two to four treatment categories had failed in the past 10 years owing to lack of efficacy, tolerability or both. The study comprised four study periods: an initial screening period of 3 to 30 days, a 30- to-40-day prospective baseline period to establish the eligibility of patients based on responses regarding headaches as reported

in an electronic diary, a three-month randomised, double-blinded, placebo-controlled treatment phase and a three-month open-label treatment phase (33).

The study participants were randomly assigned (1:1) to receive either monthly SC administered placebo or 120 mg of galcanezumab. Of the total number of patients, 230 patients were assigned to receive placebo, and 232 patients were assigned to receive treatment with galcanezumab. The patients who were randomised to treatment with galcanezumab received a loading dose of 240 mg administered as two 120 mg injections at the first visit. Patients who were randomised to placebo also received two injections during the first visit for masking purposes. The randomisation was performed by a computer-generated random sequence by means of an interactive web-response system stratified by country and migraine frequency (33).

The majority of the patients (59%) had two previous medication categories that did not provide any benefits, 31% of the patients had three previous medication categories that did not provide any benefits, and 10% of the patients had four medication categories that did not provide any benefits (33).

7.1.5 The REGAIN study

The REGAIN study was a phase 3, multicentre, randomised, double-blinded placebo-controlled study assessing the efficacy and safety of galcanezumab in the preventive treatment of CM. The study comprised five study periods consisting of an initial 3-to-45-day screening period, a 30-to-40-day prospective baseline period before randomisation to determine the patients eligibility based on daily entries into an electronic patient-reported outcome diary, a three-month randomised, double-blinded, placebo-controlled treatment period, a nine-month open-label extension period and a four-month post-treatment period to observe the washout of the study drug (39).

The study participants were randomised (2:1:1) to receive monthly SC injections of either placebo, 120 mg of galcanezumab or 240 mg of galcanezumab. The patients who were randomly assigned to the 120 mg dose treatment each month received a loading dose of 240 mg administered as two injections of 120 mg each at the first visit. The number of patients in each treatment arm were as follows: 558 patients were assigned to receive placebo, 278 patients were assigned to receive 120 mg of galcanezumab, and 277 patients were assigned to receive 240 mg of galcanezumab. To preserve blinding, all patients in each treatment group received two 1 ml injections at each monthly dosing visit containing either two placebo injections, one placebo and one galcanezumab 120 mg injection, or two galcanezumab 120 mg injections, in blinded pre-filled syringes. After the SC injection, all patients had to remain in the office for a 30-minute post-injection observation period after the first dose. Randomisation was performed by a computer-generated random sequence with an interactive web-response system and was stratified by country, acute headache medication overuse and presence of concurrent migraine preventive medication. In the placebo group, 29% of the patients had two or more failed preventives in the last five years, in the 120 mg galcanezumab group, 24% of the patients had two or more failed preventives in the last five years, and in the 240 mg galcanezumab group, 35% of the patients had two or more failed preventives in the last five years (39).

A subgroup analysis was conducted on the REGAIN study to assess the efficacy in patients who have failed ≥1 and ≥2 prior migraine preventives for efficacy and/or safety reasons, and in those who never failed (published in Ruff et al. 2019 (34)). The number of preventive failures in these subgroups referred to the number of individual medications failed in the past five years and did not refer to classes of medications. No restrictions as to which types of medications could count as a treatment failure in these subgroups were outlined, and failures could be due to either efficacy or safety/tolerability issues (34). The subgroup analyses were conducted on mean CfB in the number of MHDs across the double-blind period, mean proportions of patients with ≥50% and ≥75% reduction in monthly MHDs, overall mean reduction from baseline in monthly MHDs with acute medication use for migraine or headache, mean CfB at month 3 in the Role Function-Restrictive domain score of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ-RFR).

7.1.6 The LIBERTY study

The LIBERTY study was only applied in the comparative analyses of discontinuation between eptinezumab and erenumab. Pooled EM and CM data was applied in the analyses of discontinuation due to low drop-out rates.

The LIBERTY study was a phase 3b, double-blind, placebo-controlled, randomised trial assessing the efficacy and tolerability in patients with EM in whom previous treatment with two to four migraine preventives had been unsuccessful. The study comprised five study periods consisting of an initial screening phase (0-2 weeks), a baseline phase (4 weeks), a double-blind treatment phase (12 weeks), open-label treatment phase (156 weeks) and a follow-up phase (12 weeks). The study includes one erenumab dose of 140 mg administered subcutaneously. The comparator arm in the study is placebo administered to match the intervention (35).

Patients were randomised 1:1 to receive either erenumab 140 mg (administered as two 70 mg injections) or placebo SC. There were 121 patients randomly assigned to the erenumab group, and 125 patients were assigned to the placebo group. Patients who were randomly assigned received treatment on day 1 and then every four weeks for the 12-week double-blind treatment phase. Patients in the erenumab group received two SC injections of erenumab 70mg/1 mL (that is, a total dose of 140 mg), and those in the placebo group received a matching dose of placebo. Randomisation was performed by interactive response technology and was stratified by monthly frequency of migraine headache (4-7 vs 8-14 migraine days per month) during the baseline phase. Both treatment with erenumab and placebo were delivered via individually packaged pre-filled syringes that were identical in appearance. In the study population, 39% of patients had previously tried two preventive drugs unsuccessfully, 38% had previously tried three drugs unsuccessfully, and 23% had previously tried four drugs unsuccessfully (35).

7.1.7 The STRIVE study

The STRIVE study was only applied in the comparative analyses of discontinuation between eptinezumab and erenumab. Pooled EM and CM data were applied in the analyses of discontinuation due to low drop-out rates.

The STRIVE study was a multicentre, randomised, double-blinded, placebo-controlled, parallel-group phase 3 trial assessing the efficacy and safety of erenumab in migraine prevention. The study evaluated the effect of erenumab compared to placebo with regard to the CfB in MMDs. The trial comprised four study periods consisting of a screening period, which included ≤3 weeks of initial screening and a 4-week baseline phase, a 24-week double-blinded treatment phase, a 28-week active-treatment phase, in which patients underwent repeat randomisation and were assigned to receive of one of the two erenumab doses, and a 12-week safety follow-up phase. The study included one erenumab dose of 70 mg and one erenumab dose of 140 mg. The comparator arm in the study is placebo to match the intervention (27). Patients were randomised 1:1:1 to receive monthly SC injections of either 70 mg of erenumab, 140 mg of erenumab or placebo at day 1 and every four weeks hereafter at week 4, 8, 12, 16, and 20. A total of 955 patients underwent randomisation, and of those, 317 patients were assigned to the erenumab 70 mg group, 319 were assigned to the erenumab 140 mg group, and 319 were assigned to the placebo group. The randomisation was based on a schedule that had been generated by the sponsor before initiation of the trial and was centrally executed with the use of an interactive voice or web response system. The 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) (27).

7.1.8 Differences across studies used to inform the NMA and validity of studies

Differences in study characteristics and baseline patient demographics were assessed. All studies were multi-country studies ranging from two to 17 countries. None of the studies were initiated before March 2014. The ROA of treatment in most studies was SC injection, while the ROA for eptinezumab was IV infusions in the DELIVER trial. The migraine classifications of each study are listed in
Table 20 in section 7.3 and were generally consistent across studies. CM was consistently defined as headache on ≥15 days per month, with at least eight days fulfilling migraine criteria or having migraine features. There was a general consistency in definition of migraine days across studies (see Table 21in section 7.3). Migraine days were consistently defined as a day with a headache with features meeting the International Classification of Headache Disorders (ICHD) criteria for a migraine. There was some inconsistency regarding whether the headache meeting ICHD criteria was required to last ≥30 minutes or ≥4 hours, and some inconsistency in which version of the ICHD was used. Additionally, there was some inconsistency in the definition of migraine days in terms of whether days on which migraine-specific acute preventative medications were taken were counted as migraine days. In some studies, these medications needed to be taken alongside a headache (meeting the ICHD criteria), whereas in others they did not.

Table 8 presents the baseline demographics of the patients in the studies. Mean age, mean MHD and mean MMD were similar across trials. Some variation in the mean days of acute medication use was observed across the studies. However, demographic characteristics were similar across the included studies.

Table 8: Baseline demographics of patients from studies used to inform the NMA on chronic patients with previous treatment failures

Study	Migraine type	Failures	N	Mean age (SD)	Mean weight (SD)	Mean MHD (SD)	Mean MMD (SD)	Mean days of acute medication use (SD)	Percent male	Percent white	Percent black	Percent Asian	Source
CONQUER	Chronic	2+	193	45.32 (12.39)	-	20.94 (4.44)	18.65 (4.7)	16.20 (6.46)	12.95	68.39*	2.07	23.83	Mulleners et al. 2020 (33)
DELIVER	Chronic	2+	405	43.28 (10.82)	70.84 (14.53)	19.57 (3.81)	18.71 (4.06)	-	11.63	-	-	-	Data on file
FOCUS**	Chronic	2	-	-	-	-	PBO: 17.60 (5.6) Fremanezumab quarterly: 17.10 (5.3) Fremanezumab monthly: 16.20 (4.2)	-	-	-	-	-	Pazdera et al. 2021 (32)
NCT02066415	Chronic	2+	327	43.27 (11.18)	-	-	18.18 (4.54)	11.43 (7.06)	15.29	-	-	-	Ashina et al. 2018 (30)
REGAIN	Chronic	2+	356	43.14 (11.97)	-	-	19.51 (4.69)	15.64 (5.9)	12.36	-	-	-	Ruff et al. 2019 (34)

Baseline characteristics were pooled across treatment arms for each study. *Calculated from the reported number of white EM patients with at least two failures. **Baseline characteristics were only reported for patients with specifically two prior treatment failures (from Pazdera et al. 2021 (32)). Furthermore, mean MMD was the only baseline characteristic reported and sample size was not reported, so data could not be pooled across treatment arms.

- indicates that data were not reported. Abbreviations: CM: chronic migraine; MHD: monthly headache days; MMD: monthly migraine days; N: sample size; NR: not reported; SD: standard deviation.

7.1.9 Treatment effect modifications

NMAs require that differences in treatment effect-modifying variables are balanced across studies. As such, subgroup results were reviewed in order to identify patient characteristics which may be considered treatment effect-modifying and therefore should be balanced across studies or accounted for in the NMA. The baseline characteristics that were determined to be potential treatment effect modifiers included: MOH, baseline severity (i.e., EM versus CM and baseline MMD) and number of prior treatment failures. Some heterogeneity was observed across studies in MOH and in terms of the number of prior treatment failures for the ITT populations. However, MOH was not well-reported in studies with prior treatment failure subgroups, making it difficult to assess heterogeneity in this characteristic. Across studies, there were differences in migraine classification and baseline MMD (range of mean baseline MMD for 2+ or 3+ prior treatment failure groups were 16.20-19.51 for patients with CM), although definitions of migraine classifications were relatively consistent across studies and baseline MMD was relatively consistent within each migraine classification. To control for potential differences identified during the feasibility assessment (see full attached NMA), NMAs were conducted stratifying by EM and CM, and also stratifying by the prior number of treatment failures (2+ and 3+ respectively).

In the current application, results are only presented for the CM 2+ failure subgroups to align with Danish clinical practice for how CGRP antibodies are used. Potential differences in baseline MOH across CM populations remain a limitation of the analyses conducted in CM, although it was not feasible to assess the extent of any differences in this characteristic due to lack of reporting of baseline MOH across studies.

The review of the subgroup results showed that treatment efficacy was generally increased (as compared to placebo) in patients with more prior treatment failures, suggesting that the number of prior treatment failures may be a treatment effect modifier. Additionally, patients with CM are at a higher risk of developing a headache associated with acute MOH, which may exacerbate the disease. Subgroup analyses of MOH diagnosis at baseline (from the PROMISE-2 trial on eptinezumab) showed a greater relative reduction in MMD (eptinezumab as compared to placebo) compared to the full study population. Based on the above investigations, it was concluded that the number of prior treatment failures, baseline severity (i.e., EM versus CM, and baseline MMD) and MOH (for CM patients only) are potential treatment effect modifiers and must therefore be balanced across studies in order to provide an unbiased comparison of eptinezumab versus its comparators.

7.2 Efficacy and safety – results per study

In this section, results per study on each outcome included in the current application are presented. The following outcomes were deemed relevant by Lundbeck for the assessment of eptinezumab (see the rationale for each outcome in Appendix D and Appendix E): MMD, 50% MRR, HIT-6, MSQ, MMDs with acute medication use and AEs, serious adverse event (SAEs) and discontinuation. The results presented in the following are for patients with chronic migraine with previous failure of more than two migraine treatments.

7.2.1 Mean CfB in MMDs

Table 9 presents the results per study included in the NMA on mean CfB in MMD. All studies had a measure for mean CfB in MMDs, as seen in Table 9. Migraine days were consistently defined as a day with a headache with features meeting the ICHD criteria for a migraine.

Table 9: Results per study on mean CfB in MMD

Study	Arm	Analysis set	Timepoint	Migraine classification	Failures	Sample size	CfB	Standard error	Source
CONQUER	Galcanezumab 120 mg	Subgroup	Month 1–3	Chronic	2+	95	-6.0	0.70	Mulleners et al. 2020
CONQUER	Placebo	Subgroup	Month 1–3	Chronic	2+	98	-2.20	0.60	Mulleners et al. 2020
REGAIN	Galcanezumab 120 mg	mITT	Month 1–3	Chronic	2+	72	-5.35	0.70	Ruff et al. 2019
REGAIN	Placebo	mITT	Month 1–3	Chronic	2+	174	-1.01	0.50	Ruff et al. 2019
DELIVER	Eptinezumab 100 mg	Subgroup	Month 1–3	Chronic	2+	[redacted]	[redacted]	[redacted]	Data on file
DELIVER	Eptinezumab 300 mg	Subgroup	Month 1–3	Chronic	2+	[redacted]	[redacted]	[redacted]	Data on file
DELIVER	Placebo	Subgroup	Month 1–3	Chronic	2+	[redacted]	[redacted]	[redacted]	Data on file
FOCUS	Fremanezumab 675/225/225 mg monthly	mITT	Week 1–12	Chronic	2+	173	-4.50	0.45	Ferrari et al. 2019
FOCUS	Fremanezumab quarterly, 675 mg	mITT	Week 1–12	Chronic	2+	169	-3.90	0.46	Ferrari et al. 2019
FOCUS	Placebo	mITT	Week 1–12	Chronic	2+	167	-0.70	0.47	Ferrari et al. 2019

NCT02066415	Erenumab 140 mg	Subgroup	Month 3	Chronic	2+	92	-7.00	0.59	Ashina et al. 2018
NCT02066415	Erenumab 70 mg	Subgroup	Month 3	Chronic	2+	93	-5.40	0.61	Ashina et al. 2018
NCT02066415	Placebo	Subgroup	Month 3	Chronic	2+	142	-2.70	0.49	Ashina et al. 2018

CfB: change from baseline, mITT: modified intention-to-treat

7.2.2 50% MRR

The 50% MRR is a measure for how many patients achieve a 50% reduction in the number of MMDs. Table 10 presents the results per study included in the NMA on 50% MRR.

Table 10: Results per study on 50% MRR

Study	Arm	Analysis set	Timepoint	Migraine classification	Failures	Sample size	Events (achieved 50% response)	Source
CONQUER	Galcanezumab 120 mg	Subgroup	Month 1–3	Chronic	2+	95	30	Mulleners et al. 2020
CONQUER	Placebo	Subgroup	Month 1–3	Chronic	2+	98	9	Mulleners et al. 2020
REGAIN	Galcanezumab 120 mg	Subgroup	Month 1–3	Chronic	2+	72	21	Ruff et al. 2019
REGAIN	Placebo	Subgroup	Month 1–3	Chronic	2+	174	16	Ruff et al. 2019
DELIVER	Eptinezumab 100 mg	Subgroup	Month 1–3	Chronic	2+	[redacted]	[redacted]	Data on file
DELIVER	Eptinezumab 300 mg	Subgroup	Month 1–3	Chronic	2+	[redacted]	[redacted]	Data on file
DELIVER	Placebo	Subgroup	Month 1–3	Chronic	2+	[redacted]	[redacted]	Data on file

FOCUS	Fremanezumab 675/225/225 mg monthly	mITT	Week 12	Chronic	2+	173	51	Ferrari et al. 2019
FOCUS	Fremanezumab quarterly, 675 mg	mITT	Week 12	Chronic	2+	169	46	Ferrari et al. 2019
FOCUS	Placebo	mITT	Week 12	Chronic	2+	166	14	Ferrari et al. 2019
NCT02066415	Erenumab 140 mg	Subgroup	Month 3	Chronic	2+	92	38	Ashina et al. 2018
NCT02066415	Erenumab 70 mg	Subgroup	Month 3	Chronic	2+	93	33	Ashina et al. 2018
NCT02066415	Placebo	Subgroup	Month 3	Chronic	2+	142	20	Ashina et al. 2018

7.2.3 HIT-6

Table 11 presents the results per study included in the NMA on HIT-6. The HIT-6 consists of six items: pain, social functioning, role functioning, vitality, cognitive functioning and psychological distress. The patient answers each of the six related questions using one of the following five responses: “never”, “rarely”, “sometimes”, “very often” or “always” (40). These responses are summed to produce a total HIT-6 score ranging from 36 to 78. Higher scores indicate a greater impact of headaches on the daily life of the patient (40). DELIVER included HIT-6 data, but in terms of comparators, data was only available for erenumab from NCT02066415.

Table 11: Results per study on HIT-6

Study	Arm	Analysis set	Timepoint	Migraine classification	Failures	Sample size	CfB	Standard error	Source
DELIVER	Eptinezumab 100 mg	Subgroup	Month 1–3	Chronic	2+	[redacted]	[redacted]	[redacted]	Data on file
DELIVER	Eptinezumab 300 mg	Subgroup	Month 1–3	Chronic	2+	[redacted]	[redacted]	[redacted]	Data on file
DELIVER	Placebo	Subgroup	Month 1–3	Chronic	2+	[redacted]	[redacted]	[redacted]	Data on file
NCT02066415	Erenumab 140 mg	Subgroup	Week 9–12	Chronic	2+	91	-5.2	0.64	Abstract by Lanteri-Minet et al.
NCT02066415	Erenumab 70 mg	Subgroup	Week 9–12	Chronic	2+	86	-5.4	0.66	Abstract by Lanteri-Minet et al.
NCT02066415	Placebo	Subgroup	Week 9–12	Chronic	2+	134	-1.5	0.54	Abstract by Lanteri-Minet et al.

CfB: change from baseline

7.2.4 MSQ

The MSQ is a 14-item questionnaire that measures QoL impacts in three domains: Role Function-Restrictive (RF-R), Role Function-Preventive (RF-P) and Emotional Function (EF). RF-R includes seven items that measure the functional impact of migraine through limitations on daily social and work activities, RF-P includes four items that measure the impact of migraine through prevention of daily work and social activities, and EF includes three items that assess the emotional impact of migraine (41,42). The score ranges from 0–100, with a higher score indicating better QoL (41).

In the following, we present results per study for each subscale. Table 12 presents results on RF-R MSQ, Table 13 presents results on EF MSQ and Table 14 presents results on RF-P MSQ. MSQ data was only available for eptinezumab from the DELIVER trial and galcanezumab from CONQUER and REGAIN.

Table 12: Results per study on RF-R MSQ

Study	Arm	Analysis set	Timepoint	Migraine classification	Failures	Sample size	CfB	Standard error	Source
CONQUER	Galcanezumab 120 mg	Subgroup	Month 3	Chronic	2+	95	20.61	2.05	Mulleners et al. 2020
CONQUER	Placebo	Subgroup	Month 3	Chronic	2+	98	6.71	1.99	Mulleners et al. 2020
REGAIN	Galcanezumab 120 mg	Subgroup	Baseline-month 3	Chronic	2+	64	19.13	2.87	Ruff et al. 2019
REGAIN	Placebo	Subgroup	Baseline-month 3	Chronic	2+	160	10.67	2.12	Ruff et al. 2019
DELIVER	Eptinezumab 100 mg	Subgroup	Week 12	Chronic	2+	[redacted]	[redacted]	[redacted]	Data on file
DELIVER	Eptinezumab 300 mg	Subgroup	Week 12	Chronic	2+	[redacted]	[redacted]	[redacted]	Data on file
DELIVER	Placebo	Subgroup	Week 12	Chronic	2+	[redacted]	[redacted]	[redacted]	Data on file

NR: not reported.

Table 13: Results per study on EF MSQ

Study	Arm	Analysis set	Timepoint	Migraine classification	Failures	Sample size	CfB	Standard error	Source
CONQUER	Galcanezumab 120 mg	Subgroup	Month 3	Chronic	2+	95	24.38	2.63	Tepper et al. 2022
CONQUER	Placebo	Subgroup	Month 3	Chronic	2+	98	11.09	2.57	Tepper et al. 2022
DELIVER	Eptinezumab 100 mg	Subgroup	Week 12	Chronic	2+	[redacted]	[redacted]	[redacted]	Data on file
DELIVER	Eptinezumab 300 mg	Subgroup	Week 12	Chronic	2+	[redacted]	[redacted]	[redacted]	Data on file
DELIVER	Placebo	Subgroup	Week 12	Chronic	2+	[redacted]	[redacted]	[redacted]	Data on file

NR: not reported.

Table 14: Results per study on RF-P MSQ

Study	Arm	Analysis set	Timepoint	Migraine classification	Failures	Sample size	CfB	Standard error	Source
CONQUER	Galcanezumab 120 mg	Subgroup	Month 3	Chronic	2+	95	15.27	1.88	Tepper et al. 2022
CONQUER	Placebo	Subgroup	Month 3	Chronic	2+	98	5.37	1.83	Tepper et al. 2022
DELIVER	Eptinezumab 100 mg	Subgroup	Week 12	Chronic	2+	[redacted]	[redacted]	[redacted]	Data on file
DELIVER	Eptinezumab 300 mg	Subgroup	Week 12	Chronic	2+	[redacted]	[redacted]	[redacted]	Data on file
DELIVER	Placebo	Subgroup	Week 12	Chronic	2+	[redacted]	[redacted]	[redacted]	Data on file

NR: not reported.

7.2.5 CfB in MMD with use of acute medication

Table 15 presents the results per study included in the NMA on the CfB in MMD with use of acute medication. Data was available for eptinezumab, galcanezumab and erenumab. No data was available for fremanezumab.

Table 15: Results per study on CfB in MMD with use of acute medication

Study	Arm	Analysis set	Timepoint	Migraine classification	Failures	Sample size	CfB	Standard error	Source
CONQUER	Galcanezumab 120 mg	Subgroup	Month 1-3	Chronic	2+	95	-5.4	0.6	Mulleners et al. 2020
CONQUER	Placebo	Subgroup	Month 1-3	Chronic	2+	98	-1.6	0.6	Mulleners et al. 2020
REGAIN	Galcanezumab 120 mg	mITT	Month 1-3	Chronic	2+	72	-5.8	0.7	Ruff et al. 2019
REGAIN	Placebo	mITT	Month 1-3	Chronic	2+	174	-1.4	0.5	Ruff et al. 2019
DELIVER	Eptinezumab 100 mg	Subgroup	Month 1-3	Chronic	2+	[redacted]	[redacted]	[redacted]	Data on file
DELIVER	Eptinezumab 300 mg	Subgroup	Month 1-3	Chronic	2+	[redacted]	[redacted]	[redacted]	Data on file

DELIVER	Placebo	Subgroup	Month 1-3	Chronic	2+	[redacted]	[redacted]	[redacted]	Data on file
NCT02066415	Erenumab 140 mg	Subgroup	Month 3	Chronic	2+	92	-5.4	0.45	Ashina et al. 2018
NCT02066415	Erenumab 70 mg	Subgroup	Month 3	Chronic	2+	93	-4.1	0.46	Ashina et al. 2018
NCT02066415	Placebo	Subgroup	Month 3	Chronic	2+	142	-1.3	0.38	Ashina et al. 2018

7.2.6 Discontinuation

All-cause discontinuation and discontinuation due to AEs were analysed in a pooled EM and CM population due to the low number of discontinuations across trials. Table 16 presents the results per study on all-cause discontinuation while Table 17 presents the results per study on discontinuation due to AEs.

Table 16: Pooled EM and CM all-cause discontinuation

Study name	Time	Unit	Treatment	Dropout	N	Proportion dropout	Source
DELIVER	24	Weeks	Eptinezumab 100 mg	[redacted]	[redacted]	[redacted]	Data on file
DELIVER	24	Weeks	Eptinezumab 300 mg	[redacted]	[redacted]	[redacted]	Data on file
DELIVER	24	Weeks	Placebo	[redacted]	[redacted]	[redacted]	Data on file
LIBERTY	12	Weeks	Placebo	3	125	0.02	Reuter et al. 2018
LIBERTY	12	Weeks	Erenumab 140 mg	3	121	0.02	Reuter et al. 2018
CONQUER	12	Weeks	Placebo	4	230	0.017	Mulleners et al. 2020
CONQUER	12	Weeks	Galcanezumab 120 mg	7	232	0.03	Mulleners et al. 2020
FOCUS	12	Weeks	Placebo	13	279	0.047	Ferrari et al. 2019
FOCUS	12	Weeks	Fremanezumab 675/225/225 mg monthly	11	283	0.039	Ferrari et al. 2019
FOCUS	12	Weeks	Fremanezumab quarterly, 675 mg	4	276	0.014	Ferrari et al. 2019

Table 17: Pooled EM and CM discontinuation due to AEs

Study name	Time	Unit	Treatment	Dropout	N	Proportion dropout	Source
STRIVE	24	Weeks	Placebo	0	54	0.00	Goadsby et al. 2017
STRIVE	24	Weeks	Erenumab 70 mg	1	49	0.02	Goadsby et al. 2017
STRIVE	24	Weeks	Erenumab 140 mg	4	58	0.069	Goadsby et al. 2017
DELIVER	24	Weeks	Eptinezumab 100 mg	1	299	0.00	Ashina et al. 2022 (29)
DELIVER	24	Weeks	Eptinezumab 300 mg	6	294	0.02	Ashina et al. 2022 (29)
DELIVER	24	Weeks	Placebo	1	298	0.00	Ashina et al. 2022 (29)
LIBERTY	12	Weeks	Placebo	1	125	0.01	Reuter et al. 2018
LIBERTY	12	Weeks	Erenumab 140 mg	0	121	0.00	Reuter et al. 2018
NCT02066415	12	Weeks	Placebo	1	141	0.01	Ashina et al. 2018
NCT02066415	12	Weeks	Erenumab 70 mg	0	92	0.00	Ashina et al. 2018
NCT02066415	12	Weeks	Erenumab 140 mg	0	92	0.00	Ashina et al. 2018
CONQUER	12	Weeks	Placebo	0	230	0.00	Mulleners et al. 2020
CONQUER	12	Weeks	Galcanezumab 120 mg	1	232	0.00	Mulleners et al. 2020
FOCUS	12	Weeks	Placebo	3	277	0.01	Ferrari et al. 2019
FOCUS	12	Weeks	Fremanezumab 675/225/225 mg monthly	4	285	0.01	Ferrari et al. 2019
FOCUS	12	Weeks	Fremanezumab quarterly, 675 mg	1	276	0.00	Ferrari et al. 2019

7.2.7 Adverse events and serious adverse events

In accordance with the DMC method guideline, results on the proportions of patients who experienced an AE or an SAE were presented. Results per study are presented in Table 18.

Table 18: The proportion of patients with at least one AE or one SAE

Study name	Time	Unit	Treatment	Analysis set	N	AE	SAE	Source
DELIVER	24	Weeks	Eptinezumab 100 mg	APTS	299	127 (42.5%)	5 (1.7%)	Ashina et al. 2022 (29)
DELIVER	24	Weeks	Eptinezumab 300 mg	APTS	294	120 (40.8%)	7 (2.4%)	Ashina et al. 2022 (29)
DELIVER	24	Weeks	Placebo	APTS	298	119 (39.9%)	4 (1.3%)	Ashina et al. 2022 (29)
NCT02066415	12	Weeks	Erenumab 70 mg	≥2 failed subgroup	92	39 (42.4%)	3 (3.3%)	Ashina et al. 2018
NCT02066415	12	Weeks	Erenumab 140 mg	≥2 failed subgroup	92	53 (57.6%)	1 (1.1%)	Ashina et al. 2018
NCT02066415	12	Weeks	Placebo	≥2 failed subgroup	141	62 (44.0%)	4 (2.8%)	Ashina et al. 2018
CONQUER	12	Weeks	Galcanezumab 120 mg	Total population	232	119 (51%)	2 (1%)	Mulleners et al. 2020
CONQUER	12	Weeks	Placebo	Total population	230	122 (53%)	2 (1%)	Mulleners et al. 2020
FOCUS	12	Weeks	Fremanezumab 675/225/225 mg monthly	Total population	285	129 (45%)	4 (1%)	Ferrari et al. 2019
FOCUS	12	Weeks	Fremanezumab quarterly, 675 mg	Total population	276	151 (55%)	2 (≤1%)	Ferrari et al. 2019
FOCUS	12	Weeks	Placebo	Total population	277	134 (48%)	4 (1%)	Ferrari et al. 2019

7.3 Comparative efficacy analyses of eptinezumab and marketed CGRP antibodies

The comparative analyses of eptinezumab and marketed CGRP antibodies were based on an NMA. In the following, the methodology and PICO for the NMA are described.

For the NMA, a refinement to the eligibility criteria for the SLR was made. In brief, interventions were restricted to preventive CGRP antibodies in both EM and CM and additionally Botox A for CM (not presented in the current application). With the exception of galcanezumab 240 mg every four weeks, only dosages as per the SPC (or expected to be within label for eptinezumab) were included as eligible interventions. Galcanezumab 240 mg is not relevant for the current application and will not be presented further. The population, intervention, comparison, outcomes and study (PICO) design framework for study selection in the NMA are presented in the following.

Population

The NMA included patients with EM or CM with documented treatment failure of at least two preventive migraine medications. The populations of interest were subgroups of patients with documented treatment failure of at least two preventive migraine medications and patients with documented treatment failure of at least three preventive migraine medications failures. An analysis pooling EM and CM patients was conducted in addition to analyses stratified by EM and CM patients for endpoints that are expected to be relatively similar across EM and CM (50% and 70% MRR).

Interventions

CGRP antibodies: eptinezumab (100 mg and 300 mg every 12 weeks), erenumab (70 mg and 140 mg every four weeks), fremanezumab (675/225/225 mg every four weeks; 675 mg every 12 weeks). For the 675/225/225 mg dose, in CM, a 675 mg loading dose was followed by a 225 mg maintenance dose every four weeks, whilst for EM, a 225 mg dose was given every four weeks without a loading dose. Galcanezumab (120 mg every four weeks; 240 mg loading dose, followed by 120 mg maintenance dose every four weeks; 240 mg every four weeks). Although galcanezumab 240 mg every four weeks is not a recommended dose as per the SPC, it was included in the analyses for completeness (since it was included as a treatment arm in REGAIN and EVOLVE-1/-2). The inclusion of this treatment arm in the analysis is unlikely to impact comparative estimates for other treatment arms in the NMA, since all comparisons are indirect via placebo and results versus galcanezumab 240 mg every four weeks have limited practical implications. Galcanezumab 240 mg will not be presented in the current application.

Comparators

Placebo, best supportive care and any intervention of interest (see above) that facilitated an indirect comparison.

Outcomes

Efficacy: CfB in MMD, 50% and 75% MRR, CfB in MMD with use of acute medication, CfB in MHD. HRQoL: CfB in HIT-6, HIT-6 response rate for a ≥5-point reduction in the total score, CfB in MSQ v2.1 domains (EF, RF-P, RF-R), CfB in work productivity and activity impairment (WPAI). Discontinuations (due to AEs and all-cause discontinuation). Outcome characteristics are summarised in Table 19.

Table 19: Outcome characteristics

Domain	Outcome	Type	Timepoint ´type	Notes
Efficacy	MMD	Continuous	Time-averaged	Time-averaged continuous outcome, CfB used where available
	MMD response rates (50%, 75%)	Binary	Time-averaged	Derived from MMD CfB

	CfB in MMD with use of acute medication	Continuous	Time-averaged	Time-averaged continuous outcome, CfB used where available
	MHD	Continuous	Time-averaged	Time-averaged continuous outcome, CfB used where available
HRQoL	HIT-6	Continuous	Single point in time	CfB used where available
	HIT-6 response (defined as achieving a reduction of 5 points or more relative to baseline)	Binary	Single point in time	Derived from HIT-6 CfB
	MSQ v2.1	Continuous	Single point in time	No total score, three subdomains analysed separately
	WPAI	Continuous	Single point in time	No total score, subscores analysed separately
Tolerability	Discontinuations, due to AEs	Binary	Duration of follow-up	Number discontinued and timepoint evaluated
	Discontinuations, all-cause	Binary	Duration of follow-up	Number discontinued and timepoint evaluated

Abbreviations: AE: adverse event; CfB: change from baseline; HIT-6: Headache Impact Test; HRQoL: health-related quality of life; MHD: monthly headache days; MMD, monthly migraine days; MRR: migraine response rate; MSQ: Migraine-Specific Quality of Life Questionnaire; WPAI: work productivity and activity impairment.

Study design

Double-blind phase 2–4 RCTs with at least a 12-week double-blind period, including subgroups.

Timepoints

Comparisons of CGRP antibodies: Some outcomes of interest were reported over an interval of time, as noted in Table 19. For example, some studies reported week 12 CfB in MMD based on the CfB to the four-week interval prior to week 12 (weeks 9–12), while other studies reported based on the CfB to the 12-week interval from weeks 1–12. The primary timepoint of interest for the NMA was week 12. For efficacy outcomes (MMD, MRR, MMD with use of acute medication and MHD), averages over week 1–12 were prioritised. If 12-week interval data were not available for a study, the following hierarchy was followed:

1. The outcome corresponding to the primary endpoint was preferred (for example Week 9–12)
2. The latest available timepoint up until Week 12 (for example Week 4–8).

For HRQoL outcomes (HIT-6, HIT-6 response, MSQ, WPAI), measurements taken at week 12 were preferred. If this timepoint was not available, the latest available timepoint up until week 12 was preferred (for example week 8). For discontinuations due to AEs and all-cause discontinuation, the number of discontinuations by week 12 were preferred. If week 12 data were not available, measurements for the latest available timepoint of the double-blind phase were

preferred (for example week 24). Tables with classification of chronic migraine and migraine definition are presented in

Table **20** and Table 21.

Table 20: Classification of chronic migraine in included studies

Study	Migraine Classification	Definition
CONQUER	Chronic	Headache on ≥15 days per month, with at least 8 days fulfilling migraine criteria
DELIVER	Chronic	Headache occurring on >14 days per month, with ≥8 fulfilling migraine criteria
FOCUS	Chronic	Headache on ≥15 days per month, with at least 8 days fulfilling migraine criteria
NCT02066415	Chronic	Headache on ≥15 days per month, with at least 8 days fulfilling migraine criteria
REGAIN	Chronic	Headache on ≥15 days per month, with at least 8 days fulfilling migraine criteria

Table 21: Migraine day definitions from included studies

Study	Definition
CONQUER	A migraine headache day was defined as a calendar day with a headache lasting at least 30 min and with features meeting ICHD-3 criteria for migraine or probable migraine. Days on which a triptan or ergot was taken without symptoms meeting these criteria did not count as a migraine headache day.
DELIVER	A migraine day was defined as a day with a headache that lasted ≥4 hours and met ICHD-3 criteria C and D for migraine without aura, or that lasted ≥30 minutes and <4 hours and on which the patient took medication because he/she believed that he/she had a migraine and met ICHD-3 criteria C and D for migraine without aura.
FOCUS	A migraine day was defined as a calendar day with at least four consecutive hours of a migraine with or without aura as per ICHD-3 diagnostic criteria (no more than one ICHD-3 migraine criterion missing), or a headache of any duration treated with migraine-specific acute medications (triptans or ergot compounds).
NCT02066415	A migraine day was any calendar day on which the participant experienced a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache was defined either as a migraine with or without aura, defined in accordance with the ICHD-3 (beta version).
REGAIN	A migraine headache day was a calendar day with a headache lasting 30 minutes with features meeting ICHD-3 beta criteria for migraine or probable migraine. A headache also qualified as a

migraine if the patient believed it was a migraine at onset and was relieved by a triptan or ergot.

Robust NMA models were fitted to the data using model specifications as recommended by the NICE DSU TSD 2 (43), and fixed effect models were fitted and deemed to be most suitable due to the low number of studies per treatment comparison where limited between-study heterogeneity can be expected. Random effect models were fitted to the key efficacy outcomes of interest (CfB in MMD and 50% MRR) as part of sensitivity testing. The results were in line with the fixed effect models, but with higher uncertainty surrounding the estimates. Galcanezumab 240 mg every four weeks is not within the galcanezumab SPC but has been included in the analysis for completeness as it was studied in REGAIN. Inclusion of this treatment dosage is unlikely to impact comparative estimates for other treatment arms. In this section, plots of the results of eptinezumab 100 mg compared to included comparators and placebo are presented. Results are reported as mean differences for continuous outcomes, ORs for binary outcomes and HRs for rate outcomes. Corresponding 95% CrIs are also reported, with statistical superiority determined by whether or not the CrIs included the value of no treatment effect (0 for continuous outcomes, 1 for binary and rate outcomes).

Continuous outcomes such as CfB in MMD, CfB in HIT-6 and CfB in MSQ domains should be interpreted the following way:

- For CfB in MMD and CfB in HIT-6, results <0 favour the comparator, results >0 favour the reference because a decrease in MMD or HIT-6 indicates a clinical improvement.
- For CfB in domains of MSQ, results >0 favour the comparator, results <0 favour the reference because an increase in each MSQ domain indicates a clinical improvement.

The binary outcome 50% MRR should be interpreted the following way:

- Results >1 favour the comparator, results <1 favour the reference

The two rate outcomes all-cause discontinuation and discontinuation due to AEs should be interpreted the following way:

- Results <1 favour the comparator, results >1 favour the reference.

7.3.1 NMA results on change from baseline in MMD

Comparative analyses of data on CfB in MMD at week 12 were conducted. The network of studies included in the analysis of CfB in MMD at week 12 is presented in Figure 3.

Figure 3: Network of studies used in the NMA on change from baseline in MMD at week 12 (data on file)

The mean differences (with 95% CrIs) in CfB in MMD at week 12 are presented in Table 22. As seen in the table, [redacted] these results demonstrate that both doses of eptinezumab are as effective as the marketed CGRP antibodies in terms of reducing the mean number of MMD. Figure 4 presents a plot of the NMA results on mean CfB in MMD for all comparators compared to eptinezumab 100 mg.

Table 22: Placebo-adjusted mean differences from NMA in CfB in MMD (95% CrIs) (data on file)

Comp \ Ref	PBO	EPTI 100q12w	EPTI300q12w	ERE70q4w	ERE140q4w	FRE675q12w	FRE675/225/225q4w	GAL120q4w
PBO		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EPTI100q12w	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EPTI300q12w	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERE70q4w	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
ERE140q4w	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]

FRE675q12w	[redacted]							
FRE675/225/ 225q4w	[redacted]							
GAL120q4w	[redacted]							

Abbreviations: CfB: change from baseline; CM: chronic migraine; CrI: credible interval; EPTI100q12w: Eptinezumab 100 mg (q12w); EPTI300q12w: Eptinezumab 300 mg (q12w); 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); MMD: monthly migraine days; PBO: Placebo.
Note: the columns include the reference treatments, and the rows include the comparator treatments.

Figure 4: Plot of mean difference in CfB in MMD of eptinezumab compared to erenumab, galcanezumab and fremanezumab (data on file). Note: FRE675/225/225q4w is a dosing regimen with a 675 mg loading dose followed by monthly administrations of 225 mg fremanezumab.

7.3.2 NMA results on 50% migraine response rate

Comparative analyses of data on 50% MRR at week 12 were conducted. The network of studies included in the analysis of 50% MRR is presented in Figure 5.

Figure 5: Network of studies used in the NMA for 50% MRR (data on file)

The ORs om 50% MRR are presented in Table 24. We calculated the relative risk (RR) of eptinezumab 100 mg compared to each comparator based on the ORs, in accordance with the method suggested in the Appendix in the DMC guideline (44). In the calculations of the RR based on the OR and absolute difference based on the RR, eptinezumab 100 mg was used as the reference group. The RRs are presented in Table 23 and more details to the calculations are provided in Appendix F.

The RRs in Table 23 and the ORs in Figure 6 show that eptinezumab 100 mg is as effective as the three marketed CGRP antibodies in terms of achieving a 50% MRR

Table 23: Absolute and relative differences between eptinezumab 100 mg and marketed CGRP antibodies in 50% MRR

	Absolute difference (95% CI)	Relative risk (95% CI)
Eptinezumab 100 mg vs erenumab 70 mg	0.47% (-17.13, 21.83%)	1.01 (0.55, 1.58)
Eptinezumab 100 mg vs erenumab 140 mg	6.34% (-12.78%, 27.37%)	1.17 (0.66, 1.72)
Eptinezumab 100 mg vs fremanezumab 675 mg	5.38% (-13.82%, 27.00%)	1.14 (0.64, 1.71)
Eptinezumab 100 mg vs fremanezumab 675/225/225 mg	8.18% (-11.43%, 29.38%)	1.22 (0.70, 1.77)
Eptinezumab 100 mg vs galcanezumab 120 mg	6.15% (-11.77%, 25.84%)	1.16 (0.69, 1.68)

Table 24: ORs from NMA on 50% MRR (95% CrIs) (data on file)

Comp \ Ref	PBO	EPTI100q12w	EPTI300q12w	ERE70q4w	ERE140q4w	FRE675q12w	FRE675/225/225q4w	GAL120q4w
PBO		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EPTI100q12w	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EPTI300q12w	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERE70q4w	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
ERE140q4w	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
FRE675q12w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
FRE675/225/225q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
GAL120q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Note: the columns include the reference treatments, and the rows include the comparator treatments.

Figure 6 presents a plot of the odds ratios (OR) from the NMA on 50% MRR..

Figure 6: Plot of ORs of 50% MRR for eptinezumab compared to erenumab, fremanezumab and galcanezumab (data on file). Note: FRE675/225/225q4w is a dosing regimen with a 675 mg loading dose followed by monthly administrations of 225 mg fremanezumab.

7.3.3 NMA results on HIT-6

Comparative analyses of data on HIT-6 were conducted. The network of studies included in the analysis of HIT-6 is

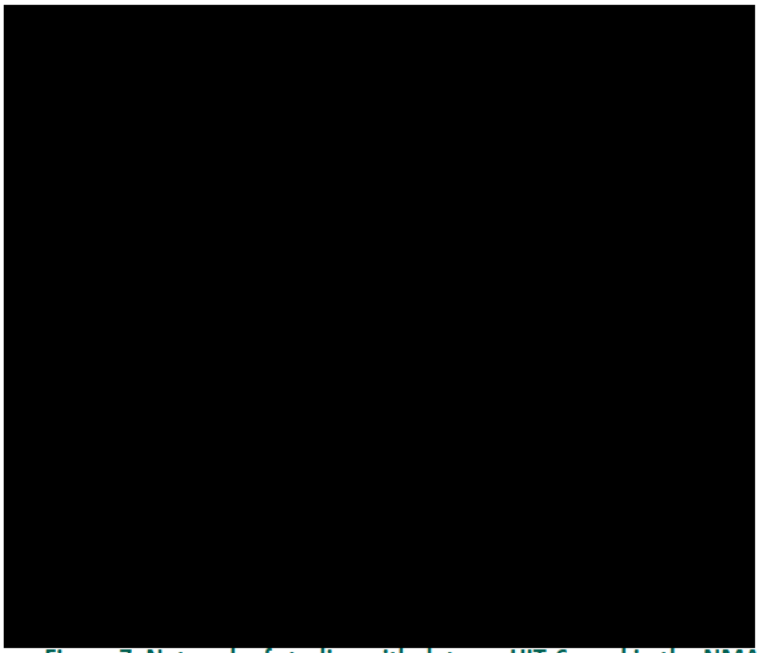

Figure 7: Network of studies with data on HIT-6 used in the NMA (data on file)

Mean differences in CfB in HIT-6 (with 95% CrIs) are presented in Table 25.

[redacted] Figure 8 presents a plot of the mean difference in CfB in HIT-6 for eptinezumab compared to erenumab 70 mg/140 mg, eptinezumab 300 mg and placebo.

Table 25: Placebo-adjusted mean difference in CfB in HIT-6 from NMA (95% CrIs) (data on file)

Comp \ Ref	PBO	EPTI100q12w	EPTI300q12w	ERE70q4w	ERE140q4w
PBO		[redacted]	[redacted]	[redacted]	[redacted]
EPTI100q12w	[redacted]		[redacted]	[redacted]	[redacted]
EPTI300q12w	[redacted]	[redacted]		[redacted]	[redacted]
ERE70q4w	[redacted]	[redacted]	[redacted]		[redacted]
ERE140q4w	[redacted]	[redacted]	[redacted]	[redacted]	

Note: the columns include the reference treatments, and the rows include the comparator treatments.

[redacted]

Figure 8: Plot of mean difference in CfB in HIT-6 of eptinezumab compared to erenumab, eptinezumab 300 mg and placebo (data on file)

7.3.4 NMA results on MSQ

Comparative analyses of data on MSQ were conducted. In the following sections, results from the comparative analyses on each subscale of the MSQ are presented.

Results on RF-R MSQ

The network of studies included in the analysis of RF-R is presented in Figure 9.

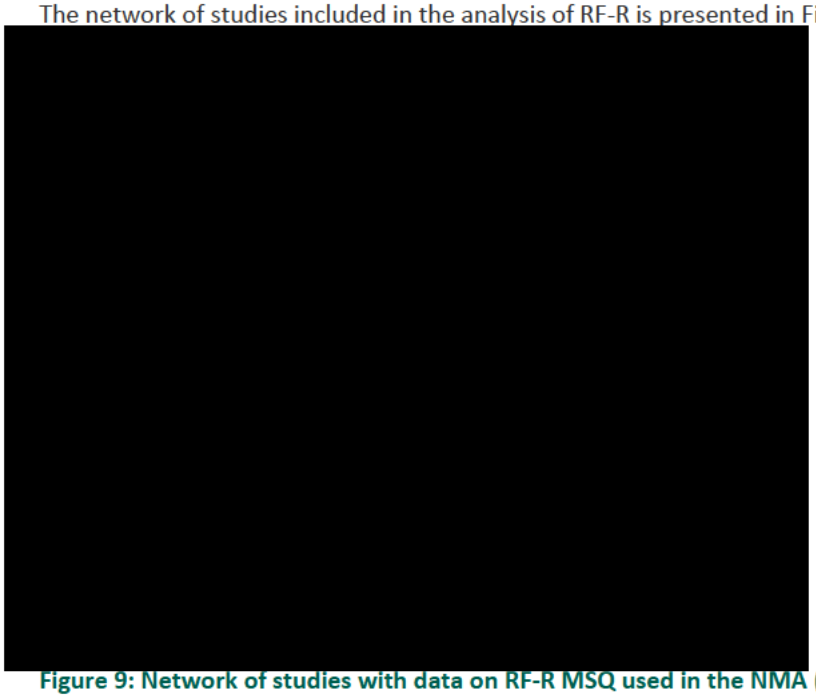

Figure 9: Network of studies with data on RF-R MSQ used in the NMA (data on file)

Mean differences in CfB in RF-R MSQ (with 95% CrIs) are presented in Table 26. Figure 10 presents a plot of the mean difference in CfB in RF-R MSQ for eptinezumab compared to galcanezumab, eptinezumab 300 mg and placebo.

Table 26: Placebo-adjusted mean differences in CfB in RF-R MSQ from NMA (95% CrIs) (data on file)

Comp \ Ref	PBO	EPTI100q12w	EPTI300q12w	GAL120q4w
PBO				
EPTI100q12w				
EPTI300q12w				
GAL120q4w				

Note: the columns include the reference treatments, and the rows include the comparator treatments.

Figure 10: Plot of mean differences in CfB in RF-R MSQ of eptinezumab compared to galcanezumab, eptinezumab 300 mg and placebo (data on file)

Results on EF MSQ

The network of studies included in the analysis of EF MSQ is presented Figure 11.

Figure 11: Network of studies with data on EF MSQ in NMA (data on file)

Mean differences in CfB in EF MSQ (with 95% CrIs) are presented in Table 27. [redacted] Figure 12 presents a plot of the mean difference in CfB in EF MSQ for eptinezumab compared to galcanezumab, eptinezumab 300 mg and placebo.

Table 27: Mean differences in CfB in EF MSQ from NMA (95% CrIs) data on file

Comp \ Ref	PBO	EPTI100q12w	EPTI300q12w	GAL120q4w
PBO		[redacted]	[redacted]	[redacted]
EPTI100q12w	[redacted]		[redacted]	[redacted]
EPTI300q12w	[redacted]	[redacted]		[redacted]
GAL120q4w	[redacted]	[redacted]	[redacted]	

Note: the columns include the reference treatments, and the rows include the comparator treatments.

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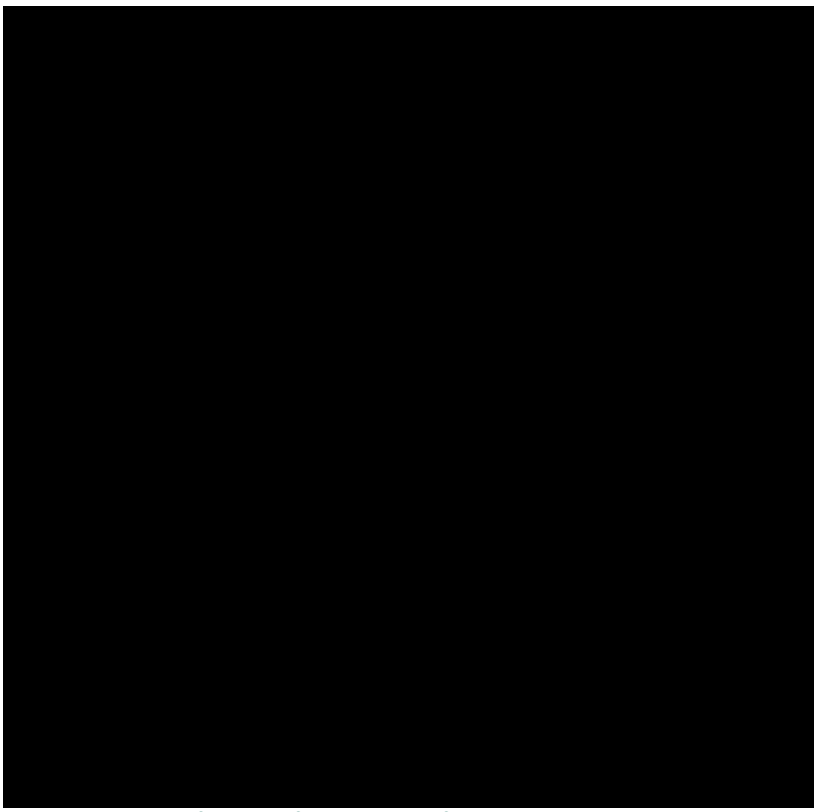

Figure 12: Plot of mean CfB in EF MSQ for eptinezumab compared to galcanezumab, eptinezumab 300 mg and placebo (data on file)

Results on RF-P MSQ

The network of studies included in the analysis of RF-P MSQ is presented Figure 13.

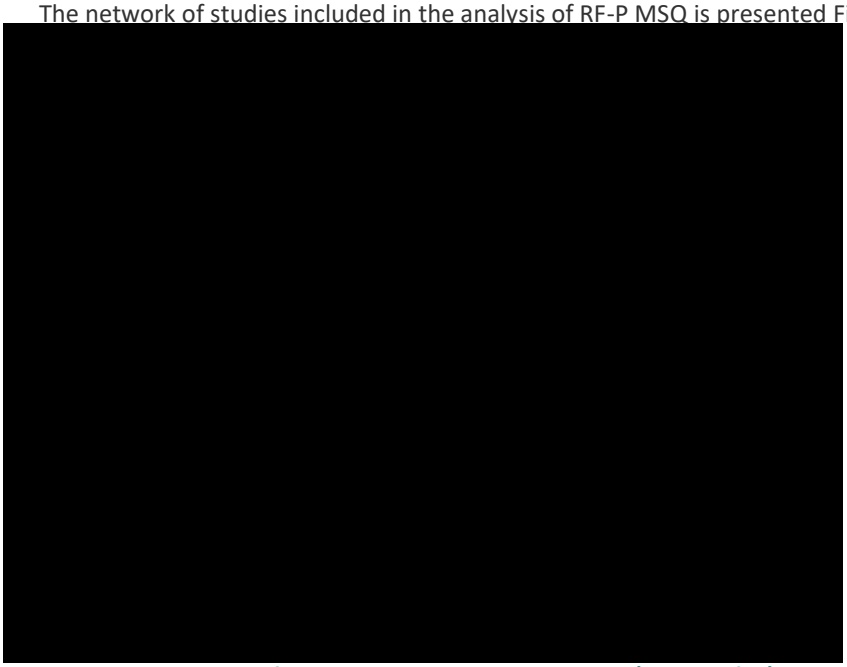

Figure 13: Network of studies with data on RF-P MSQ (data on file)

Mean differences in CfB in RF-P MSQ (with 95% CrIs) are presented in Table 28. [redacted]

Figure 14 presents a plot of the mean difference in CfB in RF-P MSQ for eptinezumab compared to placebo, eptinezumab 300 mg and galcanezumab 120 mg.

Table 28: Mean differences in CfB in RF-P MSQ from NMA (95% CrIs) data on file

Comp \ Ref	PBO	EPTI100q12w	EPTI300q12w	GAL120q4w
PBO		[redacted]	[redacted]	[redacted]
EPTI100q12w	[redacted]		[redacted]	[redacted]
EPTI300q12w	[redacted]	[redacted]		[redacted]
GAL120q4w	[redacted]	[redacted]	[redacted]	

Note: the columns include the reference treatments, and the rows include the comparator treatments.

[redacted]

Figure 14: Plot of mean difference in CfB in RF-P MSQ for eptinezumab compared to placebo, eptinezumab 300 mg and galcanezumab 120 mg at week 12 (data on file)

7.3.5 NMA results on MMDs with acute medication use

Comparative analysis of data on MMDs with acute medication use were conducted. The network of studies included in the analysis of MMDs with acute medication use is presented Figure 15.

Figure 15: Network of studies with data on CfB in MMD with use of acute medication (data on file)

Mean differences in CfB in MMDs with use of acute medication (with 95% CrIs) are presented in Table 29.

Figure 16 presents a plot of the mean difference in CfB in MMDs with acute medication use for eptinezumab compared to erenumab 70 mg/140 mg, galcanezumab 120mg, eptinezumab 300 mg and placebo.

Table 29: Placebo-adjusted mean differences in CfB in MMD with use of acute medication with (95% CrIs) (data on file)

Comp \ Ref	PBO	EPTI100q12w	EPTI300q12w	ERE70q4w	ERE140q4w	GAL120q4w
PBO						
EPTI100q12w						
EPTI300q12w						
ERE70q4w						

ERE140q4w	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
GAL120q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Note: the columns include the reference treatments, and the rows include the comparator treatments.

Figure 16: Plot of mean difference in CfB in MMDs with acute medication use eptinezumab compared to placebo, eptinezumab 300 mg, erenumab 70 mg and 140 mg and galcanezumab 120 mg at week 12 (data on file)

7.4 Comparative safety analysis of eptinezumab and marketed CGRP antibodies

The comparative analyses of discontinuation were also from the NMA. The comparative analyses on proportion of patients with at least one AE or at least one SAE were based on an indirect comparison applying Bucher's method.

7.4.1 Discontinuation

Due to the low number of all-cause discontinuations reported across studies, the all-cause discontinuation NMA has been conducted for the pooled EM and CM population. Across both all-cause discontinuation and discontinuation due to AEs, the number of discontinuations were low (<5% for all-cause discontinuation and <7% for discontinuation due to AEs across all studies), resulting in exaggerated relative differences and large credible intervals despite the differences in absolute number of discontinuations being small. In cases where studies reported zero events, a 0.5 correction was applied to all treatment arms in order to ensure model convergence (45). The network of studies included in the analysis of all-cause discontinuation is presented Figure 17.

Figure 17: Network of studies with data on all-cause discontinuation (pooled EM and CM) (data on file)

As seen, data on discontinuation were available for all antibodies. The all-cause discontinuation analysis results should be interpreted with caution due to the low number of events in all the CGRP antibody trials, resulting in very wide credibility intervals (CrIs). Hazard ratios for all-cause discontinuation are presented in

Table 30. [redacted]

Table 30: Hazard ratios (95% CrI) for all-cause discontinuation (data on file)

Comp \ Ref	PBO	EPTI100q12w	EPTI300q12w	ERE140q4w	FRE675q12w	FRE675/225/225q4wFRE675/225/225q4w	GAL120q4w
PBO		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EPTI100q12w	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EPTI300q12w	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
ERE140q4w	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
FRE675q12w	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
FRE675/225/225q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
GAL120q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Note: the columns include the reference treatments, and the rows include the comparator treatments.

Due to the low number of discontinuation due to AEs reported across studies, the NMA for discontinuation due to AEs has also been conducted for the pooled EM and CM population. The network of studies included in the analysis of discontinuation due to AEs is presented Figure 18.

Figure 18: Network of studies with data on discontinuation due to AEs (pooled EM and CM) data on file

The hazard ratios for discontinuing due to AEs are presented in Table 31.

Table 31: Hazard ratios (95% CrI) for discontinuation due to AEs (data on file)

Ref / Comp	PBO	EPTI100q12w	EPTI300q12w	ERE70q4w	ERE140q4w	FRE675q12w	FRE675/225/225q 4w	GAL120q4w
PBO		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EPTI100q12w	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EPTI300q12w	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERE70q4w	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
ERE140q4w	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
FRE675q12w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
FRE675/225/225q 4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
GAL120q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

7.4.2 Adverse events and serious adverse events

The proportion of patients with at least one AE or at least one SAE were not assessed in the NMA. Therefore, the comparative analyses of these outcomes were based on indirect comparative analyses with Bucher's method.

Table 32 presents the absolute difference in proportions and the relative difference in proportions (expressed as a RR) for experiencing at least one AE. As seen in the table, the risk of experiencing at least one AE was decreased for patients treated with both doses of eptinezumab compared to most of the marketed CGRP antibodies except compared to erenumab 70 mg, where the risk ratio was 1 or very close to 1. These results demonstrate that eptinezumab has a good safety profile compared to the marketed CGRP antibodies and offers a reduced risk of experiencing at least one AE.

Table 32: Absolute difference and relative difference in proportions with at least one AE

Comparison	Absolute difference, % (95% CI)	Relative difference, RR (95% CI)
Eptinezumab 100 mg vs erenumab 70 mg	0.08% (-11.5%, 11.6%)	1.00 (0.76, 1.32)
Eptinezumab 100 mg vs erenumab 140 mg	-15.13% (-26.7%, -3.6%)	0.74 (0.59, 0.92)
Eptinezumab 300 mg vs erenumab 70 mg	-1.57% (-13.1%, 10.0%)	0.96 (0.73, 1.27)
Eptinezumab 300 mg vs erenumab 140 mg	-16.79% (-28.3%, -5.2%)	0.71 (0.57, 0.89)
Eptinezumab 100 mg vs fremanezumab 675/225/225	-2.79% (-10.8%, 5.3%)	0.94 (0.78, 1.13)
Eptinezumab 100 mg vs fremanezumab 675	-12.24% (-20.4%, -4.1%)	0.78 (0.66, 0.92)
Eptinezumab 300 mg vs fremanezumab 675/225/225	-4.45% (-12.5%, 3.6%)	0.90 (0.75, 1.09)
Eptinezumab 300 mg vs fremanezumab 675	-13.89% (-22.0%, -5.8%)	0.75 (0.63, 0.89)
Eptinezumab 100 mg vs galcanezumab 120 mg	-8.82% (-17.3%, -0.3%)	0.83 (0.69, 0.99)
Eptinezumab 300 mg vs galcanezumab 120 mg	-10.48 % (-19.0%, -1.9%)	0.80 (0.66, 0.96)

Table 33 presents the absolute difference in proportions and the relative difference in proportions (expressed as a RR) for experiencing at least one SAE. As can be seen, both doses of eptinezumab were associated with a decreased risk of experiencing an SAE. Compared to the marketed CGRP antibodies, both doses of eptinezumab were associated with an increased risk of experiencing a SAE. However, as seen in Table 18, the proportions of patients who experience a SAE in the studies were very low and the clinical experts informed that severe AEs are rarely seen with CGRP antibodies in clinical practice.

Table 33: Absolute difference and relative difference in proportions with at least one SAE

Comparison	Absolute difference (95% CI)	Relative difference (95% CI)
Eptinezumab 100 mg vs erenumab 70 mg	-1.59% (-5.5%, 2.3%)	0.51 (0.13, 2.11)
Eptinezumab 100 mg vs erenumab 140 mg	0.59% (-2.0%, 3.2%)	1.54 (0.18, 13.00)
Eptinezumab 300 mg vs erenumab 70 mg	-0.88% (-4.9%, 3.1%)	0.73 (0.19, 2.77)
Eptinezumab 300 mg vs erenumab 140 mg	1.29% (-1.4%, 4.0%)	2.19 (0.27, 17.57)
Eptinezumab 100 mg vs fremanezumab 675/225/225	0.27% (-1.7%, 2.3%)	1.19 (0.32, 4.39)
Eptinezumab 100 mg vs fremanezumab 675	0.95% (-0.8%, 2.7%)	2.31 (0.45, 11.80)
Eptinezumab 300 mg vs fremanezumab 675/225/225	0.98% (-1.2%, 3.2%)	1.70 (0.50, 5.73)
Eptinezumab 300 mg vs fremanezumab 675	1.66% (-0.4%, 3.7%)	3.29 (0.69, 15.68)
Eptinezumab 100 mg vs galcanezumab 120 mg	0.81% (-1.1%, 2.7%)	1.94 (0.38, 9.91)
Eptinezumab 300 mg vs galcanezumab 120 mg	1.52% (-0.6%, 3.6%)	2.76 (0.58, 13.17)

8. Health economic analysis

The health economic analysis conducted was a cost-minimisation analysis. In the following, we present the rationale for choosing this methodology.

Eptinezumab is a humanised monoclonal CGRP antibody indicated for preventive treatment of adult patients with migraine who have at least four migraine days per month. Currently, three other CGRP antibodies have been evaluated and recommended by the DMC as standard treatment for patients with CM who have failed at least two different previous migraine treatments. The DMC has evaluated that the three marketed CGRP antibodies are clinically equivalent. As shown in section 7.3, eptinezumab has been demonstrated to be at least as effective as the marketed CGRP antibodies in relevant migraine treatment endpoints; thus, a cost-minimisation analysis was chosen. The results of the health economic analysis are presented as the incremental cost of treating CM patients with eptinezumab compared to erenumab, fremanezumab and galcanezumab, respectively. Uncertainty in the cost parameters included in the analysis was assessed with deterministic one-way sensitivity analyses. A budget impact analysis was also conducted to assess the budgetary impact of recommending eptinezumab.

8.1 Model

The applied model was a cost-minimisation model developed in Excel. In the model, the cost per patient of treating CM patients with eptinezumab and the included comparators (erenumab, fremanezumab and galcanezumab) was estimated. Moreover, the model included a budget impact analysis. The cost-minimisation model incorporated all relevant costs associated with treating CM patients in a Danish clinical setting. Information on the Danish clinical practice for CGRP antibody treatment of CM patients who have failed at least two different previous migraine treatments came from two clinical experts (see section 11) and the DMC's national criteria for treating CM patients with the CGRP antibodies that have already been recommended by the DMC. Half-cycle correction was not implemented in the model, as the model did not comprise any cycles or health states.

8.1.1 Time horizon, perspective and discounting in the model

The two clinical experts were consulted on the duration of treatment with the three marketed CGRP antibodies. They informed that not many patients who respond (≥30% reduction in MMD) after three months discontinue treatment with erenumab and fremanezumab (they did not have much experience with galcanezumab); after five years, up to 60% to 70% of patients are still on CGRP antibody treatment. They expected this to be the same for eptinezumab. In addition, they informed that there is no difference between the CGRP antibodies in how many patients continue treatment after the first pause, or how long they stay on treatment in clinical practice. Since there is no difference in how long patients stay on treatment with the CGRP antibodies, how many patients discontinue treatment, or how many patients re-start treatment after a treatment pause, a time horizon long enough to capture that all patients would have discontinued treatment was not applied. A time horizon of 21 months was applied in the base case. The rationale for this time horizon is described in the following.

In the national DMC criteria for treating CM with CGRP antibodies, the three marketed CGRP antibodies are compared based on a time period of 17 months, as treatment with the SC antibodies should be paused in month 17 (after 16 months of treatment) to see if patients still benefit from the treatment. Patients will continue treatment in month 18.

Since eptinezumab should be administered every three months, treatment cannot be paused after 17 months. In the model, eptinezumab is paused in month 18 for one month with start-up again in month 19. 21 months was chosen to have a time horizon that aligned the number of treatments of the monthly SC antibodies and the IV administration every three months for eptinezumab (the number of SC treatments should be three times the number of eptinezumab

treatments). An overview of the number of visits and number of treatments within the time horizon is presented in Table 34.

Table 34: Overview of the number of visits and number of treatments with the subcutaneous CGRP antibodies and eptinezumab in the base case. The P illustrates the pause

Months	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Subcutaneous CGRP antibodies																						
Visit	1			2			3						4						5			
Treatment	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	**P**	18	19	20	21
Eptinezumab																						
Visit	1			2			3			4			5			6				7		
Treatment	1			2			3			4			5			6			**P**	7		

Costs incurred after the first year in the analysis were discounted by 3.5% per year, in accordance with the Danish Ministry of Finance (46). The cost-minimisation model had a limited societal perspective, and all costs incurred by the Danish regions when treating CM patients with eptinezumab or the included comparators were included, as well as patient and transportation costs.

The model also includes the option to accounted for discontinuation through an annual discontinuation rate. When a discontinuation rate is applied, it is assumed that a patient who starts a new year of treatment will finish this year before discontinuing treatment e.g., if a discontinuation rate of 5% is applied, 100% of patients are treated in year 1, while (100*(1-0.05)) 95% is treated in year 2, (95*(1-0.05)) 90.25% of patients in year 3, and so forth. The practical implementation of this feature was done by multiplying the ratio of patients who are continuing treatment with the discounted contacts with healthcare services/discounted consumption of CGRP antibodies. Discontinuation was not applied in the base case based on the interviews with the two clinical experts who informed that very few patients discontinue CGRP antibody treatment.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

This section was not completed. A cost-minimisation methodology was applied which is based on an assumption of equal efficacy and safety between the included treatments. The similar efficacy of the included drugs was documented in the NMA presented under section 7.

8.2.1 Presentation of input data used in the model and how they were obtained

Not applicable, please see rationale above.

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

The model constructed for the current application was a cost-minimisation model with no implemented effect outcomes, and no patient characteristics have been applied in the model, as these would not have an impact on the results. The cost-minimisation model was constructed based on input from two Danish clinical experts and the national criteria for treating CM patients with CGRP antibodies set by the DMC; therefore, we expect the resource use implemented in the model to accurately reflect the actual resource use associated with treating CM patients with CGRP antibodies at Danish hospitals.

8.2.2.2 Intervention: eptinezumab

Eptinezumab in Danish clinical practice

According to one of the clinical experts, eptinezumab will in a clinical setting be administered every three months, i.e., not precisely as described in the SPC, which states that eptinezumab should be administered every 12 weeks (1). The reason was that every three months is most convenient for the patient. The IV administration would be managed by a nurse experienced in migraine.

Eptinezumab in DELIVER

In DELIVER, patients were dosed at baseline (day 0); hereafter, patients were dosed every 12 weeks. Eptinezumab 100 mg or eptinezumab 300 mg were administered via IV infusion (total volume of the infusion was 100 mL) over a period of 30 (up to 45) minutes. In the eptinezumab 100 mg arm, 292 out of 299 patients in the APTS analysis set (97.7%) received two infusions, and 289 patients (96.7%) fully completed the two infusions (22). In the eptinezumab 300 mg arm, the numbers were 289 patients (98.3%) and 286 patients (97.3%), respectively (22).

Eptinezumab in the health economic analysis

In the health economic model, all patients received 100 mg eptinezumab every three months in the base case to align with the way eptinezumab will be used in a Danish clinical setting, according to one of the experts. In a sensitivity analysis, a proportion of patients receive 300 mg eptinezumab (5%), as some patients might benefit from 300 mg instead of 100 mg. However, it is not defined who these patients are or how many patients that potentially could benefit from 300 mg; thus, we did not apply the 300 mg eptinezumab dose in the base case.

Table 35: Eptinezumab

Eptinezumab	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology	100 mg IV eptinezumab every 12th week and 300 mg eptinezumab IV every 12th week. 97.7% of patients in the 100 mg eptinezumab arm received two infusions and 96.7% fully completed the two infusions (22). In the eptinezumab 300 mg arm, the numbers were 98.3% and 97.3%, respectively (22).	All patients in the base case received 100 mg IV eptinezumab every three months. In a sensitivity analysis, 5% of patients received 300 mg IV eptinezumab every three months.	According to one of the clinical experts, eptinezumab would be administered every three months and not every 12 weeks.

Eptinezumab	Clinical documentation	Used in the model	Expected Danish clinical practice
Length of treatment	The DELIVER trial had a treatment period of 24 weeks. Hereafter, patients could be included in an extension period of 48 weeks (76 weeks in total).	The model had a time horizon of 21 months, which was chosen based on consultation of the Danish clinical experts and the DMC national criteria for CGRP antibody treatment.	According to the clinical experts, patients stay on CGRP antibody treatment for long. They expected that after five years, 60% to 70% of patients would still be on treatment.
Criteria for discontinuation	Patients in the trial discontinued treatment due to AEs or lack of effect.	Discontinuation was not included in the cost per patient analysis.	Treatment can be discontinued in the case of suboptimal effect and/or adverse events.
Eptinezumab position in Danish clinical practice	Eptinezumab is an alternative to the three marketed CGRP antibodies (erenumab, fremanezumab and galcanezumab); thus, eptinezumab should be included in the drug recommendation for patients with CM who have failed at least two different previous migraine treatments, along with the three marketed CGRP antibodies.		

8.2.2.3 Comparators: erenumab, fremanezumab and galcanezumab

Marketed CGRP antibodies in Danish clinical practice

Three other CGRP antibodies have currently been evaluated by the DMC. The DMC has published a drug recommendation and a set of national criteria for treating CM patients, who have failed at least two different previous migraine treatments with the CGRP antibodies. The drug recommendation states which of the CGRP antibodies should be the first choice when initiating patients on CGRP antibody treatment. The drug recommendation is based on price, as erenumab, fremanezumab and galcanezumab are clinically equivalent. Currently, erenumab is the first choice and should be used as the first choice for 85% of patients initiating treatment. Galcanezumab is currently the second choice and fremanezumab third choice. According to these national criteria, treatment with the SC CGRP antibodies should be paused after 17 months of treatment to see if patients still benefit from the treatment. If patients still benefit from the treatment, they continue until after month 35, where the treatment will once again be paused for one month (24). The clinical experts informed that they follow the DMC recommendation in clinical practice.

Marketed CGRP antibodies in the clinical documentation

Data on erenumab in the clinical documentation came from Study 295 and the subgroup analysis published in Ashina et al. 2018 (30) on patients with previous failure on migraine treatments. Ashina et al. 2018 (30) assessed the efficacy and safety of erenumab in patients who had failed ≥1 or ≥2 prior medication categories or never failed. We applied results from the ≥2 group.

Data on fremanezumab in the clinical documentation came from the FOCUS study that assessed the efficacy and tolerability of fremanezumab in patients with migraine who had previously not responded to two or four classes of migraine preventive medications.

Data on galcanezumab in the clinical documentation came from the CONQUER trial and a subgroup analysis from the REGAIN trial. The CONQUER trial was pre-specified and assessed the safety and efficacy of galcanezumab in patients with migraine who had not benefited from preventive medications from two to four categories. The subgroup analysis from the REGAIN trial was not specified, but assessed the efficacy in patients who have failed ≥2 and ≥1 prior migraine

preventives for efficacy and/or safety reasons and in those who never failed. Results from the studies on marketed CGRP antibodies have been presented in 7.

Marketed CGRP antibodies in the health economic analysis

No efficacy outcomes or safety outcomes were included in the model, because the model was a cost-minimisation model. The dose regimens of erenumab, fremanezumab and galcanezumab applied in the model came from the SPCs on the respective drugs and information from the clinical experts on how these drugs are used in Danish clinical practice. The applied dose regimens are presented in section 5.2.3, 5.2.4, 5.2.5, 8.5.1 and in Table 36.

Table 36: Erenumab

Comparator	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology	Patients in Study 295 received either 70 mg erenumab SC every four weeks for 12 weeks or 140 mg SC every four weeks for 12 weeks.	The dose regimen applied in the model was based on the SPC on erenumab: 70 mg or 140 mg SC every month.	According to the DMC drug recommendation, the erenumab dose applied in Danish clinical practice is 70 mg SC every month or 140 mg SC every month. We applied the 140 mg dosing regimen, as this is the most frequently applied regimen and the price is the same for a package of 70 mg and 140 mg vials.
Length of treatment	12 weeks	21 months due to the time horizon in the base case.	17 months until the first treatment pause. The clinical experts expect that patients stay on CGRP antibody treatment for a long time, and that after five years, 60% to 70% of patients would still be on treatment.
Erenumab position in the Danish clinical practice	NA	NA	Currently, erenumab is the first choice in the DMC drug recommendation for patients with CM who initiate CGRP antibody treatment.
Criteria for discontinuation	Patients discontinued in Study 295 due to AEs, lost to follow-up, non-compliance, ineligibility determined and patient request.	Discontinuation was not included in the cost per patient analysis.	Treatment can be discontinued in the case of suboptimal effect and/or adverse events.

Table 37: Fremanezumab

Comparator	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology	Quarterly fremanezumab treatment consisted of	The dose regimen applied in the model was based on the	According to the DMC drug recommendation, the

Comparator	Clinical documentation	Used in the model	Expected Danish clinical practice
	subcutaneously administered fremanezumab 675 mg. Monthly subcutaneously administered fremanezumab treatment consisted of fremanezumab 675 mg as a first dose, followed by monthly fremanezumab 225 mg.	SPC on fremanezumab and input from the clinical experts: 225 mg SC every month. The quarterly dose was not applied in the model, as the clinical experts informed that very few patients receive this dosing regimen in Danish clinical practice.	fremanezumab dose applied in Danish clinical practice is 225 mg SC every month or 675 mg every third month. According to the experts, only very few patients receive the quarterly dose. In practice, patients receive 225 mg fremanezumab subcutaneously every month.
Length of treatment	12 weeks (double-blinded period).	21 months due to the time horizon in the base case.	17 months until the first treatment pause. The clinical experts expect that patients stay on CGRP antibody treatment for a long time, and that after five years, 60% to 70% of patients would still be on treatment.
Fremanezumab position in the Danish clinical practice	NA	NA	Currently, fremanezumab is the third choice in the DMC drug recommendation for patients with CM who initiate treatment CGRP antibodies.
Criteria for discontinuation	Patients in the FOCUS study discontinued due to AEs, non-compliance or poor efficacy.	Discontinuation not included in the cost per patient analysis.	Treatment can be discontinued in the case of suboptimal effect and/or adverse events.

Table 38: Galcanezumab

Comparator	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology	Patients in the REGAIN study received galcanezumab 120 mg SC every month with a loading dose of 240 mg galcanezumab (administered as two 120 mg injections) or 240 mg SC galcanezumab monthly. Patients in the CONQUER study received galcanezumab 120 mg SC per month (with a 240 mg loading dose administered as two 120 mg injections).	The dose regimen applied in the model was based on the SPC on galcanezumab and input from the clinical experts: 120 mg galcanezumab SC once monthly, with a 240 mg loading dose as the initial dose.	According to the DMC drug recommendation, the galcanezumab dose applied in Danish clinical practice is an initial dose of 240 mg SC followed by 120 mg SC every month.

Comparator	Clinical documentation	Used in the model	Expected Danish clinical practice
Length of treatment	REGAIN: three-month double-blind, placebo-controlled treatment phase and a nine-month open-label extension. CONQUER: three months.	21 months due to the time horizon in the base case.	17 months until the first treatment pause. The clinical experts expect that patients stay on CGRP antibody treatment for a long time, and that after five years, 60% to 70% of patients would still be on treatment.
Galcanezumab position in the Danish clinical practice	NA	NA	Currently, galcanezumab is the second choice in the DMC drug recommendation for patients with CM who initiate treatment with CGRP antibodies.
Criteria for discontinuation	In the REGAIN study, patients discontinued for safety- and/or tolerability-related reasons. In the CONQUER study, patients discontinued due to AEs, protocol deviations, lack of efficacy and patient decision.	Discontinuation not included in the cost per patient analysis.	Treatment can be discontinued in the case of suboptimal effect and/or adverse events.

8.2.2.4 Relative efficacy outcomes

Not applicable, please see reason in section 8.2.

8.2.2.5 Adverse reaction outcomes

Not applicable. The clinical experts informed that they do not observe any AEs with CGRP antibody treatment that require hospital treatment. The clinical experts informed that the most frequently reported AE in patients on the current CGRP antibodies are constipation, which is reported with both erenumab and fremanezumab (they do not currently have much experience with galcanezumab). They do not observe any constipation events that require hospital treatment. Based on this, AEs were not included in the health economic analysis. AEs from the studies on the drugs included in the current application are presented in Appendix L.

8.3 Extrapolation of relative efficacy

Not applicable. The subheadings in this section in the template have been deleted.

8.4 Documentation of health-related quality of life (HRQoL)

No HRQoL was incorporated into the model, and we will not present any HRQoL data in this section. The subheadings and template tables related to this have been deleted. Comparative analyses on HRQoL are presented in 7.3 to demonstrate the equal efficacy of eptinezumab compared to marketed CGRP antibodies in terms of HRQoL.

8.5 Resource use and costs

To estimate the resource use associated with treating CM patients with eptinezumab and the three marketed CGRP antibodies, we applied the SPCs on the included drugs, the national criteria for treating with CGRP antibodies set out by the DMC and input from the consulted clinical experts. In the following, we describe each cost element and how each element was valued in the health economic analysis.

8.5.1 Drug costs

We included four drugs in the cost analysis: eptinezumab, erenumab, fremanezumab and galcanezumab. An overview of the information used to calculate the drug costs is provided in Table 39 and Table 40. The drug cost for all treatments is based on the PPP.

Eptinezumab

The dose regimen of eptinezumab applied in the base case was 100 mg IV every three months. Every three months was chosen instead of every 12 weeks as stated in the SPC, as one of the clinical experts informed that this is how eptinezumab will be used in practice. A sensitivity analysis was conducted in which a proportion of patients would receive 300 mg IV every three months (5%). Eptinezumab comes in packages with 1 vial of 100 mg eptinezumab per mL. The preliminary PPP of one package with 1 vial of 100 mg eptinezumab is DKK 9,789. Over a treatment course of 21 months, 700 mg of eptinezumab would be utilised by the patient, corresponding to 7 packages of 1 x 100 mg vials. The total pharmaceutical cost over 21 months of eptinezumab treatment is DKK 67,533.

Erenumab

The dose regimen of erenumab applied in the base case was 140 mg SC every month, as the clinical expert informed that patients receive erenumab every month and not every four weeks as stated in the SPC (23). Since the price for a package of 70 mg vials is the same as a package of 140 mg vials, we did not include a sensitivity analysis with a proportion of patients receiving 70 mg SC every month. Erenumab comes in packages of 1 x 140 mg vial or packages of 1 x 70 mg vial or 3 x 140 mg vials. The PPP of the package with 1 x 140 mg or 70 mg vial is DKK 3,098, and the PPP of the 3 x 140 mg package is DKK 9,294 (25 February 2022). Over a treatment course of 21 months, 2,940 mg of erenumab would be utilised by the patient, corresponding to 7 packages of 3 x 140 mg vials. The total pharmaceutical cost over 21 months of erenumab treatment is DKK 64,115.

Fremanezumab

The dose regimen of fremanezumab applied in the base case was 225 mg SC every month, as the clinical expert informed that only very few patients receive the quarterly fremanezumab dose. Fremanezumab comes in packages of 1 x 225 mg vial and 3 x 225 mg vials. The PPP of the package with 1 x 225 mg vial is DKK 3,550, and the PPP of the 3 x 225 mg vials is DKK 10,650 (25 February 2022). Over a treatment course of 21 months, 4,725 mg of fremanezumab would be utilised by the patient, corresponding to 7 packages of 3 x 225 mg vials. The total pharmaceutical cost over 21 months of fremanezumab treatment is DKK 73,470.

Galcanezumab

The dose regimen of galcanezumab applied in the base case was 120 mg SC galcanezumab every month, with a 240 mg SC loading dose (26). Galcanezumab comes in packages of 1 or 2 x 120 mg vials. The PPP of the package with 1 x 120 mg vial is DKK 3,247, and the PPP of the 2 x 120 mg vials is DKK 6,495 (25 February 2022). Over a treatment course of 21 months, 2,640 mg of galcanezumab would be utilised by the patient, corresponding to 22 packages of 1 x 120 mg. The total pharmaceutical cost over 21 months of galcanezumab treatment is DKK 70,446.

Table 39: Information used to estimate the drug cost of eptinezumab and comparators. Source: www.medicinpriser.dk (25 February 2022).

	Package size	Strength (mg/unit)	Price per pack, PPP (DKK)	Price per unit (DKK)
Eptinezumab	1 vial	100 mg	9,789	9,789
Erenumab	1 vial	140 mg	3,098	3,098
Fremanezumab	1 vial	225 mg	3,550	3,550
Galcanezumab	1 vial	120 mg	3,247	3,247

Table 40: The total dose (mg) and the total pharmaceutical cost (DKK) over 21 months used in the model

	Total dose (mg)	Total cost (DKK)
Eptinezumab	700	67,533
Erenumab	2,940	64,115
Fremanezumab	4,725	73,470
Galcanezumab	2,640	70,446

8.5.2 Hospital costs

Two options for estimating the hospital costs associated with treating patients with CGRP antibodies are available in the model: 1) an option to apply a micro-costing approach and 2) an option to apply DRG-tariffs. The micro-costing approach was applied in the base case as this approach improves the precision in the cost estimation and to the highest degree reflects the actual resource use associated with treating patients with eptinezumab and the three marketed CGRP antibodies. To estimate the resource use at the hospital associated with treating patients with eptinezumab, we consulted the clinical experts. To estimate the resource use at the hospital associated with treating patients with erenumab, fremanezumab and galcanezumab, the national criteria for treating CM patients with the CGRP antibodies set out by the DMC were applied.

The time horizon of the health economic model was 21 months. An overview of the number of visits and number of treatments within the time horizon for the three marketed CGRP antibodies and eptinezumab was presented in Table 34. As seen in the table, patients have visits every three months until month 6; hereafter, there is a visit every six months. After month 17, patients on the marketed CGRP antibodies pause their treatment for one month to check if they still benefit from the treatment. At month 18, patients re-start treatment. Up until month 21, patients on the SC antibodies will have a total of five visits to the hospital.

The clinical experts informed that they expect eptinezumab to follow the same criteria as the marketed CGRP antibodies. Since eptinezumab is administered IV, patients will need to go to the hospital every three months. Patients receiving eptinezumab cannot pause their treatment after 17 months, as month 17 is in the middle of a treatment course with eptinezumab. Treatment can be paused at month 18 (after 15 months of treatment) with start-up again in month 19. Up until month 21, patients on eptinezumab will have a total of seven visits.

In the national criteria for treating CM patients with the CGRP antibodies prepared by the DMC, patients visit the hospital one month prior to initiating treatment (screenings visit). We assumed that all CGRP antibodies will have this visit; thus, it was not included in the estimation of hospital resource use because this cost would be the same for all drugs.

Micro-costing approach

Lundbeck consulted the clinical experts on which healthcare personnel (HCP) are involved in the different visits in the DMC national criteria for treating with CGRP antibodies, and the visits associated with eptinezumab treatment. The clinical experts informed that it is primarily nurses who manage migraine patients on CGRP antibody treatment. Physicians are involved to a limited degree, but one of the experts informed that they aim at getting the physicians more involved at their centre. Based on this, it was assumed that the physician would be involved at the first visit and at the visit after the patient has paused treatment and re-start treatment. No other personnel is involved in the treatment.

The clinical experts informed that a control visit takes approximately 30 minutes and that the treatment is primarily managed by nurses. At the first visit, nurses train patients on erenumab, fremanezumab and galcanezumab to self-administer subcutaneously. One of the clinical experts informed that this takes only a couple of minutes; therefore, we did not include additional nurse time associated with SC training but assumed that this was included in the 30 minutes. At the first visit for patients receiving eptinezumab, it was assumed that patients would first have a short consultation with a physician (15 minutes) and then receive the IV treatment administered by a nurse.

An IV administration of eptinezumab takes 30 minutes (1). For visits to the hospital where patients on eptinezumab receive IV treatment, we applied 45 minutes of nurse time spent on preparing the patient for the administration and talking to the patient during the IV administration. At the control visits where patients on eptinezumab also receive IV treatment, we also included 45 minutes of nurse time spent on preparing the patient for the IV administration and talking to the patient during the administration. The 45 minutes of nurse time for these visits were applied as the clinical experts informed that they expected the nurse to have the consultation with the patient and check their headache diary while the patient receives the IV administration.

The clinical experts also informed that nurses spend some time on phone consultations with patients on the SC CGRP antibodies to address questions related to the SC treatment or any concerns patients might have. One clinical expert informed that they estimate 4 x 15 minutes of phone consultation with each patient for a nurse. Based on this, we included 4 x 15 minutes of nurse time spent on talking to patients on the phone. This resource use is not included for eptinezumab, as patients receiving eptinezumab do not manage treatment on their own. In addition, we assumed no post-infusion observation time, as one of the clinical experts informed that no anaphylactic reactions are known with the CGRP antibodies; therefore, he expects not to recommend that patients are observed after the infusion.

An overview of the hospital time applied in the model is presented in Table 41 for the SC CGRP antibodies and in Table 42 for eptinezumab. The total amount of time spent by nurses and physicians and the total HCP cost over a time horizon of 21 months are presented in Table 43.

The unit cost of one hour of nurse time and physician time came from the DMC document with information on current unit costs for different healthcare personnel (47). The unit costs in the document were from 2020; thus, we adjusted for inflation to a 2022 level.

Table 41: Resource use at the hospital for the subcutaneous CGRP antibodies applied in micro-costing approach

Resource	Minutes	Unit cost per hour (DKK)	Cost per visit (DKK)	Source
First visit				
Nurse time	30 minutes	447	223.5	Nurse time was informed by the clinical experts. Physician time was an assumption based on a statement from one of the clinical experts who stated that they aim at getting the physicians more involved in the CGRP antibody treatment. The applied unit cost for physician time was based on the unit cost per hour for a consultant.
Physician time	15 minutes	1,055	263.75	
Visit after treatment pause (per visit)				
Nurse time	30 minutes	447	223.5	Nurse time was informed by the clinical experts. Physician time was an assumption based on a statement from one of the clinical experts who stated that they aim at getting the physicians more involved in the CGRP antibody treatment.
Physician time	15 minutes	1,055	263.75	
Control visit after first visit (per visit)				
Nurse time	30 minutes	447	223.5	Nurse time was informed by the clinical experts. The clinical experts informed that CGRP antibody treatment is primarily managed by nurses.
Physician time	0 minutes	1,055	0	
Phone consultation (per consultation)				
Nurse time	15 minutes	447	111.75	The clinical experts informed that the nurses spend some time talking to patients on the SC drugs on the phone. One of the experts estimated 15 minutes per call.
Physician time	0 minutes	1,055	0	

Table 42: Resource use at the hospital for eptinezumab applied in micro-costing approach

Resource	Minutes	Unit cost per hour (DKK)	Cost per visit (DKK)	Source
First visit				
Nurse time	45 minutes	447	335.25	Nurse time was informed by the clinical experts. 15 minutes was added to the 30 minutes to account for the time spent by nurses preparing the patient for the administration. Physician time was an assumption based on a statement from one of the clinical experts who stated that they aim at getting the physicians more involved in the CGRP antibody treatment. The applied unit cost for physician time was based on the unit cost per hour for a consultant.
Physician time	15 minutes	1,055	263.75	
Visit after treatment pause (per visit)				
Nurse time	45 minutes	447	335.25	Nurse time was informed by the clinical experts. 15 minutes was added to the 30 minutes to account for the time spent by nurses preparing the patient for the administration. Physician time was an assumption based on a statement from one of the clinical experts who stated that they aim at getting the physicians more involved in the CGRP antibody treatment.
Physician time	15 minutes	1,055	263.75	
Control visit after first visit (per visit)				
Nurse time	45 minutes	447	335.25	Nurse time was informed by the clinical experts. 15 minutes was added to the 30 minutes to account for the time spent by nurses preparing the patient for the administration. The clinical experts informed that CGRP antibody treatment is primarily managed by nurses.
Physician time	0 minutes	1,055	0	
IV-administration visit (per visit)				
Nurse time	45 minutes	447	335.25	Infusion time was based on infusion time stated in the SPC on eptinezumab (1). The clinical experts informed that CGRP antibody treatment is primarily managed by nurses, which IV administration will also be. 15 minutes was added to the 30 minutes infusion time to account for the time spent by nurses preparing the patient for the administration.
Physician time	0 minutes	1,055	0	

Table 43: Total nurse and physician time associated with treatment with each CGRP antibody over a time horizon of 21 months

	Eptinezumab	Erenumab	Fremanezumab	Galcanezumab
Nurse time, hospital visits	315 minutes	150 minutes	150 minutes	150 minutes
Nurse time, telephone consultations	0 minutes	90 minutes	90 minutes	90 minutes
Physician time	30 minutes	30 minutes	30 minutes	30 minutes
Total HCP time	**345 minutes**	**270 minutes**	**270 minutes**	**270 minutes**
Total HCP cost (DKK)	**2,831**	**2,280**	**2,280**	**2,280**

Lundbeck also consulted the clinical experts on the usage of utensils associated with CGRP antibody treatment. They informed that the hospitals already have drip stands and refrigerators to store the drugs, and that they use swabs, needles and paper bags. Since the costs of these utensils are minimal compared to other costs included in the analysis, we did not include them in the analysis. Costs associated with using hospital rooms (treatment room and conversation room) were included. We assumed that all visits, except the IV administration visit, take place in the conversation room. The IV administration visit takes place in the treatment room. Table 44 provides an overview of the total minutes spent in a treatment room and a conversation room over a time horizon of 21 months for each CGRP antibody.

Table 44: Total use of other costs included in the micro-costing approach over a time horizon of 21 months

	Eptinezumab	Erenumab	Fremanezumab	Galcanezumab
Treatment room	315 minutes	0 minutes	0 minutes	0 minutes
Conversation room	30 minutes	150 minutes	150 minutes	150 minutes
Total room time	**345 minutes**	**150 minutes**	**150 minutes**	**150 minutes**

Note: the 30 minutes for eptinezumab in a conversation room were included, as it was assumed that the physician time included in the first visit and the visit after the treatment pause is spent in the conversation room. No additional time in a conversation room for physicians was assumed for the other CGRP antibodies, as the control visits were assumed to take place in the conversation room and that the physician and nurse were present at the same time.

The unit costs of one hour in a treatment room and one hour in a conversation room came from Sørensen et al. 2011 (48) and were adjusted for inflation to a 2022 level. Sørensen et al. 2011 (48) reported a cost per hour of a conversation room of DKK 14-18 and a cost per hour of a treatment room of DKK 42-53. After adjusting for inflation, a unit cost per hour of DKK 40 for a conversation room was applied and a unit cost per hour of DKK 73 was applied for a treatment room.

Table 45: Total costs of rooms included in the micro-costing approach over a time horizon of 21 months

	Eptinezumab	Erenumab	Fremanezumab	Galcanezumab
Treatment room cost (DKK)	378	0	0	0
Conversation room cost (DKK)	20	99	99	99

8.5.3 Patient and transportation costs

In accordance with the DMC guideline, we included transportation costs and costs associated with patient time spent on transportation to and from the hospital and treatment-related activities (49). Based on the DMC guideline, we applied a cost of DKK 181 per patient hour. We assumed a distance of 20 km to and from the hospital (40 km in total per visit) and a unit cost per kilometer of DKK 3.51, in accordance with DMC guidelines (47). Thus, a transportation cost of DKK 140 was applied for each hospital visit.

Lundbeck assumed that patients spend 30 minutes on transportation to and from the hospital (60 minutes in total). As mentioned, the clinical experts informed that each visit at the hospital takes 30 minutes. Patients on erenumab, fremanezumab and galcanezumab have a total of five hospital visits over a time horizon of 21 months. Patients on eptinezumab will have seven hospital visits over a time horizon of 21 months. An additional 15 minutes spent on physician consultation at the first visit was assumed for eptinezumab and 45 minutes was applied for each visit instead of 30 minutes. Based on the mentioned estimate of time spent on phone consultations, 4 x 15 minutes of patient time spent on phone consultations were included for the SC drugs. An overview of the patient time spend for each CGRP antibody over a time horizon of 21 months is presented in Table 46, and the total patient cost and total transportation cost over a time horizon of 21 months are presented in Table 47.

Table 46: Total patient time spent over a time horizon of 21 months

Resource	Eptinezumab	Erenumab	Fremanezumab	Galcanezumab
Total patient time over 21 months spent on treatment-related activities and transportation	735 minutes	540 minutes	540 minutes	540 minutes

Table 47: Total patient cost and transportation cost associated with treatment with each CGRP antibody

	Eptinezumab	Erenumab	Fremanezumab	Galcanezumab
Total patient cost (DKK)	2,185	1,606	1,606	1,606
Total transportation cost (DKK)	969	693	693	693

8.5.4 Adverse event costs

Constipation is the most frequently reported AE with the marketed CGRP antibodies. However, no AE costs were included in the health economic analysis, since the clinical experts informed that constipation does not require

hospital treatment and also that no other AEs associated with CGRP antibody treatment require treatment at the hospital. Moreover, the proportions of patients with at least one AE or at least one SAE in section 7.4 are similar between all CGRP antibodies. The AE tables from the studies on each drug are presented in the following.

Table 48: Summary of treatment-emergent AEs in APTS population from DELIVER. Source: CSR (data on file).

AE, n (%)	Placebo	Eptinezumab	
	(n=298)	100 mg (n=299)	300 mg (n=294)
Patients with TEAE	[redacted]		
Patients with SAEs			
Patients with TEAEs leading to IMP			
Patients with TEAEs leading to withdrawal			
Deaths			
Total number of TEAEs			
Total number of SAEs			

Table 49: Treatment-emergent AEs that occurred in ≥2% of galcanezumab-treated patients treated with either dose of galcanezumab and greater than placebo in REGAIN. Source: Detke et al. 2018

AE, n (%)	Placebo	Galcanezumab	
	(n=558)	120 mg (n=273)	240 mg (n=282)
Patients with ≥1 events	279 (50)	159 (58)	160 (57)
Injection-site pain	24 (4)	17 (6)	20 (7)
Nasopharyngitis	26 (5)	17 (6)	9 (3)
Upper respiratory tract infection	13 (2)	9 (3)	9 (3)
Injection-site reaction	10 (2)	8 (3)	15 (5)
Injection-site erythema	5 (1)	4 (1)	13 (5)
Fatigue	10 (2)	6 (2)	6 (2)
Back pain	14 (3)	9 (3)	2 (1)
Urinary tract infection	7 (1)	6 (2)	4 (1)
Abdominal pain	9 (2)	6 (2)	4 (1)
Diarrhea	9 (2)	3 (1)	6 (2)
Injection-site pruritus	1 (0)	0 (0)	7 (2)
Migraine	5 (1)	5 (2)	4 (1)
Influenza-like illness	3 (1)	5 (2)	4 (1)
Neck pain	8 (1)	7 (3)	0 (0)
Oropharyngeal pain	3 (1)	2 (1)	5 (2)
Sinusitis	5 (1)	4 (1)	8 (3)
Arthralgia	5 (1)	1 (0)	5 (2)
Pyrexia	2 (0)	5 (2)	1 (0)

Table 50: Summary of AEs in NCT02066415 with ≥2 failed prior medications. Source: Ashina et al. 2018.

AE, n (%)	Placebo	Erenumab	
	(n=141)	70 mg (n=92)	140 mg (n=92)
Any AE	62 (44)	39 (42.4)	53 (57.6)
Grade ≥2	35 (24.8)	17 (18.5)	26 (28.3)
Grade ≥3	7 (5)	5 (5.4)	3 (3.3)
Any SAE	4 (2.8)	3 (3.3)	1 (1.1)
AE leading to treatment discontinuation	1 (0.7)	0 (0)	0 (0)

Table 51: Summary of AEs in the total population in CONQUER. Source: Mulleners et al. 2020

AE, n (%)	Placebo (n=230)	Galcanezumab 120 mg (n=232)
Deaths	0 (0)	0 (0)
Patients with ≥1 serious adverse event	2 (1)	2 (1)
Patients with adverse event leading to discontinuation	0 (0)	1 (<1)
Patients with ≥1 treatment-emergent adverse event	122 (53)	119 (51)
Patients with ≥1 treatment-emergent adverse event related to treatment	34 (15)	37 (16)
Anticipated treatment-emergent adverse events		
Any injection site related adverse event	23 (10)	16 (7)
Erythema	6 (3)	8 (3)
Pain	13 (6)	5 (2)
Pruritus	0 (0)	0 (0)
Odema	0 (0)	2 (1)
Discolouration	1 (<1)	1 (<1)
Hypersensitivity	0 (0)	1 (<1)
Induration	4 (2)	1 (<1)
Paraesthesia	3 (1)	1 (<1)
Swelling	0 (0)	1 (<1)
Bruising	4 (2)	0 (0)
Haematoma	1 (<1)	0 (0)
Reaction	6 (3)	0 (0)
Constipation	5 (2)	5 (2)
Vertigo	4 (2)	1 (<1)
Pruritus	1 (<1)	1 (<1)
Urticaria	1 (<1)	0 (0)

All other treatment-emergent AE ≥1 (5%) in any group		
Nasopharyngitis	21 (9)	16 (7)
Influenza	7 (3)	11 (5)
Upper respiratory tract infection	5 (2)	5 (2)
Back pain	6 (3)	4 (2)
Bronchitis	2 (1)	4 (2)
Fatigue	1 (<1)	4 (2)
Gastroenteritis	3 (1)	4 (2)
Nausea	5 (2)	4 (2)
Oropharyngeal pain	2 (1)	4 (2)
Sinusitis	5 (2)	4 (2)
Urinary tract infection	4 (2)	2 (1)
Migraine	5 (2)	1 (<1)
Insomnia	5 (2)	0 (0)

Table 52: Summary of AEs in the total population in FOCUS. Source: Ferrari et al. 2019

AE, n (%)	Placebo (n=277)	Quarterly fremanezumab (n=276)	Monthly fremanezumab (n=285)
≥1 AE	134 (48)	151 (55)	**129 (45)**
≥ SAE	4 (1)	2 (<1)	**4 (1)**
≥ treatment -related adverse event	55 (20)	**57 (21)**	**55 (19)**
Adverse events leading to discontinuation	3 (1)	**1 (<1)**	**4 (1)**
Adverse events			
Injection-site erythema	15 (5)	19 (7)	**16 (6)**
Injection-site induration	12 (4)	12 (4)	**13 (5)**
Injection-site pain	8 (3)	11 (4)	**9 (3)**
Nasopharyngitis	11 (4)	13 (5)	**7 (2)**
Fatigue	3 (1)	9 (3)	**9 (3)**
Insomnia	2 (<1)	6 (2)	**7 (2)**
Upper respiratory tract infection	3 (1)	**4 (1)**	**9 (3)**
Diarrhoea	3 (1)	7 (3)	**2 (<1)**
Dizziness	3 (1)	5 (2)	**4 (1)**
Constipation	2 (<1)	7 (3)	**1 (<1)**
Influenza	2 (<1)	2 (<1)	**6 (2)**
Injection-site pruritus	3 (1)	3 (1)	**5 (2)**
Back pain	5 (2)	5 (2)	**2 (<1)**
Injection-site bruising	2 (<1)	2 (<1)	**5 (2)**
Injection-site paraesthesia	3 (1)	4 (1)	**3 (1)**
Increased weight	1 (<1)	4 (1)	**3 (1)**
Upper abdominal pain	0	4 (1)	**2 (<1)**
Gastroenteritis	7 (3)	3 (1)	**3 (1)**

Injection-site rash	2 (<1)	3 (1)	**3 (1)**
Nausea	6 (2)	4 (1)	**2 (<1)**
Urinary tract infection	5 (2)	3 (1)	**3 (1)**
Anxiety	0	3 (1)	**2 (<1)**
INR increased	2 (<1)	3 (1)	**2 (<1)**
Migraine	9 (3)	2 (<1)	**3 (1)**
Neck pain	0	2 (<1)	**3 (1)**
Pain in extremity	3 (1)	2 (<1)	**3 (1)**
Alopecia	2 (<1)	2 (<1)	**2 (<1)**
Arthralgia	3 (1)	2 (<1)	**2 (<1)**
Asthenia	3 (1)	1 (<1)	**3 (1)**
Hypertension	2 (<1)	3 (1)	**1 (<1)**
Injection-site warmth	0	1 (<1)	**3 (1)**
Rash	2 (<1)	1 (<1)	**3 (1)**

8.6 Results

8.6.1 Base case overview

Table 53: Base case overview

Intervention	Eptinezumab, sold under the brand name Vyepti®
Comparators	Erenumab, fremanezumab and galcanezumab
Type of model	Cost-minimisation model
Patient population	CM patients who have failed at least two different previous preventive migraine treatments
Time horizon	21 months
Treatment line	Third line after failure with at least two previous migraine treatments
Measurement and valuation of health effects	Not included

Included costs	Drug costs Hospital costs Patient costs Transportation costs
Dosage of included pharmaceuticals	Eptinezumab: 100 mg IV every three months Erenumab: 70/140 mg SC every month Fremanezumab: 225 mg SC every month Galcanezumab: loading dose of 240 mg SC and then 120 mg SC every month
Average time on treatment	In the model, a treatment duration of 21 months was applied in the base case, in accordance with the DMC national criteria for CGRP antibody treatment and when eptinezumab treatment can be paused.
Other important assumptions	**Assumptions in the micro-costing approach** - At control visits that fall together with an IV administration of eptinezumab, 45 minutes of nurse time was assumed as for administration visits as the nurse can talk to the patient during the IV administration. - At the first visit, 45 minutes of HCP time will be used for patients on eptinezumab: 15 minutes of physician time and 30 minutes of nurse time. - Phone consultations were included for the SC CGRP antibodies. No phone consultations were included for eptinezumab. - No utensils were included. - Discontinuation rate: 0%.

8.6.2 Base case results

An incremental cost of eptinezumab of DKK 5,123 was estimated in the cost per patient analysis of eptinezumab compared to erenumab. The incremental cost is over a time horizon of 21 months. The main cost driver is drug costs, and it is important to note that the incremental cost is estimated based on PPPs.

Table 54: Base case results of eptinezumab compared to erenumab over a time horizon of 21 months, DKK

Per patient	Eptinezumab	Erenumab	Difference
Total costs	**73,915**	**68,792**	**5,123**
Drug costs	67,533	64,115	3,418
Hospital costs	3,229	2,379	850

Per patient	Eptinezumab	Erenumab	Difference
Patient and transportation costs	3,154	2,299	855
Incremental cost	5,123		
ICER (per QALY)	Not applicable		

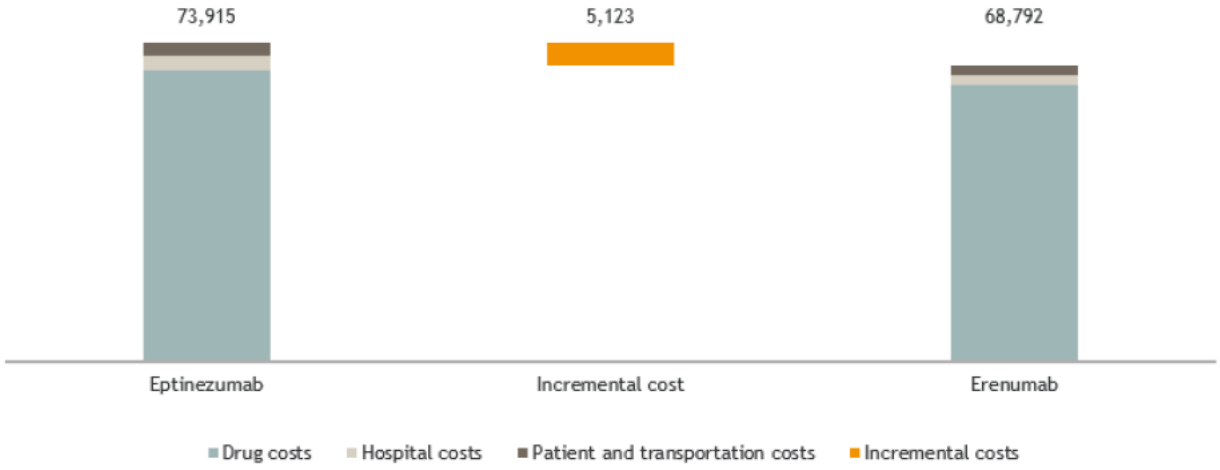

Figure 19: Graph illustrating the result of the cost per patient analysis of eptinezumab and erenumab over a time horizon of 21 months

An incremental cost of eptinezumab of DKK -4,232 was estimated in the cost per patient analysis of eptinezumab compared to fremanezumab. The incremental cost is over a time horizon of 21 months. The main cost driver is drug costs, and it is important to note that the incremental cost is estimated based on PPPs.

Table 55: Base case results of eptinezumab compared to fremanezumab over a time horizon of 21 months, DKK

Per patient	Eptinezumab	Fremanezumab	Difference
Total costs	**73,915**	**78,147**	**-4,232**
Drug costs	67,533	73,470	-5,937
Hospital costs	3,229	2,379	850
Patient and transportation costs	3,154	2,299	855
Incremental cost	-4,232		
ICER (per QALY)	Not applicable		

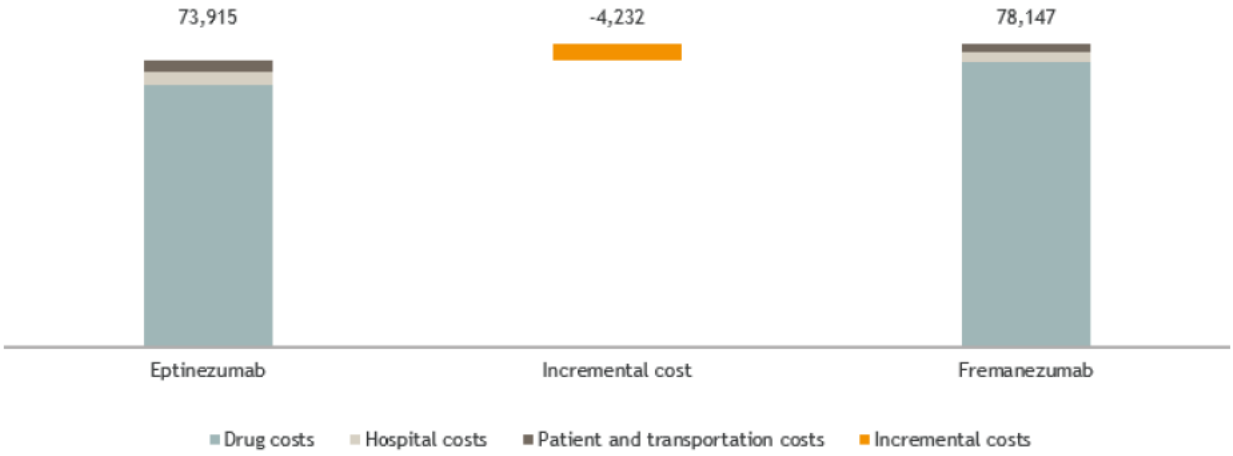

Figure 20: Graph illustrating the result of the cost per patient analysis of eptinezumab and fremanezumab over a time horizon of 21 months

An incremental cost of eptinezumab of DKK -1,208 was estimated in the cost per patient analysis of eptinezumab compared to galcanezumab. The incremental cost is over a time horizon of 21 months. The main cost driver is drug costs, and it is important to note that the incremental cost is estimated based on PPPs.

Table 56: Base case results of eptinezumab compared to galcanezumab over a time horizon of 21 months, DKK

Per patient	Eptinezumab	Galcanezumab	Difference
Total costs	**73,915**	**75,123**	**-1,208**
Drug costs	67,533	70,446	-2,913
Hospital costs	3,229	2,379	850

Per patient	Eptinezumab	Galcanezumab	Difference
Patient and transportation costs	3,154	2,299	855
Incremental cost	-1,208		
ICER (per QALY)	Not applicable		

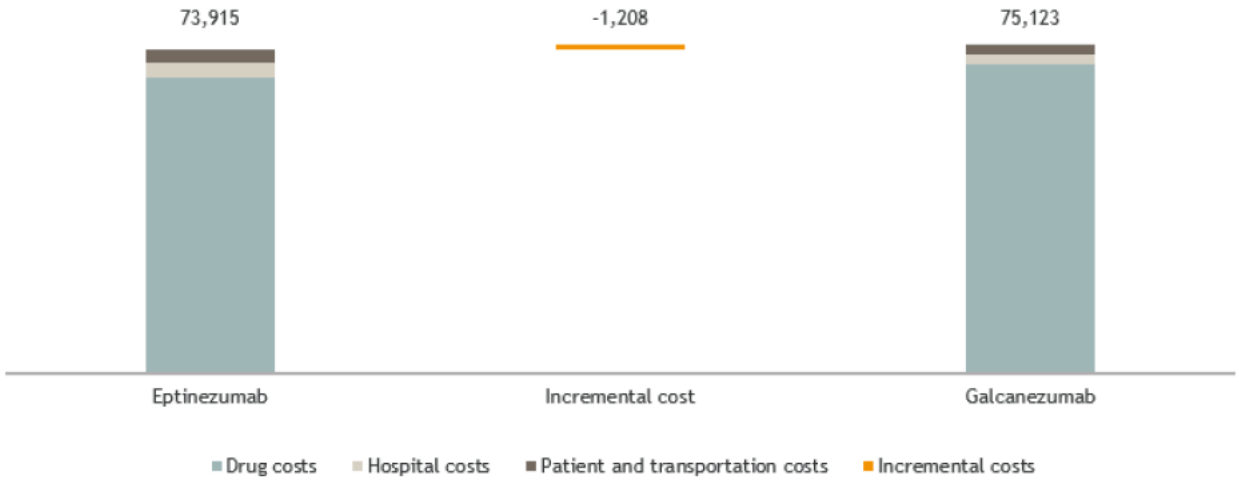

Figure 21: Graph illustrating the result of the cost per patient analysis of eptinezumab and galcanezumab over a time horizon of 21 months

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

The health economic analysis presented in the current application is a cost-minimisation analysis; thus, the only parameters in the model were costs. Various deterministic one-way sensitivity analyses were conducted in which the resource use included in the cost-minimisation analysis was changed. Moreover, a scenario analysis was conducted where the time horizon was changed to 10 years to assess the impact of a longer time horizon, as the clinical experts informed that patients stay on CGRP antibody treatment for a long time. In this sensitivity analysis, an annual discontinuation rate of 25% was assumed. The clinical experts were consulted on how long patients typically remain on treatment with CGRP antibodies. Treatment with CGRP antibodies was initiated in Denmark in 2019, i.e., no patient has yet received treatment with a CGRP antibody for 10 years. The experts stated that around 70-80% continue treatment after the first three months (i.e., achieve a 30% reduction in their MMDs), and that approximately 60-70% of those who continue after three months still receive treatment after five years. Since the discontinuation rate is an uncertain estimate in the model, it is flexible for the user to adjust this rate according to estimates.
The conducted one-way sensitivity analyses and the changes applied are presented in Table 57. We present the incremental cost in each sensitivity analysis and the incremental cost from the base case.

Table 57: One-way sensitivity analyses conducted

	Change	Reason
Time horizon of 10 years	Changing the time horizon from 21 months to 10 years.	The clinical experts informed Lundbeck that patients stay on CGRP antibody treatment for a long time, and the impact of expanding the time horizon was assessed (assuming a dropout rate of 25% each year to account for the fact that patients discontinue treatment each year). The discontinuation rate was based on input from the clinical experts and is flexible for the user to change.
Longer IV administration visits in the eptinezumab arm	An IV administration visit takes 1 hour instead of 45 minutes.	A sensitivity analysis with a longer hospital time for IV administrations was conducted to assess the impact of prolonging these visits.
Exclusion of phone consultations associated with subcutaneous CGRP antibodies	Excluding the 4 x 15-minute phone consultations assumed for the SC CGRP antibodies.	Since these consultations were only included for the SC antibodies, the impact of removing them from the analysis was assessed.
Small proportion receives 300 mg eptinezumab	5% of patients receive 300 mg instead of 100 mg in the eptinezumab arm.	According to the SPC on eptinezumab, some patients might benefit from 300 mg (1). It is not established who these patients are, but to accommodate that this is stated in the SPC, a sensitivity analysis was conducted where a small percentage of patients on eptinezumab received 300 mg instead of 100 mg.

Table 58: One-way sensitivity analyses results (incremental costs, DKK)

	Erenumab	Fremanezumab	Galcanezumab
Base case	**5,123**	**-4,232**	**-1,208**
Time horizon of 10 years (with an annual discontinuation rate of 25%)	14,097	-3,953	4,900
Longer IV administration visits in the eptinezumab arm	6,332	-3,023	1
Exclusion of phone consultations associated with subcutaneous CGRP antibodies	6,049	-3,305	-282
Small proportion receives 300 mg eptinezumab	11,876	2,522	5,546

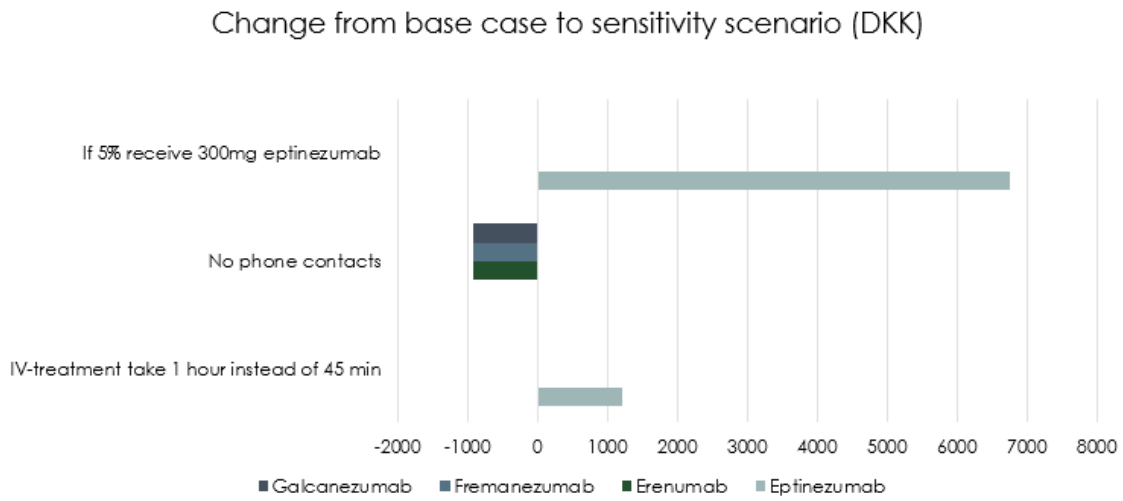

Figure 22: Tornado diagram of one-way sensitivity analyses

As seen in Table 58, the sensitivity analyses with the larges impacts on the result of the base case were increasing the time horizon to 10 years and if a small proportion of patients receives 300 mg. The sensitivity analysis where the time horizon is increased to 10 years was conducted because it is uncertain how long patients stay on CGRP antibody treatment. However, the clinical experts informed that there is no difference between the marketed GCRP antibodies in terms of how long patients stay on treatment. They expect the same for eptinezumab. The sensitivity analysis where 5% receive 300 mg instead of 100 mg eptinezumab was conducted as some patients might benefit from 300 mg. However, it is not established who these patients are, and it is uncertain how many patients could benefit from 300 mg instead of 100 mg.

8.7.2 Probabilistic sensitivity analyses

No probabilistic sensitivity analysis (PSA) was conducted in the current application because the health economic analysis consisted of a cost-minimisation analysis and costs were the only parameter in the analysis.

9. Budget impact analysis

The purpose of the budget impact analysis is to estimate the budgetary impact of recommending eptinezumab as the standard treatment of CM in patients who have failed at least two different previous preventive migraine treatments. The budget impact is estimated per year in the first five years after the recommendation of eptinezumab. The budget impact analysis compares the expenditures in a scenario where eptinezumab is recommended as a possible standard treatment and a scenario where eptinezumab is not recommended as a possible standard treatment. The total budget impact per year is the difference between the two scenarios. The expenditure per patient is equivalent to the cost per patient without patient and transportation costs.

9.1.1 Number of patients and expected market share

The number of patients was based on the number of new patients estimated by the migraine expert committee in the previous CGRP antibody evaluation by the DMC (galcanezumab) (21). In the evaluation of galcanezumab, the expert committee estimated that 1,200 new patients would be candidates for CGRP antibody treatment each year. The clinical experts were asked if they agreed with the 1,200 new patients each year and they found the estimate reasonable.

Currently, erenumab is the first choice in the DMC drug recommendation and galcanezumab is the second choice. Erenumab should be used by 85% of new patients; 15% can start treatment with the other drugs. Based on this, we assumed that 85% of the new patients will receive erenumab, and the remaining 15% will be distributed equally between eptinezumab, fremanezumab and galcanezumab. In the scenario where eptinezumab is not introduced, no patients will receive eptinezumab, erenumab will get 85% of patients, and the remaining 15% of patients will be shared by fremanezumab and galcanezumab.

Table 59: Number of new patients expected to be treated over the next five-year period – if eptinezumab is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Eptinezumab	60	60	60	60	60
Erenumab	1,020	1,020	1,020	1,020	1,020
Fremanezumab	60	60	60	60	60
Galcanezumab	60	60	60	60	60
Total number of new patients	1,200	1,200	1,200	1,200	1,200

Table 60: Number of new patients expected to be treated over the next five-year period – if eptinezumab is NOT recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Eptinezumab	0	0	0	0	0

	Year 1	Year 2	Year 3	Year 4	Year 5
Erenumab	1,020	1,020	1,020	1,020	1,020
Fremanezumab	90	90	90	90	90
Galcanezumab	90	90	90	90	90

9.1.2 Expenditure per patient

Table 61: Costs per patient per year – if eptinezumab is recommended, DKK

	Year 1	Year 2	Year 3	Year 4	Year 5
Eptinezumab	40,992	40,992	40,718	40,992	30,812
Erenumab	38,506	35,276	34,900	38,262	35,276
Fremanezumab	43,930	40,248	39,872	43,686	40,248
Galcanezumab	43,541	36,915	36,539	40,050	36,915

Table 62: Costs per patient per year - if eptinezumab is NOT recommended, DKK

	Year 1	Year 2	Year 3	Year 4	Year 5
Eptinezumab	0	0	0	0	0
Erenumab	38,506	35,276	34,900	38,262	35,276
Fremanezumab	43,930	40,248	39,872	43,686	40,248
Galcanezumab	43,541	36,915	36,539	40,050	36,915

9.2 Budget impact

An overview of the result of the budget impact analysis is presented in Table 63. The budget impact of recommending eptinezumab for use at the Danish hospitals is DKK -0.14 million in year 5. The result shows that at a PPP level, eptinezumab offers a saving in both year 1 and year 5 in the budget impact analysis. Over all five years, the budget impact is DKK -0.33 million. The main driver is drug costs, and it is important to note that the costs presented in Table 63 are based on PPPs.

Table 63: Expected budget impact of recommending eptinezumab for chronic migraine patients who have failed at least two different previous migraine treatments (million, DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Eptinezumab is recommended	**46.98**	**79.29**	**103.26**	**122.89**	**136.32**
Of which: Drug costs	45.36	76.55	99.95	119.00	131.98
Of which: hospital costs	1.63	2.73	3.31	3.88	4.34
Eptinezumab is NOT recommended	**47.15**	**79.34**	**103.23**	**122.88**	**136.46**
Of which: Drug costs	45.55	76.67	100.01	119.10	132.23
Of which: Hospital costs	1.60	2.67	3.23	3.78	4.23
Budget impact of the recommendation	**-0.16**	**-0.06**	**0.03**	**0.01**	**-0.14**

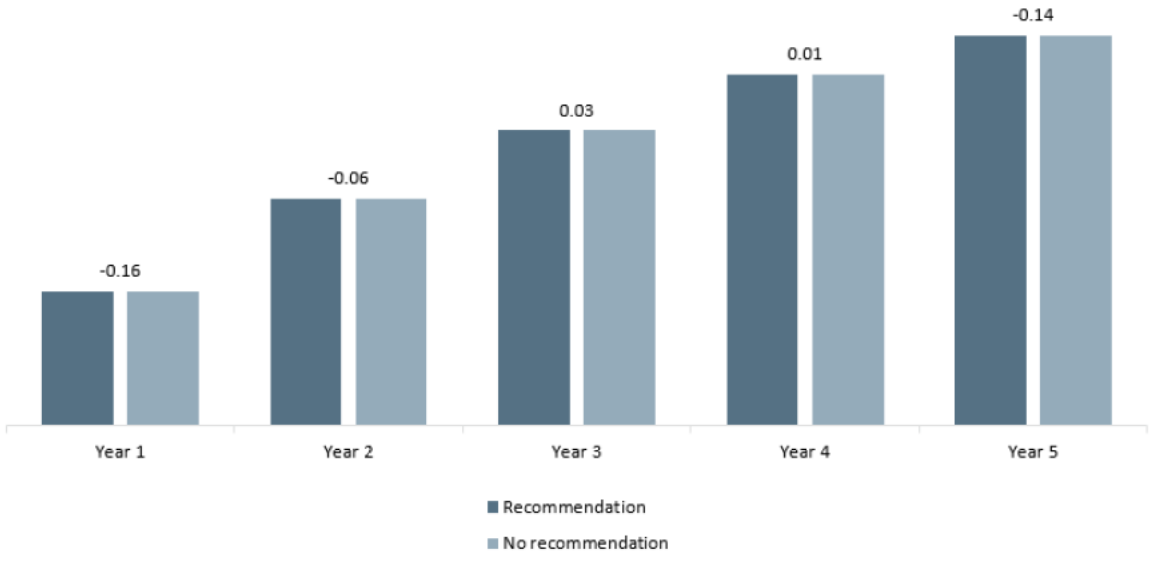

Figure 23: Illustration of the budget impact if eptinezumab is recommended and if it is not recommended

10. Discussion on the submitted documentation

Migraine is a widespread neurological condition that causes decreased functional ability, reductions in QoL and is one of the diseases in Denmark that causes the highest amount of absences from work (9). Migraine patients who visit the Danish Headache Centres are severely impacted by their condition. Chronic migraine patients are impacted patients who may require regular support to manage their migraine and comorbid conditions. Prompt and comprehensive preventive treatment is essential to reduce migraine disability, avoid dependence on and overuse of acute treatment, and hinder disease progression.

Treatment of migraine requires attention to the physical and psychological aspects of care. Preventive treatment aims to reduce migraine attack frequency, severity, duration and debilitation, and to improve patient functioning and HRQoL. Current migraine-preventive care is dominated by genericised oral drugs that either lack efficacy or have unfavourable AE profiles. Later treatment lines, such as onabotulinumtoxin A, are characterised by inconvenient intramuscular injections. As a new drug class for preventive migraine therapy, CGRP antibodies offer multiple advantages compared with agents indicated for earlier lines of treatment, such as improved tolerability and a significantly improved AE profile. However, the current options remain limited and there is still a need for additional CGRP antibody treatments that offer powerful, fast, and sustained efficacy, as defined by high response rates as well as reductions of migraine days and headache severity.

Eptinezumab is a new CGRP antibody and is the first and only CGRP antibody indicated in migraine prevention in adults that is administered quarterly via an IV infusion lasting 30 minutes. The IV ROA of eptinezumab results in a fast onset of effect and the speed of onset is particularly considered one of the most important attributes of preventive treatment in migraine along with response durability (50,51). Also, many patients may prefer quarterly administration, which, in turn, may increase treatment adherence (52). Patient preference research shows that a significant proportion of patients (26.2%) prioritise a fast onset of action over other treatment attributes, and the durability of therapeutic effect was also one of the most important treatment attributes among all queried patients.

As part of preparing the current application to the DMC, Lundbeck consulted two clinical experts. The clinical experts highlighted the possibility of an IV CGRP antibody to induce fast pain coverage due to the fast impact on the CGRP receptor system (within two hours). This offers other therapeutic possibilities than the marketed CGRP antibodies and means that healthcare professionals can work with other and more intensive treatment courses.

The current application provides an assessment of eptinezumab compared to marketed CGRP antibodies in patients with chronic migraine who have failed at least two different previous preventive treatments. The comparative efficacy of eptinezumab and marketed CGRP antibodies were assessed in an NMA. Findings from the NMA demonstrate that overall eptinezumab is as effective and safe as marketed CGRP antibodies based on results in valid and clinically relevant migraine outcomes.

The NMA provides a comprehensive review of clinical efficacy by exploring a range of outcome measures. The NMA was based on an SLR of data on comparator treatments in third- and fourth-line treatment for migraine prevention published up to 22 June 2021, ensuring that all relevant data were identified using a systematic approach. The SLR identified the relevant comparator trials, and all evidence considered was from phase 2 and 3 RCTs to ensure a high quality of data. The data identified in the SLR were combined with data on eptinezumab from the phase 3b DELIVER clinical trial, which assessed migraine patients with at least two prior treatment failures. As such, all studies included within the networks were randomised trials, generally implying within-study validity of the evidence base. The literature search conducted in the current application was based on the SLR to adjust the literature search to the PICO of the current application.

A feasibility assessment was conducted prior to conducting the NMAs to identify available data for analysis and to assess heterogeneity across studies (see section 7.1.8 and 7.1.9). Key study characteristics were identified as being generally similar across studies, for example the definitions of migraine classification typically followed the ICHD criteria. Potential treatment effect modifiers were identified through a targeted review of subgroup results from clinical trials captured in the SLR. In particular, the number of prior treatment failures, severity (MMD) and baseline MOH were identified as potential treatment effect modifiers. Analyses stratifying for two of these factors (migraine classification and prior number of treatment failures) were conducted in order to reduce bias resulting from any imbalance in treatment effect modifiers across trials. Robust NMA models were fitted to the data using model specifications as recommended by the NICE DSU TSD (43), and fixed effect models were fitted and deemed to be most suitable due to the low number of studies per treatment comparison, due to which, limited between-study heterogeneity can be expected. Random effect models were fitted for the key efficacy outcomes of interest (CfB in MMD and 50% MRR) separately for the EM and CM populations, and results were generally consistent with the fixed effect models, although the results were associated with larger uncertainty, which was reflected in the wider credible intervals. The analyses were stratified by both migraine class and the number of prior treatment failures to account for differences in baseline severity between EM and CM, and for differences in treatment effect between different treatment failure subgroups.

A primary limitation of this analysis was the scarcity 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. For the analysis of all-cause discontinuation and discontinuations due to AEs, few discontinuations were reported, which resulted in wide CrIs and application of pooled EM/CM data. The feasibility assessment 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 CM comparisons. This may have resulted in an unbalanced influence of MOH on the treatment effect across studies.

The primary timepoint of interest for the analyses was week 12. However, differences in dosing led to differences in reporting of outcomes at this timepoint, which resulted in four-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 some limitations in terms of comparability between four-week and 12-week interval data.

In addition to the findings from the NMA, showing eptinezumab to be an effective and safe alternative to the marketed CGRP antibodies, eptinezumab also offers a new ROA. The new ROA may benefit patients with adherence problems or be an alternative to patients who require immediate prevention, as eptinezumab offers a fast onset of action.

A health economic analysis consisting of a cost-minimisation analysis was also conducted. The cost-minimisation analysis included all relevant costs associated with treating CM patients with eptinezumab and the SC antibodies erenumab, fremanezumab and galcanezumab. Over a time horizon of 21 months, incremental costs of DKK 5,123, -4,232 and -1,208 were estimated for eptinezumab compared to erenumab, fremanezumab and galcanezumab, respectively. The budget impact at a PPP level of recommending eptinezumab at the Danish hospitals was DKK -0.33 million over all five years. To assess if the result of the base case was sensitive to any changes in any parameters in the model, deterministic sensitivity analyses were conducted. The parameter with the largest impact on the result of the

base case was increasing the base case time horizon and if a small proportion of patients receive 300 mg eptinezumab instead of 100 mg. The results of the health economic analysis demonstrate that eptinezumab can be recommended at the Danish hospitals without increasing the overall budget impact. The health economic analysis presented in the current application is based on PPPs and does not reflect confidential rebates on eptinezumab and the marketed CGRP antibodies.

11. List of experts

- Lars Bendtsen, Co-director, Danish Headache Center in Glostrup
- Helge Kasch, Associate Professor, Senior Consultant Research Neurologist, Viborg Regional Hospital

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Appendix A – Literature search for efficacy and safety of eptinezumab and comparator(s)

In this appendix, a description of how the literature search was performed is provided. Below, the objective of the literature search and a description the applied databases, registers etc. are provided. We describe the development of the search strategy and search strings and specify the inclusion and exclusion criteria for the search, followed by a description of the systematic selection of studies and reasons for exclusion of full-text articles. Finally, a description of the strengths and weaknesses of the performed literature search is provided with a statement on the quality of unpublished data.

Objective of the literature search

The objective of the literature search was to address the efficacy and safety of:

1. eptinezumab compared to erenumab in CM patients who have failed two previous migraine treatments;
2. eptinezumab compared to fremanezumab in CM patients who have failed two previous migraine treatments; and
3. eptinezumab compared to galcanezumab in CM patients who have failed two previous migraine treatments.

Databases

Relevant literature was searched for in the databases Medline (via PubMed) and CENTRAL (via Cochrane Library) on 24 January 2022. Moreover, the US NIH registry and results database and the EU Clinical Trials Register were searched for ongoing trials not yet published with the intervention and comparators in CM. Conference material was not specifically searched for. Ongoing trials were searched for by searching for interventional studies including patients >18 years with CM who have failed previous migraine treatment where eptinezumab, erenumab, fremanezumab or galcanezumab were included as interventions and/or comparators. In the US NIH registry and results database, studies with the recruitment status of Suspended, Terminated, Completed, Withdrawn, or Unknown were excluded. In the EU Clinical Trials Register, studies with the Trial Protocol status of Completed or Prematurely Ended were excluded. The searches were completed in February 2022. In addition to the databases, the EPAR, SPCs and previous DMC evaluations of the three marketed CGRP antibodies were also consulted.

Table 64: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Medline	PubMed	Up until today	24.01.2022
CENTRAL	Cochrane library	Up until today	24.01.2022

Table 65: Registers included in the search

Database	Platform	Search strategy	Date of search
US NIH registry & results database	https://clinicaltrials.gov	Trials registered as "not yet recruiting", "recruiting", "active not recruiting" and "enrolling by invitation" were searched for. Moreover, the search included trials within the condition "Migraine" and applied the term for the generic name of the drugs (e.g., eptinezumab, erenumab etc.). Only trials where the patient population consisted of adult patients with chronic migraine who has failed previous preventive migraine treatments were listed (see Table 67).	07.02.2022
EU Clinical Trials Register	EU Clinical Trials Register	Trials listed as ongoing were included and the terms Migraine and the generic name of the drugs were applied. Only trials where the patient population consisted of adult patients with chronic migraine who has failed previous preventive migraine treatments were listed.	10.02.2022

No relevant conference material to include. The search in the US NIH registry and results database resulted in seven ongoing trials. In Table 66, the trials are listed, including information on the NCT number, title, procedure, intervention, comparator and estimated study completion date for each study as it is described in the US NIH registry and results database. The search on EU Clinical Trials Register did not result in any relevant trials.

Table 66: Ongoing trials registered in the US NIH registry and results database (https://clinicaltrials.gov)

NCT number	Title	Patient population	Intervention	Comparator	Estimated study completion date
NCT04418765	A Study to Evaluate the Efficacy and Safety of Eptinezumab for the Prevention of Migraine in Participants That Are Not Helped by Previous Preventive Treatments (DELIVER)	Migraine patients with unsuccessful prior preventive treatment	Eptinezumab	Placebo	September 2, 2022
NCT04361721	Neurophysiological, Biomolecular and Psychological Aspects	CM patients who had previously failed at least 2 preventive treatments	Erenumab	None	June 30, 2021

NCT number	Title	Patient population	Intervention	Comparator	Estimated study completion date
	of Erenumab Treatment in Chronic Migraine				
NCT03971071	A Study to Evaluate the Efficacy and Safety of Erenumab in Adults With Medication Overuse Headache	Subjects with CM who have a history of at least 1 preventive treatment failure and are diagnosed with MOH	Erenumab	Placebo	May 11, 2023
NCT04628429	CGRP Inhibition, Autonomic Function, and Migraine (CGRP-1)	Patients who have been diagnosed with CM (≥15 headache days per month 8 of which with migrainous features) or EM (with or without aura) both according to the diagnostic criteria of the International Classification of Headache Disorders, third edition (ICHD-3) and have been unsuccessfully treated with first-line prophylactic medication	Erenumab, fremanezumab and galcanezumab	None	December 31, 2022

Search strategy

A systematic literature search was conducted, applying relevant search terms for the condition (migraine), the intervention and comparators as well as a filter to identify RCTs and a filter to exclude irrelevant publication types and study designs. The search was conducted in Medline (via PubMed) and CENTRAL (via Cochrane Library) on 24 January 2022. The specific search terms and number of hits in Medline and CENTRAL can be found in Table 68 and Table 69, respectively. Both Medical Subject Headings (MeSH) terms and free-text search containing alternative spellings and names were applied.

A two-stage selection process was applied on the hits identified in the electronic database searches. First, hits were screened based on title and abstract; each title and abstract were reviewed against the inclusion/exclusion criteria listed in Table 67 by two independent reviewers. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured. The results of the two reviewers were compared and any disagreements resolved by discussion until a consensus was met. If necessary, a third independent reviewer made the final decision. The next stage was review based on full-text publications, again based on the inclusion/exclusion criteria by two independent reviewers. In cases where the publication did not give enough information to be sure it meet the inclusion/exclusion criteria, the publication was excluded at this stage to ensure that only relevant publications were ultimately included in the literature search. The results of the two reviewers were compared and any disagreements resolved by discussion until a consensus was met. If necessary, a third independent reviewer made the final decision. Inclusion/exclusion criteria are presented in Table 67.

Table 67: Inclusion and exclusion criteria

Study/ID	Inclusion criteria	Exclusion criteria
Population	• Adults (≥18 years) with CM who have failed at least two different previous migraine treatments	• Studies in children or adolescents (<18 years) • Any other conditions, e.g., EM or headache
Interventions	• Anti-CGRPs approved or under investigation for migraine prevention, including: ◦ Eptinezumab ◦ Erenumab ◦ Fremanezumab ◦ Galcanezumab	• Other approved or investigational treatments for migraine prevention • Products for acute treatment of migraine • Non-pharmacological treatments (e.g., lifestyle interventions or devices)
Comparator	• Any pharmacological treatment, including placebo	• Products for acute treatment of migraine

Study/ID	Inclusion criteria	Exclusion criteria
		• Non-pharmacological treatments (e.g., lifestyle interventions or devices)

Outcomes	• Efficacy outcomes, including but not limited to:
	  ○ Reduction in MMDs
	  ○ Proportion of patients with reduction in migraine days (≥50% preferred, but ≥75% or 100% reduction included as well)
	  ○ Reduction in headache days
	  ○ Reduction in the number of days rescue medication is used per month
	• HRQoL measures, including but not limited to:
	  ○ HIT-6
	  ○ MSQ
	  ○ MIDAS
	• Safety outcomes (including AEs and discontinuation)
		• Any non-relevant outcomes
		• Outcomes in mixed populations not reported separately for the population of interest

Study design	• RCTs (phase II, III and IIII)	• Any other study design, including:
		  – Phase I RCTs
		  – Interventional non-RCTs
		  – Observational studies
		  – Case reports/case studies
		  – Economic evaluations
		  – Guidelines
		  – Meta-analyses
		• Non-systematic or narrative reviews
		• Publications reporting pooled analyses of RCTs were deprioritised at extraction stage, unless reporting novel data specifically in a prior treatment failure population.

Study/ID	Inclusion criteria	Exclusion criteria
Publication type	• Full-text publications • Peer-reviewed journal articles • HTA submissions	• Editorials, notes, comments or letters • Abstracts • Posters • Letters • Comments
Language restrictions	• English	• Non-English-language publications
Date restrictions	None	

Abbreviations: CGRP: calcitonin gene-related peptide; HIT-6: Headache Impact Test; HRQoL: health-related quality of life; MIDAS: Migraine Disability Assessment; MSQ: migraine-specific quality-of-life questionnaire, RCT: randomised controlled trial.

Table 68: Search strategy in PubMed (Medline)

Group	No.	Query	Results
Migraine and migraine prevention	#1	"Migraine Disorders"[Mesh]	29,706
	#2	Migran*[Title/Abstract]	26,419
	#3	"chronic migraine"[Title/Abstract]	2,635
	#4	#1 OR #2 AND #3	1,933
	#5	"Primary Prevention"[Mesh]	166,714
	#6	*prevent*[Title/Abstract] OR *prophyla*[Title/Abstract]	1,729,653
	#7	#5 OR #6	1,854,794

Group	No.	Query	Results
	#8	#4 AND #7	745
Interventions	#9	"Calcitonin Gene-Related Peptide Receptor Antagonists"[MeSH Terms]	771
	#10	"eptinezumab"[Supplementary Concept] OR "eptinezumab"[All Fields] OR "ald 403"[All Fields] OR "ald403"[All Fields] OR "vyepti"[All Fields] OR "erenumab"[Supplementary Concept] OR "erenumab"[All Fields] OR "amg334"[All Fields] OR "amg 334"[All Fields] OR "aimovig"[All Fields] OR "fremanezumab"[Supplementary Concept] OR "fremanezumab"[All Fields] OR "tev48125"[All Fields] OR "tev 48125"[All Fields] OR "ajovy"[All Fields] OR "galcanezumab"[Supplementary Concept] OR "galcanezumab"[All Fields] OR "ly 2951742"[All Fields] OR "ly2951742"[All Fields] OR "emgality"[All Fields]	596
	#11	#9 OR #10	1,197
Identification of randomised controlled trials	#12	"randomized controlled trial"[pt] OR "randomized controlled trials as topic"[mh] OR "random allocation"[mh] OR "double-blind method"[mh] OR "single-blind method"[mh] OR random*[tw] OR "Placebos"[Mesh] OR placebo[tiab] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw] OR dumm*[tw]))	1,646,710
Exclusion of irrelevant publication types and study designs	#13	"epidemiologic studies"[MeSH Terms] OR ("epidemiologic"[All Fields] AND "studies"[All Fields]) OR "epidemiologic studies"[All Fields] OR ("case control studies"[MeSH Terms] OR ("case control"[All Fields] AND "studies"[All Fields]) OR "case control studies"[All Fields] OR ("case"[All Fields] AND "control"[All Fields] AND "studies"[All Fields]) OR "case control studies"[All Fields]) OR ("cohort studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "cohort studies"[All Fields]) OR ("cross sectional studies"[MeSH Terms] OR ("cross sectional"[All Fields] AND "studies"[All Fields]) OR "cross sectional studies"[All Fields] OR ("cross"[All Fields] AND "sectional"[All Fields] AND "studies"[All Fields]) OR "cross sectional studies"[All Fields]) OR "observational study"[Publication Type]	3,067,147
	#14	"Cohort"[Title/Abstract] AND ("study"[Title/Abstract] OR "studies"[Title/Abstract] OR "analys*"[Title/Abstract])	594,985
	#15	("follow up"[Title/Abstract] OR "uncontrolled"[Title/Abstract] OR "non randomized"[Title/Abstract] OR "non randomised"[Title/Abstract]) AND ("study"[Title/Abstract] OR "studies"[Title/Abstract])	719,857
	#16	("LONGITUDINAKL"[Title/Abstract] OR "retrospective"[Title/Abstract] OR "prospective"[Title/Abstract]) AND ("study"[Title/Abstract] OR "studies"[Title/Abstract] OR "review"[Title/Abstract] OR "analys*"[Title/Abstract] OR "cohort*"[Title/Abstract])	1,367,862

Group	No.	Query	Results
	#17	"cross sectional"[Title/Abstract] OR "Review"[Publication Type] OR "Editorial"[Publication Type] OR "Letter"[Publication Type] OR "Comment"[Publication Type]	5,338,078
	#18	"case not*"[Title/Abstract] OR "case repor*"[Title/Abstract] OR "survey"[Title/Abstract]	1,056,274
	#19	#16 OR #17 OR #18 OR #19 OR #20 OR #21	9,255,205
Final search	**#20**	**#8 AND #11 AND #12 NOT #19**	**64**

Table 69: Search strategy in the Cochrane library (CENTRAL)

Group	No.	Query	Results
Migraine and migraine prevention	#1	[mh "migraine disorders"]	2,877
	#2	migrain*:ti,ab,kw	8,713
	#3	#1 or #2	8,713
	#4	"chronic migraine":ti,ab,kw	1,213
	#5	#3 and #4	1,213
	#6	[mh "primary prevention"]	4,506
	#7	(prevent* or prophyla*):ti,ab,kw	262,507
	#8	#6 or #7	263,696
	#9	#5 and #8	763
Interventions	#10	[mh "calcitonin gene-related peptide receptor antagonists"]	61
	#11	((("calcitonin gene related peptide receptor" or CGRP) NEAR/3 (antagonist* or receptor-block* or inhibitor* or antibod*)) or anti-CGRP*):ti,ab,kw	463

Group	No.	Query	Results
	#12	(eptinezumab or ald-403 or ald403 or vyepti or erenumab or amg334 or amg-334 or aimovig or fremanezumab or tev48125 or tev-48125 or ajovy or galcanezumab or ly-2951742 or ly2951742 or emgality or atogepant or agn241689 or agn-241689 or mk8031 or mk-8031 or rimegepant or bms-927711 or bms927711 or nurtec):ti,ab,kw	1,249
	#13	#10 or #11 or #12	1,379
Identification of randomised controlled trials	#14	"Randomized Controlled Trial":pt or "Controlled Clinical Trial":pt or randomized:ti,ab or randomised:ti,ab or "Clinical Trials as Topic" or randomly:ti,ab or trial:ti or controlled:ti,ab or control group*:ti,ab or active control*:ti,ab or parallel-group:ti,ab	1,364,508
Exclusion of irrelevant publication types and study designs	#15	Observational study:pt or Review:pt or Editorial:pt or Letter:pt or Comment:pt or Guideline:pt or (observational OR longitudinal OR retrospective):ti,ab,kw	105,063
	#16	(“Case not*” OR “Case repor*”):ti,ab,kw	56
	#17	#15 and #16	5
Final search	#18	#9 and #13 and #14 not #17	**416**

Systematic selection of studies

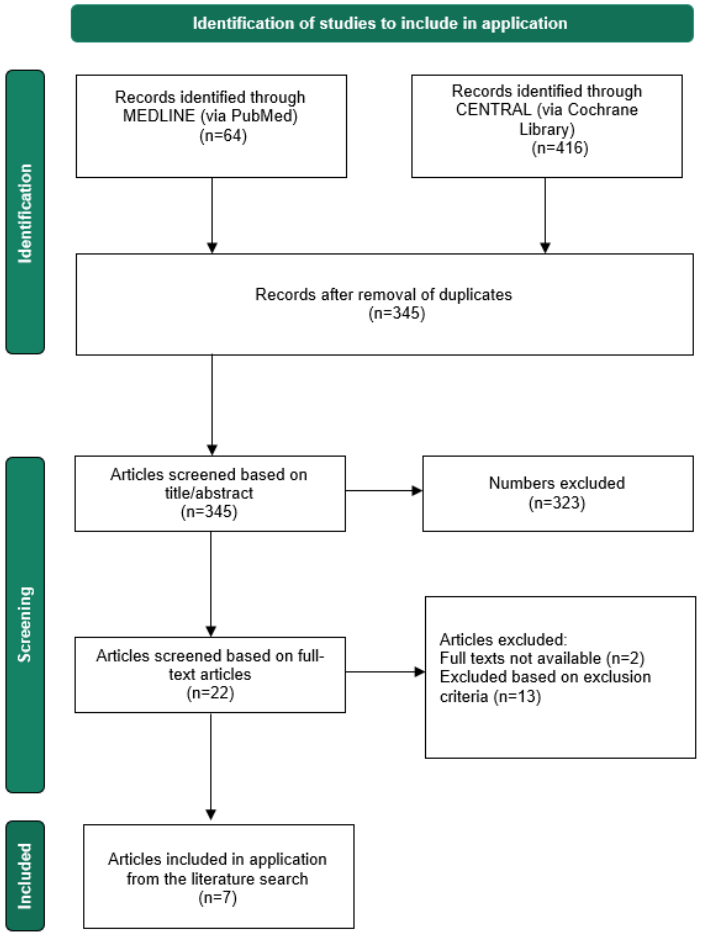

Figure 24: PRISMA diagram illustrating the selection process

Table 70: List of excluded articles after full-text assessment and an explanation as to why the article was excluded

Reference	Intervention	Reason for exclusion
Bangs et al. 2020: Safety and tolerability of monthly galcanezumab injections in patients with migraine: integrated results from migraine clinical studies	Galcanezumab	Bangs et al. integrated data from three double-blind phase 3 studies (EVOLVE-1, EVOLVE-2 and REGAIN). The study was excluded because patients did not meet the defined population inclusion criterion.
Detke et al. 2018: Galcanezumab in chronic migraine The randomized, double-blind, placebo-controlled REGAIN study	Galcanezumab	Excluded because the article reported results from the total patient population in the REGAIN study (not chronic population with ≥2 treatment failures).
Ford et al. 2020: Changes in patient functioning and disability: results from a phase 3, double-blind, randomized, placebo-controlled clinical trial evaluating galcanezumab for chronic migraine prevention (REGAIN)	Galcanezumab	Excluded because the patient population did not meet the defined population inclusion criterion.
Okonkwo et al. 2021: Efficacy of galcanezumab in patients with migraine and history of failure to 3–4 preventive medication categories: subgroup analysis from CONQUER study	Galcanezumab	Okonkwo et al. included patients with CM or EM who had documented treatment failure of three to four standard-of-care migraine preventive medication categories in the past 10 years (either due to inadequate efficacy (after at least two months at maximum tolerated dose), safety or tolerability reasons, or both). The study was excluded because of the inclusion criteria in the study that patients must have failed three to four previous treatments, which was more than the defined population inclusion criterion for the current application.
Lipton et al. 2019: Erenumab in chronic migraine Patient-reported outcomes in a randomized double-blind study	Erenumab	Excluded because the patient population did not meet the defined population inclusion criterion (only approximately 50% of patients had failed previous prophylactic treatments).
Tepper et al. 2017: Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial	Erenumab	Did not report results on the patient population of interest (≥2 treatment failures).

Reference	Intervention	Reason for exclusion
Tepper et al. 2017: Patient-Reported Outcomes in Patients with Chronic Migraine Receiving Placebo or Erenumab (AMG 334) in a Phase 2, Randomized, Double-Blind Study	Erenumab	Full text was not available.
Silberstein et al. 2019: Impact of Fremanezumab on Response Rates, Migraine Days, and Acute Medication Use in Patients with Chronic Migraine Who Have Failed at Least One Prior Migraine Preventive Medication	Fremanezumab	Full text was not available.
Silberstein et al. 2017: Fremanezumab for the Preventive Treatment of Chronic Migraine	Fremanezumab	Did not report results on the patient population of interest (≥2 treatment failures).
Bigal et al. 2015: Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study	Fremanezumab	Excluded because the patient population did not meet the defined population inclusion criterion.
Spierings et al. 2021: Efficacy and safety of fremanezumab in patients with migraine and inadequate response to prior preventive treatment: subgroup analyses by country of a randomized, placebo-controlled trial	Fremanezumab	Evaluated results from the FOCUS study by country.
Martin et al. 2021: Impact of baseline characteristics on the efficacy and safety of eptinezumab in patients with migraine: subgroup analyses of PROMISE-1 and PROMISE-2	Eptinezumab	Did not include results on the outcomes of interest.
Lipton et al. 2020: Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2	Eptinezumab	Lipton et al. 2020 reports results from the overall patient population from the PROMISE-2 trial; thus, the article was excluded based on the population exclusion criteria.

Reference	Intervention	Reason for exclusion
Lipton et al. 2019: Eptinezumab demonstrated early and sustained reductions in HIT-6 total score over time in patients with chronic migraine in the promise-2 trial	Eptinezumab	Did not report results on the patient population of interest (≥2 treatment failures).
Silberstein et al. 2020: Eptinezumab for the prevention of chronic migraine: efficacy and safety through 24 weeks of treatment in the phase 3 PROMISE-2 (Prevention of migraine via IV ALD403 safety and efficacy–2) study	Eptinezumab	PROMISE-2 publication: excluded due to the defined population inclusion criterion.

Table 71: Overview of studies included in the application

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
DELIVER	The aim of the study is to evaluate the efficacy of eptinezumab for the prevention of migraine in patients with unsuccessful prior preventive treatments.	The study is an interventional, phase 3b, randomised, double-blind, parallel-group, multi-national placebo-controlled study with an extension period.	Patients with EM or CM with unsuccessful prior preventive treatments	The intervention consisted of either 100 mg eptinezumab or 300 mg eptinezumab administered by IV infusion. The comparator was placebo to match the intervention.	The primary outcome was CfB in the number of MMD from weeks 1 to 12.	The key secondary outcomes were the proportions of patients with a ≥50% and ≥75% reduction in response from baseline in MMDs from weeks 1 to 12. Another key secondary outcome was CfB in number of MMDs (weeks 13 to 24).
NCT02066415	The aim of the study is to evaluate the efficacy and safety of monthly erenumab	The study is a multicentre, randomised, double-blind,	Patients with CM who had previously failed preventive	The intervention consisted of either 70 mg or 140 mg erenumab	The primary endpoint was change in MMD from baseline to	The key secondary endpoints were achievement of ≥50% and ≥75% reduction from baseline in MMD and CfB in monthly

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
	(70 mg or 140 mg) compared to placebo in patients with CM.	placebo-controlled 12-week parallel-group study.	treatment(s) (≥1, ≥2 prior failed medication categories) and patients with CM who had never failed	administered subcutaneously. Patients received erenumab 70 mg or erenumab 140 mg at day 1 and at week 4 and 8 hereafter. The comparator was placebo to match the intervention.	month 3 of the double-blind treatment phase.	acute MSMD (use of triptans or ergots).
FOCUS	The aim of the study is to investigate the efficacy and tolerability of fremanezumab in patients with migraine who have responded inadequately to two to four classes of preventive migraine medications.	The study is an international, multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3b trial.	Patients aged 18-70 years who had EM or CM and had documented failure with two to four classes of migraine preventive medications in the past 10 years	The intervention consisted of subcutaneously administered quarterly fremanezumab (month 1: 675 mg, months 2 and 3: placebo) or monthly fremanezumab (month 1: 225 mg in EM and 675 mg in CM, months 2 and 3: 225 mg in both migraine groups). The comparator was monthly placebo to match the intervention.	The primary outcome was mean CfB in the monthly average number of migraine days during the 12-week treatment period.	The secondary outcomes included the CfB in the monthly average number of migraine days during the four-week period after the first dose of study drug and the proportions of patients with a 50% or greater response.
REGAIN	The aim of the study is to evaluate the	The study is a phase 3,	Patients aged 18-65 years with a	The intervention consisted of	The primary objective was to	The key secondary outcomes included mean proportions of

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
	efficacy of galcanezumab in patients with CM who have failed ≥2 and ≥1 prior migraine preventives for efficacy and/or safety reasons, and in those who never failed.	randomised, double-blind placebo-controlled study in patients with CM.	diagnosis of CM (with or without aura) who had never had treatment failure or who had failed ≥2 and ≥1 prior migraine preventives	monthly SC injections of either galcanezumab 120 mg (with a loading dose of 240 mg) or galcanezumab 240 mg. The comparator was monthly SC injections of placebo.	assess if at least one dose of galcanezumab was superior to placebo in overall mean CfB in the number of MHDs across the double-blind period.	patients with ≥50% and ≥75% reduction in monthly MHDs, overall mean reduction from baseline in monthly MHDs with acute medication use for migraine headache and mean CfB at month 3 in the Role Function-Restrictive domain score of the Migraine Specific Quality of Life Questionnaire version 2.1 (MSQ-RFR).
CONQUER	The aim of the study is to assess the safety and efficacy of galcanezumab in patients with migraine who had not benefited from preventive medications from two to four categories.	The study is a multicentre, randomised, double-blind, placebo-controlled phase 3b trial.	Patients were 18-75 years of age, with EM or CM, with migraine onset before the age of 50 years, who had a documented failure to preventive medications from two to four drug categories in the past 10 years due to lack of efficacy or tolerability, or both.	The intervention consisted of subcutaneously administered galcanezumab 120 mg per month (with a loading dose of 240 mg administered as two 120 mg injections) for three months. The comparator was monthly subcutaneously administered placebo to match the intervention.	The primary objective was to compare galcanezumab and placebo on the overall mean CfB in the number of monthly migraine headache days during the three-month double-blind treatment period in the total population (EM and CM).	There were nine gated key secondary objectives for the study. The first key secondary objective compared galcanezumab and placebo on the primary endpoint in the EM subpopulation. The remaining key secondary objectives compared galcanezumab with placebo on response rates (mean percentage of patients with ≥50%, ≥75%, and 100% reduction from baseline in monthly migraine headache days across months 1–3) and mean CfB in the MSQ-RFR score at month 3, for the total population and also for the EM subpopulation.

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
LIBERTY	The aim of the study is to assess the efficacy and tolerability of erenumab in patients with EM in whom previous treatment with two to four migraine preventives had been unsuccessful.	The study is a randomised, double-blind, placebo-controlled phase 3b study.	Patients were 18-65 years of age with a history of EM with or without aura for at least 12 months. Patients also had to have previously been treated unsuccessfully (in terms of either efficacy or tolerability, or both) with between two and four of the preventive treatments.	The intervention consisted of subcutaneously administered erenumab 140 mg dosed as two 70 mg injections) every four weeks for a period of 12 weeks. The comparator was placebo to match the intervention.	The primary endpoint was the proportion of patients who achieved at least a 50% reduction in the number of monthly migraine days from baseline and during the third month of the double-blind treatment phase.	The secondary efficacy endpoints were CfB in monthly acute migraine-specific medication days, the proportion of patients with a 75% or greater or 100% reduction from baseline in monthly migraine days, and CfB in scores on the everyday activities and physical activity subdomains of the Migraine Physical Function Impact Diary.
STRIVE	The aim of the study is to evaluate the effect of erenumab compared to placebo on the CfB in monthly migraine days.	The study is a multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3b trial.	Patients were 18-65 years of age with a history of migraine with or without aura for at least 12 months before screening.	The intervention consisted of subcutaneously administered injections with either 70 mg erenumab or 140 mg erenumab at day 1 and weeks 4, 8, 12, 16, and 20.	The primary endpoint was the change in mean number of migraine days per month from baseline to the final three months (months 4 through 6) of the double-blind treatment phase.	The secondary endpoints were a 50% or greater reduction in mean migraine days per month, change in the number of days with use of acute migraine-specific medication, and change in scores in the physical-impairment and everyday-activities domains of the Migraine Physical Function Impact Diary.

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
				The comparator was placebo to match the intervention.		

Quality assessment

The performed literature search has a number of strengths. The search was conducted in the two databases, Medline and CENTRAL, as requested by the DMC, to identify relevant literature to address the objective of the literature search. The PICO and the inclusion and exclusion criteria were defined prior to the literature search. Relevant search terms were applied for the condition, the intervention and the comparators, and a broad search was conducted without time limits to minimise the risk of not identifying relevant studies.

Unpublished data

Unpublished data on the DELIVER trial were applied. Comparative analyses from an unpublished NMA report were also applied.

Appendix B Main characteristics of included studies

In the following tables, main characteristics of the trials included in the comparative analyses are presented. As data from the STRIVE trial and LIBERTY trial was applied in pooled EM and CM analyses on discontinuation, these two trials were also described.

- Table 72: Main characteristics of the DELIVER trial.
- Table 73: Main characteristics of Study 295.
- Table 74: Main characteristics of the FOCUS study.
- Table 75: Main characteristics of the CONQUER study.
- Table 76: Main characteristics of the REGAIN trial.
- Table 77: Main characteristics of the LIBERTY trial.
- Table 78: Main characteristics of the STRIVE trial.

Table 72: Main characteristics of the DELIVER trial (eptinezumab)

Trial name: A study to evaluate the efficacy and safety of eptinezumab for the prevention of migraine in patients that are not helped by previous preventive treatments (DELIVER)	**NCT number:** NCT04418765
Objective	The overall objective of the trial is to evaluate the efficacy of eptinezumab for the prevention of migraine in patients with unsuccessful prior preventive treatments.
Publications – title, author, journal, year	None at the time of preparing this application. Publications are expected to be available in the second quarter of 2022.
Study type and design	Interventional, phase 3b, randomised, double-blind, parallel-group, multi-national placebo-controlled study with an extension period to evaluate the efficacy and safety of eptinezumab for the prevention of migraine in patients with unsuccessful prior preventive treatment. The study consisted of a screening period, a placebo-controlled period and an extension period. 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 MHDs/>14 MHDs). The patients received treatments by IV infusion over 30 minutes (up to 45 minutes) starting from the baseline visit; hereafter, the patients were dosed every 12 weeks (that is, a total of two doses).

Trial name: A study to evaluate the efficacy and safety of eptinezumab for the prevention of migraine in patients that are not helped by previous preventive treatments (DELIVER)	**NCT number:** NCT04418765
Sample size (n)	**APRS (total: 892)** Placebo: 299 patients Eptinezumab 100 mg: 299 patients Eptinezumab 300 mg: 294 patients **APTS (total: 891)** Placebo: 298 patients Eptinezumab 100 mg: 299 patients Eptinezumab 300 mg: 294 patients **FAS (total: 890)** Placebo: 298 patients Eptinezumab 100 mg: 299 patients Eptinezumab 300 mg: 293 patients

Main inclusion and exclusion criteria	**Inclusion criteria (from clinicaltrials.gov)** • The patient has a diagnosis of migraine with a history of chronic or episodic migraines of at least 12 months prior to the screening visit. • The patient has a migraine onset of ≤50 years of age. • The patient has ≥4 migraine days per month for each month within the past three months prior to the screening visit. • The patient has demonstrated compliance with the Headache e-Diary by entry of data for at least 24 of the 28 days prior to randomisation. • The patient fulfils the following criteria for CM or EM in prospectively collected information in the e-Diary during the screening period: For patients with CM: Migraine occurring on ≥8 days and headache occurring on >14 days and for patients with EM: Migraine occurring on ≥4 days and headache occurring on ≤14 days. • The patient has documented evidence of treatment failure (must be supported by medical record or by physician's confirmation specific to each treatment) in the past 10 years of two to four different migraine preventive medications. • The patient has a history of either previous or active use of triptans for migraine. **Exclusion criteria (from clinicaltrials.gov)** • The patient has experienced failure on a previous treatment targeting the CGRP pathway. • The patient has a treatment failure on valproate/divalproex or botulinum toxin A/B and the treatment is not the latest preventive medication prior to study inclusion. The medication is regarded as the latest if the medication start date is after the start date of the other preventive medications and the medication stop date is after the stop date of the other preventive medications. • The patient has confounding and clinically significant pain syndromes, (e.g., fibromyalgia, chronic low back pain, complex regional pain syndrome). • The patient has a diagnosis of acute or active temporomandibular disorder. • The patient has a history or diagnosis of chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, or unusual migraine subtypes such as hemiplegic migraine (sporadic and familial), ophthalmoplegic migraine, and migraine with neurological accompaniments that are not typical of migraine aura (diplopia, altered consciousness, or long duration).

Trial name: A study to evaluate the efficacy and safety of eptinezumab for the prevention of migraine in patients that are not helped by previous preventive treatments (DELIVER)	**NCT number:** NCT04418765
	• The patient has a psychiatric condition that is uncontrolled and/or untreated for a minimum of six months prior to the screening visit. Patients with a lifetime history of psychosis and/or mania in the last five years prior to the screening visit are excluded. • The patient has a history of clinically significant cardiovascular disease or vascular ischaemia or thromboembolic events (e.g., cerebrovascular accident, deep vein thrombosis, or pulmonary embolism).
Intervention	• Eptinezumab 100 mg (administrated intravenously) • Eptinezumab 300 mg (administrated intravenously) Patients were dosed at baseline (day 0); hereafter, the patients were dosed every 12 weeks. Placebo, eptinezumab 100 mg, or eptinezumab 300 mg was administered via IV infusion (total volume of the infusion was 100 mL) over a period of 30 (up to 45) minutes.
Comparator(s)	Placebo to match the intervention (see above). Placebo was only administered in the placebo-controlled period; thereafter, the patients in the placebo group received eptinezumab 100 mg or 300 mg.
Follow-up time	See Figure 1.
Is the study used in the health economic model?	No. The presented health economic analysis was a cost-minimisation analysis with a cost-minimisation model, i.e., no efficacy data was included in the model.

Primary, secondary and exploratory endpoints	**Primary endpoint** • Change from baseline in the number of MMDs: weeks 1 to 12 **Key secondary endpoints** • Response: ≥50% reduction from baseline in MMDs: weeks 1 to 12 • Response: ≥75% reduction from baseline in MMDs: weeks 1 to 12 • Change from baseline in the number of MMDs: weeks 13 to 24 **Secondary endpoints** • Response: ≥50% reduction from baseline in MMDs: weeks 13 to 24 • Response: ≥75% reduction from baseline in MMDs: weeks 13 to 24 • Response: 100% reduction from baseline in MMDs (average of 4-weekly results, across weeks 1 to 12) • Response: ≥50% reduction from baseline in MHDs: weeks 1 to 12 • Response: ≥75% reduction from baseline in MHDs: weeks 1 to 12 • Response: 100% reduction from baseline in MHDs (average of 4-weekly results, across weeks 1 to 12 • Change from baseline in the number of MHDs: weeks 1 to 12 • Change from baseline in the percentage of migraines/headaches 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 • 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 • Patient Global Impression of Change (PGIC) score at week 12 • PGIC score at week 24 • Change from baseline in the number of MMDs in patients with MOH: weeks 1 to 12 • Migraine on the day after first dosing – most bothersome symptom (MBS) score at week 12, as measured relative to baseline

Exploratory endpoints

- Change from baseline in the number of monthly headache episodes for each 12-week period
- Change from baseline in the number of monthly migraine attacks for each 12-week period
- Response: 100% reduction from baseline in MMDs (average of 4-weekly results, across weeks 13 to 24)
- Response: ≥50% reduction from baseline in MHDs (weeks 13 to 24)
- Response: ≥75% reduction from baseline in MHDs (weeks 13 to 24)
- Response: 100% reduction from baseline in MHDs (average of 4-weekly results, across weeks 13 to 24)
- Change from baseline in the percentage of migraine/headaches with severe pain intensity (weeks 13 to 24)
- Change from baseline in the number of MMDs in patients with MOH (weeks 13 to 24)
- MBS score at Week 24, as measured relative to baseline

Endpoints included in this application:

To demonstrate that eptinezumab is as effective and safe as the marketed CGRP antibodies, we present results on the following endpoints: **MMD (primary endpoint)**, 50% MRR, HIT-6, MSQ, MMDs with acute medication use, discontinuation due to AEs, all-cause discontinuation, proportion of patients with at least one AE and proportion of patients with at least one SAE. No endpoints were included in the health economic model.

Method of analysis

The efficacy analyses were based on the FAS for the placebo-controlled period, and the safety analyses were based on the APTS for the placebo-controlled period.

CfB in the number of MMDs for the 6 first 4-week intervals was analysed using a restricted maximum likelihood (REML) based mixed model for repeated measures (MMRM). The model included the fixed effects of month (weeks 1 to 4, 5 to 8, 9 to 12, 13 to 16, 17 to 20, and 21 to 24), country, stratification (MHDs at baseline: ≤14 MHDs/>14 MHDs), and treatment as factors; baseline MMDs as a continuous covariate; treatment-by-month interaction; baseline score-by-month interaction; and stratum-by-month interaction. An unstructured variance structure was used to model the within-patient errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The estimand for the primary endpoint 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 AEs 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. The intercurrent events addressed were:

- use of acute medication to treat a headache;
- use of preventive migraine medication;
- withdrawal due to lack of efficacy;
- withdrawal due to an adverse event;
- withdrawal for other reasons; and
- interruption/termination of infusions.

The attributes for the estimand included:

- treatment condition – comparing eptinezumab 100 mg and 300 mg to placebo;
- population – as defined in the inclusion and exclusion criteria;
- endpoint – the change from Baseline in the number of MMDs across weeks 1 to 12; and
- population-level summary – the least squares mean difference between eptinezumab and placebo for the endpoint.

The mean difference between each dose of eptinezumab and placebo was estimated based on the least squares means for the treatment-by-month interaction in the MMRM. The primary comparisons were the contrasts between each dose of eptinezumab and placebo averaged across weeks 1 to 12.

	The key secondary endpoints 50% and 75% response were analysed using logistic regression with baseline MMDs as a continuous covariate and treatment and stratification (MHDs at baseline: ≤14 MHDs/>14 MHDs) as factors. The logistic regression model was fitted using the maximum likelihood method and the logit link function. The key secondary endpoint CfB in the number of MMDs (weeks 13 to 24) was analysed using the same MMRM as for the primary endpoint. The comparisons were the contrasts between each dose of eptinezumab and placebo averaged across weeks 13 to 24. The key secondary endpoint CfB to week 12 in HIT-6 score was analysed using an MMRM similar to the one used for the primary endpoint. All the visits from the placebo-controlled period were included in the analysis. The comparisons were the contrasts between each dose of eptinezumab and placebo at week 12.
Subgroup analyses	The primary efficacy analysis (MMRM) was repeated 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) and high frequency EM (8≤ MMDs ≤14), and CM (MMDs ≥8)
Other relevant information	None

Table 73: Main characteristics of NCT02066415

Trial name: A study to evaluate the efficacy and safety of Erenumab in chronic migraine prevention	**NCT number**: NCT02066415
Objective	The objective of this study is to assess the safety and efficacy of erenumab compared to placebo in adults with CM.

Publications – title, author, journal, year

Publications

1) Tepper S, Ashina M, Reuter U, Brandes JL, Doležil D, Silberstein S, Winner P, Leonardi D, Mikol D, Lenz R. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2017 Jun;16(6):425-434. doi: 10.1016/S1474-4422(17)30083-2. Epub 2017 Apr 28.

2) Ashina M , Tepper S , Brandes JL , Reuter U, Boudreau G , Dolezil D , Cheng S, Zhang F, Lenz R, Klatt J. Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study. Cephalalgia. 2018; 38(10) 1611–1621. DOI: 10.1177/0333102418788347.

Publications automatically indexed to this study by NCT number

3) Lipton RB, Dodick DW, Kudrow D, Reuter U, Tenenbaum N, Zhang F, Lima GPDS, Chou DE, Mikol DD. Reduction in migraine pain intensity in patients treated with erenumab: A post hoc analysis of two pivotal randomized studies. Cephalalgia. 2021 Dec;41(14):1458-1466. doi: 10.1177/03331024211028966. Epub 2021 Aug 18.

4) Tepper SJ, Ashina M, Reuter U, Hallström Y, Broessner G, Bonner JH, Picard H, Cheng S, Chou DE, Zhang F, Klatt J, Mikol DD. Reduction in acute migraine-specific and non-specific medication use in patients treated with erenumab: post-hoc analyses of episodic and chronic migraine clinical trials. J Headache Pain. 2021 Jul 23;22(1):81. doi: 10.1186/s10194-021-01292-w.

5) Lipton RB, Burstein R, Buse DC, Dodick DW, Koukakis R, Klatt J, Cheng S, Chou DE. Efficacy of erenumab in chronic migraine patients with and without ictal allodynia. Cephalalgia. 2021 Oct;41(11-12):1152-1160. doi: 10.1177/03331024211010305. Epub 2021 May 13.

6) Lipton RB, Tepper SJ, Silberstein SD, Kudrow D, Ashina M, Reuter U, Dodick DW, Zhang F, Rippon GA, Cheng S, Mikol DD. Reversion from chronic migraine to episodic migraine following treatment with erenumab: Results of a post-hoc analysis of a randomized, 12-week, double-blind study and a 52-week, open-label extension. Cephalalgia. 2021 Jan;41(1):6-16. doi: 10.1177/0333102420973994. Epub 2020 Dec 3.

7) Brandes JL, Diener HC, Dolezil D, Freeman MC, McAllister PJ, Winner P, Klatt J, Cheng S, Zhang F, Wen S, Ritter S, Lenz RA, Mikol DD. The spectrum of response to erenumab in patients with chronic migraine and subgroup analysis of patients achieving ≥50%, ≥75%, and 100% response. Cephalalgia. 2020 Jan;40(1):28-38. doi: 10.1177/0333102419894559. Epub 2019 Dec 9.

8) Ashina M, Kudrow D, Reuter U, Dolezil D, Silberstein S, Tepper SJ, Xue F, Picard H, Zhang F, Wang A, Zhou Y, Hong F, Klatt J, Mikol DD. Long-term tolerability and nonvascular safety of erenumab, a novel calcitonin gene-related peptide receptor antagonist for prevention of migraine: A pooled analysis of four placebo-controlled trials with long-term extensions. Cephalalgia. 2019 Dec;39(14):1798-1808. doi: 10.1177/0333102419888222. Epub 2019 Nov 10.

9) Lipton RB, Tepper SJ, Reuter U, Silberstein S, Stewart WF, Nilsen J, Leonardi DK, Desai P, Cheng S, Mikol DD, Lenz R. Erenumab in chronic migraine: Patient-reported outcomes in a randomized double-blind study. Neurology. 2019 May 7;92(19):e2250-e2260. doi: 10.1212/WNL.0000000000007452. Epub 2019 Apr 17.

10) Tepper SJ, Diener HC, Ashina M, Brandes JL, Friedman DI, Reuter U, Cheng S, Nilsen J, Leonardi DK, Lenz RA, Mikol DD. Erenumab in chronic migraine with medication overuse: Subgroup analysis of a randomized trial. Neurology. 2019 May 14;92(20):e2309-e2320. doi: 10.1212/WNL.0000000000007497. Epub 2019 Apr 17.

Study type and design	Multicentre, phase II, randomised, double-blinded placebo-controlled study. The study comprised four study periods consisting of an initial screening phase (up to three weeks), a four-week baseline phase, a 12-week double-blind treatment phase and a 12-week safety follow-up phase. Patients were randomised 3:2:2 to receive either placebo, erenumab 70 mg or erenumab 140 mg once every four weeks for the 12-week double-blind treatment phase. The randomisation was stratified by region (North America vs Europe) and medication overuse (presence vs absence). The patients received treatment by SC injections starting from baseline visit at day 1; hereafter, the patients were dosed after four weeks and eight weeks during the treatment phase (that is, a total of three doses). Patients, sponsor site personnel and study personnel were all masked to treatment assignment.
Sample size (n)	**Total population** Placebo: 286 patients Erenumab 70 mg: 191 patients Erenumab 140 mg: 190 patients **Failed at least two previous treatments** Placebo: 142 patients Erenumab 70 mg: 93 patients Erenumab 140 mg: 92 patients

Trial name: A study to evaluate the efficacy and safety of Erenumab in chronic migraine prevention	**NCT number**: NCT02066415
Main inclusion and exclusion criteria	**Inclusion criteria (from ClinicalTrials.gov):** • History of at least 5 attacks of migraine without aura and/or migraine with visual sensory, speech and/or language, retinal or brainstem aura. • History of ≥15 headache days per month of which ≥8 headache days were assessed by the subject as migraine day. • ≥4 distinct headache episodes, each lasting ≥4 hours OR if shorter, associated with use of a triptan or ergot-derivative on the same calendar day based on the e-Diary calculations. • Demonstrated at least 80% compliance with the e-Diary. **Exclusion criteria (from ClinicalTrials.gov):** • History of cluster headache or hemiplegic migraine headache. • Unable to differentiate migraine from other headaches. • Failed >3 medication categories due to lack of efficacy for prophylactic treatment of migraine. • Received botulinum toxin in head or neck region within four months prior to screening. • Used a prohibited migraine prophylactic medication, device or procedure within two months prior to the start of the baseline phase.
Intervention	• Erenumab 70 mg (administered subcutaneously) • Erenumab 140 mg (administered subcutaneously) Participants received erenumab 70 mg or erenumab 140 mg at day 1 and at week 4 and 8 hereafter.
Comparator(s)	Placebo to match intervention
Follow-up time	12 weeks
Is the study used in the health economic model?	No

Trial name: A study to evaluate the efficacy and safety of Erenumab in chronic migraine prevention	**NCT number**: NCT02066415
Primary, secondary and exploratory endpoints	**Primary endpoint (from ClinicalTrials.gov):** • Change from baseline in monthly migraine days: baseline and last four weeks of the 12-week treatment phase. **Secondary endpoints (from ClinicalTrials.gov):** • Percentage of participants with at least a 50% reduction in monthly migraine days from baseline: baseline and last four weeks of the 12-week treatment phase. • Change from baseline in monthly acute migraine-specific medication treatment days: baseline and last four weeks of the 12-week treatment phase. • Change from baseline in cumulative monthly headache hours: baseline and last four weeks of the 12-week treatment phase. • Number of participants with AEs: day 1 to week 24. • Number of participants who developed antibodies to erenumab: baseline and week 2, 4, 8, 12 and 24.
Method of analysis	Efficacy analyses of the never failed, ≥1, and ≥ 2 prior preventive treatment failure(s) subgroups were considered as prespecified and were planned before the unblinding of treatment assignment. Safety analyses for all subgroups and efficacy analyses of the subgroup with ≥3 prior preventive treatment failures were post hoc. Efficacy analyses comprised the primary endpoint of CfB in MMD and key secondary endpoints: Achievement of ≥50% and ≥75% reduction from baseline in MMD, and CfB in monthly acute MSMD (e.g., the use of triptans or ergots). Each erenumab group (70 mg or 140 mg) was compared to placebo (reference group). For continuous endpoints, adjusted analyses utilised a generalised linear mixed model, which included treatment, visit, treatment by visit interaction, the two stratification factors (region and medication overuse status) and baseline value as covariates, and assumed a first-order autoregressive covariance structure. Observed data were used in analyses without imputation for missing data. For dichotomous endpoints, odds ratios were estimated from a stratified Cochran-Mantel-Haenszel test after imputation of missing data as non-response. The main study was not designed or powered to compare differences in efficacy between subgroups. Subgroup analyses included here were not adjusted for multiplicity under a pre-specified hypothesis testing procedure. Statistical significance was determined by comparing descriptive p-values with a nominal significance level at p ≤0.05. AEs were tabulated for the subgroup without prior preventive treatment failure and the subgroups with ≥1, ≥2 and ≥3 prior preventive treatment failure(s) (30).

Trial name: A study to evaluate the efficacy and safety of Erenumab in chronic migraine prevention	**NCT number**: NCT02066415
Subgroup analyses	Subgroups were defined on the basis of prior migraine preventive treatment failure either for lack of efficacy and/or unacceptable tolerability, as recorded by the investigator. The number of prior preventive treatment failures for any given subject was based on medication categories. The never failed group included treatment-naïve patients and patients who had been exposed to a preventive treatment but did not fail it due to lack of efficacy and/or unacceptable tolerability. The following were classified as migraine preventive treatment categories: topiramate; beta blockers (e.g. propranolol or metoprolol); tricyclic antidepressants (e.g. amitriptyline or nortriptyline); divalproex sodium or sodium valproate; calcium channel blockers (e.g. flunarizine or verapamil); serotonin-norepinephrine reuptake inhibitors; botulinum toxin; antihypertensives (lisinopril or candesartan); or other medications (30).
Other relevant information	None

Table 74: Main characteristics of the FOCUS study

Trial name: An efficacy and safety study of Fremanezumab in adults with migraine	**NCT number:** NCT03308968
Objective	The purpose of this study is to evaluate the efficacy, safety, and tolerability of monthly and quarterly SC injections of fremanezumab compared with SC injections of placebo in participants with CM or EM who have responded inadequately to two to four classes of prior preventive treatments.
Publications – title, author, journal, year	**Publications automatically indexed to this study by NCT number** 1) MaassenVanDenBrink A, Terwindt GM, Cohen JM, Barash S, Campos VR, Galic M, Ning X, Kärppä M. Impact of age and sex on the efficacy of fremanezumab in patients with difficult-to-treat migraine: results of the randomized, placebo-controlled, phase 3b FOCUS study. J Headache Pain. 2021 Dec 18;22(1):152. doi: 10.1186/s10194-021-01336-1. 2) Nahas SJ, Naegel S, Cohen JM, Ning X, Janka L, Campos VR, Krasenbaum LJ, Holle-Lee D, Kudrow D, Lampl C. Efficacy and safety of fremanezumab in clinical trial participants aged ≥60 years with episodic or chronic migraine: pooled results from 3 randomized, double-blind, placebo-controlled phase 3 studies. J Headache Pain. 2021 Nov 24;22(1):141. doi: 10.1186/s10194-021-01351-2. 3) Ashina M, Cohen JM, Galic M, Campos VR, Barash S, Ning X, Kessler Y, Janka L, Diener HC. Efficacy and safety of fremanezumab in patients with episodic and chronic migraine with documented inadequate response to 2 to 4 classes of migraine preventive medications over 6 months of treatment in the phase 3b FOCUS study. J Headache Pain. 2021 Jul 10;22(1):68. doi: 10.1186/s10194-021-01279-7. 4) Pazdera L, Cohen JM, Ning X, Campos VR, Yang R, Pozo-Rosich P. Fremanezumab for the Preventive Treatment of Migraine: Subgroup Analysis by Number of Prior Preventive Treatments with Inadequate Response. Cephalalgia. 2021 Sep;41(10):1075-1088. doi: 10.1177/03331024211008401. Epub 2021 May 14. 5) Spierings ELH, Kärppä M, Ning X, Cohen JM, Campos VR, Yang R, Reuter U. Efficacy and safety of fremanezumab in patients with migraine and inadequate response to prior preventive treatment: subgroup analyses by country of a randomized, placebo-controlled trial. J Headache Pain. 2021 Apr 16;22(1):26. doi: 10.1186/s10194-021-01232-8. 6) Ferrari MD, Diener HC, Ning X, Galic M, Cohen JM, Yang R, Mueller M, Ahn AH, Schwartz YC, Grozinski-Wolff M, Janka L, Ashina M. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. Lancet. 2019 Sep 21;394(10203):1030-1040. doi: 10.1016/S0140-6736(19)31946-4. Epub 2019 Aug 16. Erratum in: Lancet. 2019 Oct 29;:.

Trial name: An efficacy and safety study of Fremanezumab in adults with migraine	**NCT number:** NCT03308968
Study type and design	International, multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3b trial. The study comprised several study periods consisting of an initial screening visit, a 28-day run-in period, a 12-week double-blind, placebo-controlled treatment period, a 12-week open-label period and a follow-up visit six months after the last treatment dose. Patients were randomly assigned 1:1:1 to receive subcutaneously administered placebo, monthly fremanezumab or quarterly fremanezumab during the 12-week treatment period. The randomisation was stratified by migraine classification (chronic or EM), sex, country and failure to two to three migraine preventive medication classes plus valproic, acid or valproate. The sponsor, investigators, study staff and participants were masked to treatment assignment during the double-blind period. The patients received treatment with fremanezumab or placebo by SC injections starting from baseline; hereafter, the patients were dosed once a month for two months (that is, a total of three doses).
Sample size (n)	**Total population** Placebo: 279 Monthly fremanezumab: 283 Quarterly fremanezumab: 276 **Patients with chronic migraine** Placebo: 167 Monthly fremanezumab: 173 Quarterly fremanezumab: 169

Trial name: An efficacy and safety study of Fremanezumab in adults with migraine	**NCT number:** NCT03308968

Main inclusion and exclusion criteria

Inclusion criteria (from ClinicalTrials.gov):

- The participant has a diagnosis of migraine with onset at ≤50 years of age.
- The participant has a body weight of ≥45 kilograms.
- The participant has a history of migraine for ≥12 months prior to screening.
- Women of childbearing potential (WOCBP) whose male partners are potentially fertile (that is; no vasectomy) must use highly effective birth control methods for the duration of the study and the follow-up period and for 6.0 months after discontinuation of investigational medicinal product (IMP).
- Men must be sterile, or if they are potentially fertile/reproductively competent (not surgically [that is; vasectomy] or congenitally sterile) and their female partners are of childbearing potential, must use, together with their female partners, acceptable birth control methods for the duration of the study and for 6 months after discontinuation of the IMP.

Exclusion criteria (from ClinicalTrials.gov):

- At the time of screening visit, participant is receiving any preventive migraine medications, regardless of the medical indication for more than five days and expects to continue with these medications.
- Participant has received onabotulinumtoxinA for migraine or for any medical or cosmetic reasons requiring injections in the head, face, or neck during the three months before screening visit.
- The participant has used an intervention/device (for example; scheduled nerve blocks and transcranial magnetic stimulation) for migraine during the two months prior to screening.
- The participant uses triptans/ergots as preventive therapies for migraine.
- Participant uses non-steroidal anti-inflammatory drugs (NSAIDs) as preventive therapy for migraine on nearly daily basis for other indications. Note: Low dose aspirin (for example; 81 mg) used for cardiovascular disease prevention is allowed.

Trial name: An efficacy and safety study of Fremanezumab in adults with migraine	**NCT number:** NCT03308968
Intervention	• Monthly fremanezumab treatment (administered subcutaneously with prefilled syringe) • Quarterly fremanezumab treatment (administered subcutaneously with prefilled syringe) For all participants, quarterly fremanezumab treatment consisted of subcutaneously administered fremanezumab 675 mg (three injections of fremanezumab 225 mg/1,5mL) as a first dose, followed by matched monthly placebo for two months. For participants with EM, monthly fremanezumab treatment consisted of subcutaneously administered fremanezumab 225 mg (one injection of fremanezumab 225mg/1.5mL) and two matching placebo injections as a first dose, followed by monthly fremanezumab 225 mg for two months. For participants with CM, monthly fremanezumab treatment consisted of subcutaneously administered fremanezumab 675 mg (three injections of fremanezumab 225 mg/1,5mL) as a first dose, followed by monthly fremanezumab 225 mg (one injection of fremanezumab 225mg/1.5mL) for two months.
Comparator(s)	Placebo. For all participants, placebo consisted of three subcutaneously administered injections as a first dose, followed by monthly single injections of placebo to match the intervention (see above).
Follow-up time	The study consisted of a screening visit, a run-in period (28 days), a 12-week double-blind, placebo-controlled treatment period, a 12-week open-label period, and a follow-up visit six months after the last dose of fremanezumab (31).
Is the study used in the health economic model?	No

Primary, secondary and exploratory endpoints	**Primary endpoint (from ClinicalTrials.gov):** • Change from baseline in monthly average number of migraine days during the 12-week period after the first dose of fremanezumab: baseline to week 12 **Secondary endpoint (from ClinicalTrials.gov):** • Percentage of participants reaching at least 50 percent (%) reduction from baseline in monthly average number of migraine days during the 12 week period after the first dose of fremanezumab: baseline to week 12 • Change from baseline in monthly average number of headache days of at least moderate severity during the 12 week period after the first dose of fremanezumab: baseline to week 12 • Change from baseline in monthly average number of migraine days during the 4 week period after the first dose of fremanezumab: baseline to week 4 • Percentage of participants reaching of least 50% reduction from baseline in monthly average number of migraine days during the 4 week period after the first dose of fremanezumab: baseline to week 4 • Change from baseline in monthly average number of days of use of any headache medication during the 12 week period after the first dose of fremanezumab: Baseline to week 12 • Change from baseline in monthly average number of headache days of at least moderate severity during the 4 week period after the first dose of fremanezumab: Baseline to week 4 • Number of participants with adverse events and who did not complete the study due to adverse events: Baseline to week 12 • Number of participants with adverse events and who did not complete the study due to adverse events: week 12 to 24 • Number of participants with potentially clinically significantly abnormal serum chemistry results: baseline to week 12 • Number of participants with potentially clinically significantly abnormal serum chemistry results: week 12 to 24 • Number of participants with potentially clinically significant abnormal hematology results: baseline to week 12 • Number of participants with potentially clinically significant abnormal hematology results: week 12 to 24 • Number of participants with potentially clinically significant abnormal coagulation laboratory test results: baseline to week 12 • Number of participants with potentially clinically significant abnormal coagulation laboratory test results: week 12 to 24 • Number of participants with potentially clinically significant abnormal urinalysis laboratory test results: baseline to week 12

	• Number of participants with potentially clinically significant abnormal urinalysis laboratory test results: week 12 to 24 • Number of participants with potentially clinically significant abnormal vital signs values: baseline to week 12 • Number of participants with potentially clinically significant abnormal vital signs values: week 12 to 24 • Number of participants with shift from baseline to week 12 in electrocardiogram parameters: baseline, week 12 • Number of participants with shift from baseline to week 24 in electrocardiogram parameters: baseline, week 24 • Number of participants who received concomitant medications for adverse events: baseline up to week 12 • Number of participants who received concomitant medications for adverse events: week 12 to 24
Method of analysis	The ITT analysis set comprised all randomly assigned participants. The safety analysis set comprised all randomly assigned participants who received at least one dose of study drug. Patients in the ITT analysis set who received at least one dose of study drug and had at least 10 days of post-baseline efficacy assessments for the primary outcome (modified ITT analysis set) were included in all efficacy analyses (31). The primary efficacy outcome was analysed with an analysis of covariance (ANCOVA) method with treatment, sex, region, special group of treatment failure, migraine classification, and treatment-by-migraine classification interaction as fixed effects and baseline number of migraine days and years since onset of migraine as covariates. Continuous secondary and exploratory efficacy outcomes were analysed in the same ways as the primary efficacy outcome. For the proportion of responders, a logistic regression model was used with the following effects: treatment, sex, region, special group of treatment failure (yes or no), and migraine classification (chronic or episodic). Stratification factors (as randomised) were used in the model. Patients who discontinued treatment early were considered non-responders for the overall analysis and for each month after discontinuation (31).
Subgroup analyses	A subgroup analysis was performed in the following subgroups: • Patients with inadequate response to prior treatment with two classes of migraine preventive medications • Patients with inadequate response to prior treatment with three classes of migraine preventive medications • Patients with inadequate response to prior treatment with four classes of migraine preventive medications.
Other relevant information	None

Table 75: Main characteristics of the CONQUER study

Trial name: A study of galcanezumab in adults with treatment-resistant migraine (CONQUER)	**NCT number:** NCT03559257
Objective	The objective of the study is to assess the safety and efficacy of galcanezumab in patients with migraine who have experienced previous unsuccessful treatment with preventive medications from two to four categories.
Publications – title, author, journal, year	**Publications automatically indexed to this study by NCT number** 1) Tepper SJ, Ailani J, Ford JH, Nichols RM, Li LQ, Kemmer P, Hand AL, Tockhorn-Heidenreich A. Effects of Galcanezumab on Health-Related Quality of Life and Disability in Patients with Previous Failure of 2-4 Migraine Preventive Medication Categories: Results from a Phase IIIb Randomized, Placebo-Controlled, Multicenter Clinical Trial (CONQUER). Clin Drug Investig. 2022 Jan 18. doi: 10.1007/s40261-021-01115-5. [Epub ahead of print] 2) Okonkwo R, Tockhorn-Heidenreich A, Stroud C, Paget MA, Matharu MS, Tassorelli C. Efficacy of galcanezumab in patients with migraine and history of failure to 3-4 preventive medication categories: subgroup analysis from CONQUER study. J Headache Pain. 2021 Sep 30;22(1):113. doi: 10.1186/s10194-021-01322-7. 3) Reuter U, Lucas C, Dolezil D, Hand AL, Port MD, Nichols RM, Stroud C, Tockhorn-Heidenreich A, Detke HC. Galcanezumab in Patients with Multiple Previous Migraine Preventive Medication Category Failures: Results from the Open-Label Period of the CONQUER Trial. Adv Ther. 2021 Nov;38(11):5465-5483. doi: 10.1007/s12325-021-01911-7. Epub 2021 Sep 20. 4) Citrome L, Sánchez Del Rio M, Dong Y, Nichols RM, Tockhorn-Heidenreich A, Foster SA, Stauffer VL. Benefit-Risk Assessment of Galcanezumab Versus Placebo for the Treatment of Episodic and Chronic Migraine Using the Metrics of Number Needed to Treat and Number Needed to Harm. Adv Ther. 2021 Aug;38(8):4442-4460. doi: 10.1007/s12325-021-01848-x. Epub 2021 Jul 15. 5) Kuruppu DK, Tobin J, Dong Y, Aurora SK, Yunes-Medina L, Green AL. Efficacy of galcanezumab in patients with migraine who did not benefit from commonly prescribed preventive treatments. BMC Neurol. 2021 Apr 23;21(1):175. doi: 10.1186/s12883-021-02196-7. 6) Schwedt TJ, Kuruppu DK, Dong Y, Standley K, Yunes-Medina L, Pearlman E. Early onset of effect following galcanezumab treatment in patients with previous preventive medication failures. J Headache Pain. 2021 Mar 25;22(1):15. doi: 10.1186/s10194-021-01230-w. 7) Mulleners W, Kim B, Láinez M, Lanteri-Minet M, Pozo-Rosich P, Wang S, et al. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial. The lancet Neurology. 2020;19(10):814-825.

Trial name: A study of galcanezumab in adults with treatment-resistant migraine (CONQUER)	**NCT number:** NCT03559257
Study type and design	Interventional, multicentre, randomised, placebo-controlled, double-blinded, parallel phase 3b study consisting of four study periods: a 3-30 day screening period, a one-month prospective baseline period, a three-month randomised, double-blinded, placebo-controlled treatment period and a three-month open-label treatment phase. Patients were randomised 1:1 to receive subcutaneously administered placebo or galcanezumab 120 mg. Randomisation was stratified by country and migraine frequency (low-frequency EM, high-frequency EM or chronic migraine). The patients received treatment by SC injections each month during a period of three months (that is, a total of three doses).
Sample size (n)	**Total population** Placebo: 230 patients Galcanezumab 120 mg: 232 patients **Chronic migraine population** Placebo: 98 patients Galcanezumab 120 mg: 95 patients

Trial name: A study of galcanezumab in adults with treatment-resistant migraine (CONQUER)	**NCT number:** NCT03559257
Main inclusion and exclusion criteria	**Inclusion criteria (from ClinicalTrials.gov):** • The patient has a diagnosis of migraine or chronic migraine. • The patient has a history of migraine headaches of at least one year prior to screening, and the migraine must have onset before the age of 50. • The patient has a history of at least four days with migraine headache and at least one day without migraine headache per month on average within the past three months. • The patient has a history of unsuccessful treatment with two to four standard-of-care migraine preventive medication categories in the past ten years due to inadequate efficacy and/or for safety/tolerability reasons. **Exclusion criteria (from ClinicalTrials.gov):** • The patient has a lifetime history of persistent daily headache, cluster headaches or migraine subtypes, such as hemiplegic migraine, ophthalmoplegic migraine and migraine with brainstem aura. • The patient has, within the last thirty days or five half-lives (whichever was longer), participated in or is currently enrolled in another clinical trial involving an investigational product. • The patient has a current use or prior exposure to galcanezumab or another CGRP antibody. • The patient is pregnant or nursing.
Intervention	Galcanezumab 120 mg (administered subcutaneously). Patients assigned to the treatment group received a loading dose of 240 mg galcanezumab, administered as two 120 mg injections at baseline (day 0 of the treatment period). Hereafter, the patients were dosed with 120 mg galcanezumab once every month for a total period of three months.
Comparator(s)	Placebo to match the intervention (see above). Patients assigned to the placebo group also received two injections at the first visit for masking purposes.
Follow-up time	The study comprised four study periods: a 3-to-30-day screening period; a one-month prospective baseline period to establish patient eligibility on the basis of responses regarding headaches as reported in an electronic diary (e-Diary); a three-month randomised, double-blind, placebo-controlled treatment phase; and a three-month open-label treatment phase. There is no follow-up period hereafter.

Trial name: A study of galcanezumab in adults with treatment-resistant migraine (CONQUER)	**NCT number:** NCT03559257
Is the study used in the health economic model?	No

Primary, secondary and exploratory endpoints	**Primary endpoint (from ClinicalTrials.gov):** • Overall mean change from baseline in the number of monthly migraine headache days in the total population: baseline, month 1 through month 3 **Secondary endpoints (from ClinicalTrials.gov):** • Overall mean change from baseline in the number of monthly migraine headache days in participants with episodic migraine: baseline, month 1 through month 3 • Percentage of participants with ≥50% reduction from baseline in monthly migraine headache days: baseline, month 1 through month 3 • Percentage of participants with episodic migraine with ≥50% reduction from baseline in monthly migraine headache day: baseline, month 1 through month 3 • Mean change from baseline in the role function-restrictive domains of the MSQ v2.1: baseline to month 3 • Mean change from baseline in the role function-restrictive domain score of the MSQ v2.1 in participants with episodic migraine: baseline to month 3 • Percentage of participants with episodic migraine with ≥75% reduction from baseline in monthly migraine headache days: baseline, month 1 through month 3 • Percentage of participants with episodic migraine with 100% reduction from baseline in monthly migraine headache days: baseline, month 1 through month 3 • Percentage of participants with ≥75% reduction from baseline in monthly migraine headache days: baseline, month 1 through month 3 • Percentage of participants with 100% reduction from baseline in monthly migraine headache days: baseline, month 1 through month 3 • Overall mean change from baseline in the number of monthly days with acute headache medication use: baseline, month 1 through month 3 • Overall mean change from baseline in the number of monthly headache days: baseline, month 1 through month 3 • Mean change from baseline in the migraine disability assessment test (MIDAS) total score: baseline to month 3 • Mean change from baseline in the 4-item migraine interictal burden scale (MIBS-4): baseline to month 3 • Mean change from baseline in the work productivity and activity impairment questionnaire (WPAI): baseline to month 3 • Mean change from baseline in the patient global impression of severity (PGI-S): baseline to month 3

	• Mean change from baseline in the European quality of life questionnaire 5 dimensions 5 Levels (EQ-5D-5L) - health state index (US): baseline to month 3 • Mean change from baseline in the EQ-5D-5L - health state index (UK): baseline to month 3 • Mean change from baseline in the EQ-5D-5L - VAS Score: baseline to month 3
Method of analysis	The efficacy and safety analysis population included all patients who were randomly assigned and received at least one dose of study drug. The primary treatment comparisons were the contrast between treatments over the entire three-month double-blind treatment phase unless otherwise specified in the protocol as at month 3. For the primary outcome, patients had to have had greater than 50% compliance with the e-Diary in a given month for the month to be considered assessable. The 95% CIs or SEs for the difference in least-squares means or ORs between treatment groups are shown. To control for type I error, the key secondary analyses were tested by means of a gated testing approach at a two-sided alpha level of 0·05. If the null hypothesis was rejected for the primary endpoint in the total population, key secondary endpoints were sequentially tested following the gatekeeping hierarchy. CfB of continuous variables with repeated measures was analysed by use of a restricted maximum likelihood-based repeated measures approach in combination with the Newton-Raphson algorithm. The model included the fixed, categorical effects of treatment, pooled country, month, and treatment-by-month interaction, as well as the continuous, fixed covariates of baseline value and baseline value-by-month interaction. Baseline migraine frequency category (low EM, high EM, and chronic migraine) was included when applicable. A common unstructured covariance structure was used to model the within-patient errors. If the model failed to converge, the Fisher scoring algorithm was implemented. If the model still failed to converge, the model was fit by means of covariance matrices in a subsequent order until model convergence was achieved: heterogeneous Toeplitz, heterogeneous first-order autoregressive, Toeplitz, first-order autoregressive. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. For continuous variables without repeated measures, the CfB to last-observation-carried-forward endpoint was analysed by use of an analysis of covariance model. Binary variables with repeated measures were analysed in a generalised linear mixed model as pseudo-likelihood-based mixed-effects repeated measures analysis. The model included the fixed, categorical effects of treatment month, and treatment-by-month interaction, as well as the continuous, fixed covariate of baseline value. Baseline migraine frequency category was included when applicable. For categorical efficacy variables without repeated measures, comparisons between treatment groups were done by use of logistic regressions. The logistic model included the main effect of treatment, baseline migraine frequency category, and appropriate baseline value as a covariate. For safety categorical variables and categorical variables of demographics and baseline characteristics, comparisons between treatment groups were done by use of Fisher's exact test. Analyses of the chronic migraine subpopulation were prespecified for the primary endpoint and for 30% response rate but were otherwise done post-hoc. Significance tests were based on least-squares means or ORs with a two-sided alpha of 0.05 (two-sided 95% CIs) (33).

Trial name: A study of galcanezumab in adults with treatment-resistant migraine (CONQUER)	**NCT number:** NCT03559257
Subgroup analyses	A subgroup analysis was performed in the following subgroups: • Patients aged 65-75 years • Patients with EM • Patients with CM
Other relevant information	None

Table 76: Main characteristics of the REGAIN study

Trial name: Evaluation of Galcanezumab in the prevention of chronic migraine	**NCT number:** NCT02614261
Objective	The objective of the study is to evaluate the efficacy and safety of galcanezumab in the preventive treatment of CM.

Publications – title, author, journal, year

Publications automatically indexed to this study by NCT number

1) Ailani J, Kuruppu DK, Rettiganti M, Oakes T, Schroeder K, Wietecha L, Port M, Blumenfeld AM. Does "wearing off" of efficacy occur in galcanezumab-treated patients at the end of the monthly treatment cycle? Post hoc analyses of four phase III randomized trials. Headache. 2022 Feb;62(2):198-207. doi: 10.1111/head.14257. Epub 2022 Jan 25.

2) Citrome L, Sánchez Del Rio M, Dong Y, Nichols RM, Tockhorn-Heidenreich A, Foster SA, Stauffer VL. Benefit-Risk Assessment of Galcanezumab Versus Placebo for the Treatment of Episodic and Chronic Migraine Using the Metrics of Number Needed to Treat and Number Needed to Harm. Adv Ther. 2021 Aug;38(8):4442-4460. doi: 10.1007/s12325-021-01848-x. Epub 2021 Jul 15.

3) Pozo-Rosich P, Samaan KH, Schwedt TJ, Nicholson RA, Rettiganti M, Pearlman EM. Galcanezumab Provides Consistent Efficacy Throughout the Dosing Interval Among Patients with Episodic and Chronic Migraine: A Post Hoc Analysis. Adv Ther. 2021 Jun;38(6):3154-3165. doi: 10.1007/s12325-021-01708-8. Epub 2021 May 5.

4) Ament M, Day K, Stauffer VL, Skljarevski V, Rettiganti M, Pearlman E, Aurora SK. Effect of galcanezumab on severity and symptoms of migraine in phase 3 trials in patients with episodic or chronic migraine. J Headache Pain. 2021 Feb 6;22(1):6. doi: 10.1186/s10194-021-01215-9. Erratum in: J Headache Pain. 2021 Aug 26;22(1):100.

5) Kuruppu DK, North JM, Kovacik AJ, Dong Y, Pearlman EM, Hutchinson SL. Onset, Maintenance, and Cessation of Effect of Galcanezumab for Prevention of Migraine: A Narrative Review of Three Randomized Placebo-Controlled Trials. Adv Ther. 2021 Mar;38(3):1614-1626. doi: 10.1007/s12325-021-01632-x. Epub 2021 Feb 5. Review.

6) Dodick DW, Doty EG, Aurora SK, Ruff DD, Stauffer VL, Jedynak J, Dong Y, Pearlman EM. Medication overuse in a subgroup analysis of phase 3 placebo-controlled studies of galcanezumab in the prevention of episodic and chronic migraine. Cephalalgia. 2021 Mar;41(3):340-352. doi: 10.1177/0333102420966658. Epub 2020 Nov 3.

7) Ailani J, Andrews JS, Rettiganti M, Nicholson RA. Impact of galcanezumab on total pain burden: findings from phase 3 randomized, double-blind, placebo-controlled studies in patients with episodic or chronic migraine (EVOLVE-1, EVOLVE-2, and REGAIN trials). J Headache Pain. 2020 Oct 17;21(1):123. doi: 10.1186/s10194-020-01190-7.

8) Ford J, Tassorelli C, Leroux E, Wang S, Ayer D, Nichols R, Detke H. Changes in patient functioning and disability: results from a phase 3, double-blind, randomized, placebo-controlled clinical trial evaluating galcanezumab for chronic migraine prevention (REGAIN). Qual Life Res. 2021 Jan;30(1):105-115. doi: 10.1007/s11136-020-02623-1. Epub 2020 Sep 15.

9) Stauffer VL, Turner I, Kemmer P, Kielbasa W, Day K, Port M, Quinlan T, Camporeale A. Effect of age on pharmacokinetics, efficacy, and safety of galcanezumab treatment in adult patients with migraine: results from six phase 2 and phase 3 randomized clinical trials. J Headache Pain. 2020 Jun 23;21(1):79. doi: 10.1186/s10194-020-01148-9.

10) Bangs ME, Kudrow D, Wang S, Oakes TM, Terwindt GM, Magis D, Yunes-Medina L, Stauffer VL. Safety and tolerability of monthly galcanezumab injections in patients with migraine: integrated results from migraine clinical studies. BMC Neurol. 2020 Jan 17;20(1):25. doi: 10.1186/s12883-020-1609-7. Erratum in: BMC Neurol. 2020 Mar 13;20(1):90.

11) Kielbasa W, Quinlan T. Population Pharmacokinetics of Galcanezumab, an Anti-CGRP Antibody, Following Subcutaneous Dosing to Healthy Individuals and Patients With Migraine. J Clin Pharmacol. 2020 Feb;60(2):229-239. doi: 10.1002/jcph.1511. Epub 2019 Sep 4.

12) Ruff DD, Ford JH, Tockhorn-Heidenreich A, Sexson M, Govindan S, Pearlman EM, Wang SJ, Khan A, Aurora SK. Efficacy of galcanezumab in patients with chronic migraine and a history of preventive treatment failure. Cephalalgia. 2019 Jul;39(8):931-944. doi: 10.1177/0333102419847957. Epub 2019 May 19.

13) Förderreuther S, Zhang Q, Stauffer VL, Aurora SK, Láinez MJA. Preventive effects of galcanezumab in adult patients with episodic or chronic migraine are persistent: data from the phase 3, randomized, double-blind, placebo-controlled EVOLVE-1, EVOLVE-2, and REGAIN studies. J Headache Pain. 2018 Dec 29;19(1):121. doi: 10.1186/s10194-018-0951-2.

14) Nichols R, Doty E, Sacco S, Ruff D, Pearlman E, Aurora SK. Analysis of Initial Nonresponders to Galcanezumab in Patients With Episodic or Chronic Migraine: Results From the EVOLVE-1, EVOLVE-2, and REGAIN Randomized, Double-Blind, Placebo-Controlled Studies. Headache. 2019 Feb;59(2):192-204. doi: 10.1111/head.13443. Epub 2018 Nov 21.

15) Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. Neurology. 2018 Dec 11;91(24):e2211-e2221. doi: 10.1212/WNL.0000000000006640. Epub 2018 Nov 16.

Study type and design	Phase 3, randomised, double-blind, placebo-controlled trial. The study comprised three study periods consisting of a 3 month randomised, double-blind, placebo-controlled treatment period, a 9 month open-label extension period and a 4 month posttreatment period. Patients were randomised 2:1:1 to receive monthly subcutaneously administered injections of either placebo, galcanezumab 120 mg (with a loading dose of 240 mg) or galcanezumab 240 mg for the 3 month double-blind period.
Sample size (n)	**Total population** Placebo: 558 patients Galcanezumab 120 mg: 278 patients Galcanezumab 240 mg: 277 patients **Population who has previously failed at least two migraine treatments** Placebo: 177 patients Galcanezumab 120 mg: 74 patients Galcanezumab 240 mg: 105 patients

Trial name: Evaluation of Galcanezumab in the prevention of chronic migraine	**NCT number:** NCT02614261
Main inclusion and exclusion criteria	**Inclusion criteria (from ClinicalTrials.gov):** • Have a diagnosis of chronic migraine as defined by International Headache Society (IHS) ICHD-3 beta guidelines (1.3) (ICHD-3 2013), with a history of migraine headaches of at least 1 year prior to screening, and migraine onset prior to age 50. **Exclusion criteria (from ClinicalTrials.gov):** • Are currently enrolled in or have participated within the last 30 days or within 5 half-lives (whichever is longer) in a clinical trial involving an investigational product. • Current use or prior exposure to galcanezumab or another CGRP antibody. • Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to galcanezumab. • History of persistent daily headache, cluster headache or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and migraine with brainstem aura (basilar-type migraine) defined by IHS ICHD-3 beta.
Intervention	• Galcanezumab 120 mg (administered subcutaneously) • Galcanezumab 240 mg (administered subcutaneously)
Comparator(s)	Placebo to match the intervention (see above).
Follow-up time	The study comprised three study periods consisting of a 3 month randomised, double-blind, placebo-controlled treatment period, a 9 month open-label extension period and a 4 month posttreatment period.
Is the study used in the health economic model?	No

Trial name: Evaluation of Galcanezumab in the prevention of chronic migraine	**NCT number:** NCT02614261
Primary, secondary and exploratory endpoints	**Primary endpoint (from ClinicalTrials.gov):** • Overall mean change from baseline in the number of monthly migraine headache days: baseline, month 1 through month 3 **Secondary endpoints (from ClinicalTrials.gov):** • Number of participants with reduction from baseline ≥50%, ≥75% and 100% in monthly migraine headache days: baseline, month 1 through month 3 • Mean change from baseline in the MSQ RF-R domain: baseline, month 3 • Overall mean change from baseline in the number of monthly migraine headache days requiring medication for the acute treatment of migraine or headache: baseline, month 1 through month 3 • Mean change from baseline in the PGI-S score: baseline to month 3 • Overall mean change from baseline in headache hours: baseline, month 1 through month 3 • Overall mean change from baseline on the MIDAS total score: baseline to month 3 • Percentage of participants developing anti-drug antibodies (ADA) to galcanezumab: baseline, month 1 through month 3 • Pharmacokinetics (PK): area under the concentration time curve (AUC) of galcanezumab: baseline to month 3 • Plasma concentration of CGRP: 3 months • Serum concentrations of galcanezumab: 3 months

Trial name: Evaluation of Galcanezumab in the prevention of chronic migraine	**NCT number:** NCT02614261
Method of analysis	Analyses were performed on the ITT population, which included all patients who received at least one dose of galcanezumab or placebo. Subgroup analyses for repeated continuous and binary measures were conducted using restricted maximum likelihood-based mixed models with repeated measures (MMRM) and generalised linear mixed model, respectively. Overall mean CfB, which was the average mean CfB across months 1–3, was estimated from the model. Response rates were calculated as the mean percentage of responders using the categorical, pseudo–likelihood-based repeated-measures analysis assessing overall response rate across months 1, 2, and 3. Treatment-by-subgroup interactions were included in the models. Baseline acute medication overuse status (presence or absence) was included within the statistical model. Failures to prior preventive treatments were determined on the basis of reasons for stopping prior preventives listed on the prior therapy case report form, which collected any migraine preventive medications that had been taken in the past 5 years. Failure to prior preventive treatment was defined as cessation of drug for efficacy-related reasons (''non-response'' or ''inadequate response'') or safety/tolerability reasons. Preventive treatments reported by the clinical investigative sites were further restricted to medications identified in the treatment guidelines as having been investigated for preventive use and having at least level C evidence of efficacy based on American Academy of Neurology/American Headache Society treatment guidelines (34).
Subgroup analyses	Subgroup analyses were conducted among patients who failed ≥2 and ≥1 prior preventives and who never failed previously.
Other relevant information	None.

Table 77: Main characteristics of the LIBERTY study (erenumab)

Trial name: Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study (LIBERTY)	**NCT number: NCT03096834**
Objective	The aim of the study was to compare the efficacy and tolerability of erenumab with placebo in a well-defined group of patients with episodic migraine who had previously not responded adequately to two-to-four preventive treatments, or who could not tolerate these treatments (35).
Publications – title, author, journal, year	**Publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):** 1) Ferrari MD, Reuter U, Goadsby PJ, Paiva da Silva Lima G, Mondal S, Wen S, Tenenbaum N, Pandhi S, Lanteri-Minet M, Stites T. Two-year efficacy and safety of erenumab in participants with episodic migraine and 2-4 prior preventive treatment failures: results from the LIBERTY study. J Neurol Neurosurg Psychiatry. 2022 Mar;93(3):254-262. doi: 10.1136/jnnp-2021-327480. Epub 2021 Nov 29. 2) Goadsby PJ, Reuter U, Lanteri-Minet M, Paiva da Silva Lima G, Hours-Zesiger P, Fernandes C, Wen S, Tenenbaum N, Kataria A, Ferrari MD, Klatt J. Long-Term Efficacy and Safety of Erenumab: Results From 64 Weeks of the LIBERTY Study. Neurology. 2021 Apr 28. pii: 10.1212/WNL.0000000000012029. doi: 10.1212/WNL.0000000000012029. [Epub ahead of print] 3) Lanteri-Minet M, Goadsby PJ, Reuter U, Wen S, Hours-Zesiger P, Ferrari MD, Klatt J. Effect of erenumab on functional outcomes in patients with episodic migraine in whom 2-4 preventives were not useful: results from the LIBERTY study. J Neurol Neurosurg Psychiatry. 2021 May;92(5):466-472. doi: 10.1136/jnnp-2020-324396. Epub 2021 Jan 5. 4) Reuter U, Goadsby PJ, Lanteri-Minet M, Wen S, Hours-Zesiger P, Ferrari MD, Klatt J. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. Lancet. 2018 Nov 24;392(10161):2280-2287. doi: 10.1016/S0140-6736(18)32534-0. Epub 2018 Oct 22.
Study type and design	A 12-week, randomised, double-blind, placebo-controlled phase 3b study. Patients were randomly assigned (1:1) to either placebo or erenumab via interactive response technology. The randomisation list was generated by Cenduit, a vendor providing interactive voice response services. Cenduit also allocated participants to groups. Randomisation was stratified by monthly frequency of migraine headache (4–7 vs 8–14 migraine days per month) during the baseline phase (35).

Trial name: Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study (LIBERTY)	**NCT number: NCT03096834**
Sample size (n)	246 were randomly assigned: 121 to the erenumab group and 125 to the placebo group. 118 patients in the erenumab arm and 122 in the placebo arm completed the double-blind treatment phase (35).
Main inclusion and exclusion criteria	**Inclusion criteria (from ClinicalTrials.gov):** • Documented history of migraine in the 12 months prior to screen • 4-14 days per month of migraine symptoms • >=80% diary compliance during the baseline period • Failure of previous migraine prophylactic treatments **Exclusion criteria (from ClinicalTrials.gov):** • >50 years old at migraine onset • Pregnant or nursing • History of cluster or hemiplegic headache • Evidence of seizure or psychiatric disorder • Score of over 19 on Beck Depression Inventory-2 • Active chronic pain syndrome • Cardiac or hepatic disease
Intervention	Erenumab. Patients in the erenumab group received two subcutaneous injections of erenumab 70 mg/1 mL (total dose 140 mg).
Comparator(s)	Placebo. Those in the placebo group received a matching dose of placebo.
Follow-up time	The study included a screening phase (0–2 weeks), baseline phase (four weeks), double-blind treatment phase (12 weeks), open-label treatment phase (156 weeks) and a follow-up phase (12 weeks).
Is the study used in the health economic model?	No

Trial name: Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study (LIBERTY)	**NCT number: NCT03096834**
Primary, secondary and exploratory endpoints	The primary endpoint (35): • Proportion of patients who achieved at least a 50% reduction from their individual baseline in the number of MMDs during the third month of the double-blind treatment phase (i.e., weeks 9–12). A migraine day was defined as any calendar day on which the patient had onset, continuation, or recurrence of a qualified migraine as recorded in the e-Diary. A qualified migraine was defined as a migraine with or without aura lasting at least 30 min and manifesting with at least two headache features or at least one associated non-headache feature, or both. Any calendar day on which acute migraine-specific medication was used was also counted as a migraine day. Secondary efficacy endpoints (35): • CfB in MMDs • CfB in monthly acute migraine-specific medication days (including triptans or ergotamine derivatives) • Proportion of patients with a 75% or greater or 100% reduction from baseline in MMDs • CfB in scores on the everyday activities and physical activity subdomains of the Migraine Physical Function Impact Diary All secondary efficacy endpoints were assessed for weeks 9–12 of the double-blind treatment phase. The primary and secondary efficacy endpoints were also analysed at weeks 0–4 and weeks 5–8 as exploratory endpoints to assess the overall time course of efficacy. Safety, tolerability, and immunogenicity were also assessed by recording observed or reported adverse events and by physical examination, measurement of vital signs, clinical laboratory assessments and electrocardiography (ECG).

Method of analysis	The randomised analysis set included all randomly assigned patients (i.e., ITT population) and was the basis for summaries of patient disposition, demographics and baseline disease characteristics. The full analysis set, which was used for efficacy analyses, included all randomly assigned patients who started their study medication, completed at least one post-baseline monthly migraine day measurement in the double-blind treatment phase, and were analysed on the basis of the pre-planned randomised treatment. The safety analysis set included all randomly assigned patients who received at least one dose of study drug. Analyses were based on actual treatment received. Demographic variables and other baseline characteristics were summarised with descriptive statistics. We used the Cochran-Mantel-Haenszel test to measure the association between 50% responder rate and treatment group; analysis was stratified by migraine frequency, with a one-sided significance level of 0.025 (0.05 two-sided). ORs, 95% CIs, and two-sided p values are reported. Patients with missing data for monthly migraine days at month 3 of the double-blind treatment phase were imputed as non-responders. The continuous change from baseline efficacy endpoints (least-square means) was analysed with a linear mixed-effects model, including treatment group, baseline value, stratification factors, study visit, and the interaction of treatment group with study visit, without any imputation for missing data (35). The dichotomous secondary efficacy endpoints derived from corresponding continuous endpoints were analysed with the stratified Cochran-Mantel-Haenszel test after imputation of missing data as non-response. Estimates (treatment difference or OR) of erenumab compared with placebo with associated 95% CI and p values are reported. For continuous variables, $p_{interaction}$ was defined from the modified primary model with additional terms of subgroup and subgroup-by-treatment-group interaction as two additional effects. For the subgroup of dichotomous variables, $p_{interaction}$ was calculated via logistic regression that included treatment group, stratification factor, subgroup factor, and treatment-by-subgroup-factor interaction as fixed effects, with the baseline value as covariate (35). The adjusted mean changes from baseline, SEs and 95% CIs for each subgroup and the nominal p value for subgroup-by-treatment interactions were calculated. For safety analyses, the Medical Dictionary for Regulatory Activities (version 20.1) was used to code all AEs. AEs were tabulated as participant incidence and exposure-adjusted participant incidence. Summary statistics were provided for laboratory data, ECG, vital signs and immunogenicity assessments. We used SAS (version 9.4) for all statistical analyses (35).
Subgroup analyses	In previous studies of erenumab for prevention of episodic migraine, patients in whom more than two drug classes were not effective were excluded. A post-hoc analysis of the primary and secondary efficacy endpoints at week 12 on the basis of treatment failure of previous preventive medication (two treatment failures vs more than two treatment failures) (35).

Trial name: Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study (LIBERTY)	**NCT number: NCT03096834**
Other relevant information	The study was only used in a pooled EM/CM analysis of discontinuation due to low drop-out rates.

Table 78: Main characteristics of the STRIVE study (erenumab)

Trial name: A Controlled Trial of Erenumab for Episodic Migraine (STRIVE)	**NCT number:** NCT02456740
Objective	To evaluate the efficacy and safety of erenumab in migraine prevention

Publications – title, author, journal, year

Publications:

1) Buse DC, Lipton RB, Hallström Y, Reuter U, Tepper SJ, Zhang F, Sapra S, Picard H, Mikol DD, Lenz RA. Migraine-related disability, impact, and health-related quality of life among patients with episodic migraine receiving preventive treatment with erenumab. Cephalalgia. 2018 Sep;38(10):1622-1631. doi: 10.1177/0333102418789072. Epub 2018 Aug 7.

2) Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, Sapra S, Picard H, Mikol DD, Lenz RA. A Controlled Trial of Erenumab for Episodic Migraine. N Engl J Med. 2017 Nov 30;377(22):2123-2132. doi: 10.1056/NEJMoa1705848.

3) Sunfa Cheng, Herman Picard, Feng Zhang, Osa Eisele, Daniel Mikol. Efficacy and safety of erenumab for migraine prevention: an overview. Japanese Journal of Headache 45(3): 493-505, 2019.

4) Zhou Y, Zhang F, Starcevic Manning M, Hu Z, Hsu CP, Chen PW, Peng C, Loop B, Mytych DT, Paiva da Silva Lima G. Immunogenicity of erenumab: A pooled analysis of six placebo-controlled trials with long-term extensions. Cephalalgia. 2022 Mar 10:3331024221075621. doi: 10.1177/03331024221075621. [Epub ahead of print]

5) Ashina M, Goadsby PJ, Dodick DW, Tepper SJ, Xue F, Zhang F, Brennan F, Paiva da Silva Lima G. Assessment of Erenumab Safety and Efficacy in Patients With Migraine With and Without Aura: A Secondary Analysis of Randomized Clinical Trials. JAMA Neurol. 2022 Feb 1;79(2):159-168. doi: 10.1001/jamaneurol.2021.4678.

6) Lipton RB, Dodick DW, Kudrow D, Reuter U, Tenenbaum N, Zhang F, Lima GPDS, Chou DE, Mikol DD. Reduction in migraine pain intensity in patients treated with erenumab: A post hoc analysis of two pivotal randomized studies. Cephalalgia. 2021 Dec;41(14):1458-1466. doi: 10.1177/03331024211028966. Epub 2021 Aug 18.

7) Tepper SJ, Ashina M, Reuter U, Hallström Y, Broessner G, Bonner JH, Picard H, Cheng S, Chou DE, Zhang F, Klatt J, Mikol DD. Reduction in acute migraine-specific and non-specific medication use in patients treated with erenumab: post-hoc analyses of episodic and chronic migraine clinical trials. J Headache Pain. 2021 Jul 23;22(1):81. doi: 10.1186/s10194-021-01292-w.

8) Diener HC, Ashina M, Ritter S, Paiva Da Silva Lima G, Rasmussen S, Zielman R, Tfelt-Hansen P. Erenumab prevents the occurrence of migraine attacks and not just migraine days: Post-hoc analyses of a phase III study. Cephalalgia. 2021 Oct;41(11-12):1262-1267. doi: 10.1177/03331024211010308. Epub 2021 May 3.

9) Broessner G, Reuter U, Bonner JH, Dodick DW, Hallström Y, Picard H, Zhang F, Lenz RA, Klatt J, Mikol DD. The Spectrum of Response to Erenumab in Patients With Episodic Migraine and Subgroup Analysis of Patients Achieving ≥50%, ≥75%, and 100% Response. Headache. 2020 Oct;60(9):2026-2040. doi: 10.1111/head.13929. Epub 2020 Aug 26.

10) Pavlovic JM, Paemeleire K, Göbel H, Bonner J, Rapoport A, Kagan R, Zhang F, Picard H, Mikol DD. Efficacy and safety of erenumab in women with a history of menstrual migraine. J Headache Pain. 2020 Aug 3;21(1):95. doi: 10.1186/s10194-020-01167-6.

11) Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, Wright IK, Chou DE, Klatt J, Picard H, Lenz RA, Mikol DD. One-year sustained efficacy of erenumab in episodic migraine: Results of the STRIVE study. Neurology. 2020 Aug 4;95(5):e469-e479. doi: 10.1212/WNL.0000000000010019. Epub 2020 Jul 7.

12) Ashina M, Kudrow D, Reuter U, Dolezil D, Silberstein S, Tepper SJ, Xue F, Picard H, Zhang F, Wang A, Zhou Y, Hong F, Klatt J, Mikol DD. Long-term tolerability and nonvascular safety of erenumab, a novel calcitonin gene-related peptide receptor antagonist for prevention of migraine: A pooled analysis of four placebo-controlled trials with long-term extensions. Cephalalgia. 2019 Dec;39(14):1798-1808. doi: 10.1177/0333102419888222. Epub 2019 Nov 10.

Study type and design	A multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trial. Patients were randomly assigned in a 1:1:1 ratio to receive monthly subcutaneous injections of 70 mg of erenumab, 140 mg of erenumab, or placebo at day 1 and weeks 4, 8, 12, 16, and 20, administered by trained staff at the trial sites. Randomisation was based on a schedule that had been generated by the sponsor before initiation of the trial and was centrally executed with the use of an interactive voice or web response system. 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). The patients, site personnel, and trial-sponsor personnel were not aware of the trial-group assignments (27).
Sample size (n)	A total of 955 patients underwent randomisation (317 to the 70 mg erenumab group, 319 to the 140 mg erenumab group, and 319 to the placebo group), and 858 patients (89.8%) completed the six-month double-blind treatment phase (27).

Trial name: A Controlled Trial of Erenumab for Episodic Migraine (STRIVE)	**NCT number:** NCT02456740
Main inclusion and exclusion criteria	**Inclusion criteria (from ClinicalTrials.gov):** • History of migraine (with or without aura) for ≥12 months prior to screening according to the IHS ICHD-3 classification • Migraine frequency: ≥4 and <15 migraine days per month on average across the three months prior to screening and during baseline • Headache frequency: <15 headache days per month on average across the three months prior to screening and baseline • Demonstrated at least 80% compliance with the e-Diary **Exclusion criteria (from ClinicalTrials.gov):** • Older than 50 years of age at migraine onset • History of cluster headache or hemiplegic migraine headache • Unable to differentiate migraine from other headache • No therapeutic response with >2 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial • Used a prohibited medication, device, or procedure within two months prior to the start of the baseline phase or during the baseline phase • Concomitant use of two or more medications with possible migraine prophylactic effects within two months prior to the start of the baseline phase or during the baseline phase. If only one prophylactic medication is used, the dose must be stable within two months prior to the start of the baseline phase and throughout the study.
Intervention	Monthly subcutaneous injections of 70 mg of erenumab, 140 mg of erenumab
Comparator(s)	Placebo to match intervention
Follow-up time	The trial had four phases: screening (≤3 weeks of initial screening and a four-week baseline phase), the double-blind treatment phase (24 weeks), the active treatment phase, in which patients underwent repeat randomisation and were assigned to receive 70 mg or 140 mg of erenumab (28 weeks), and a safety follow-up phase (12 weeks) (27).

Trial name: A Controlled Trial of Erenumab for Episodic Migraine (STRIVE)	**NCT number:** NCT02456740
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	The primary objective of the trial was to compare erenumab with placebo with regard to the primary endpoint of the change in mean number of migraine days per month from baseline to the final three months (months 4 through 6) of the double-blind treatment phase. A migraine day was defined as any calendar day on which the patient had onset, continuation, or recurrence of a qualified migraine as recorded in the electronic diary. A qualified migraine was defined as a migraine (with or without aura) lasting at least 30 minutes and manifesting with at least two pain features, at least one associated non-pain feature, or both. Any calendar day on which acute migraine–specific medication was used was counted as a migraine day (27). The first-tier secondary endpoints were at least a 50% reduction from baseline in the mean number of migraine days per month and the change from baseline in the mean number of days of use of acute migraine-specific medication (including triptans or ergotamine derivatives) per month, and the second-tier secondary endpoints were the change from baseline in both the MPFID-PI score and MPFID-EA score. Secondary endpoints were assessed and averaged over the final three months of the double-blind treatment phase (27).
Method of analysis	The primary endpoint and continuous secondary endpoints were analysed with the use of a linear mixed-effects model without any imputation of missing data. Sensitivity analyses were conducted with multiple imputation under missing-at-random and missing-not-at-random assumptions. For the secondary endpoint of a 50% or greater reduction in mean MMDs, a stratified Cochran–Mantel–Haenszel test was used after imputation of missing data as non-response. Sensitivity analyses for this endpoint included a generalised linear mixed-effects model without any imputation of missing data. The significance of the between-group differences with regard to the primary and secondary endpoints was determined after multiplicity adjustment with a pre-specified hierarchical gatekeeping procedure and Hochberg-based testing procedures to maintain the two-sided, study-wise, type I error rate at an alpha level of 0.05. The primary endpoint was tested separately for each erenumab dose at an alpha level of 0.04 for 70 mg and of 0.01 for 140 mg. First-tier and second-tier secondary endpoints were then tested sequentially with the use of the procedure. The full analysis set in the final protocol included all the patients who underwent randomisation. The efficacy endpoints are reported with the use of the following efficacy analysis set: patients who received at least one dose of erenumab or placebo and had at least one post-baseline measurement for migraine days per month during the double-blind treatment phase, analysed according to randomly assigned trial regimen. The efficacy analysis set meets the criteria for a full analysis set. The safety analysis set included all the patients who underwent randomisation and received at least one dose of erenumab or placebo, analysed according to randomly assigned trial regimen unless the dose received throughout the double-blind treatment phase differed from the one that had been randomly assigned (27).

Trial name: A Controlled Trial of Erenumab for Episodic Migraine (STRIVE)		**NCT number:** NCT02456740
Subgroup analyses	None mentioned	
Other relevant information	The study was only used in a pooled EM/CM analysis of discontinuation due to low drop-out rates.	

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 79: Baseline characteristics of patients in DELIVER and Ashina et al. 2018 applied in the comparative analysis of efficacy and safety of eptinezumab and erenumab

	DELIVER				Ashina et al. 2018			
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Erenumab 70 mg (n: 93)	Erenumab 140 mg (n: 92)	Placebo (n: 142)	Total (n: 327)
Age (years)								
Mean (SD)	44.6 (10.76)	43.1 (10.2)	43.8 (10.83)	43.8 (10.61)	42.9 (11.2)	44.2 (10.6)	42.9 (11.5)	NR
Median (min, max)	46 (18,74)	44 (18, 66)	44 (18,73)	44.5 (18,74)	NR	NR	NR	NR
Gender, n (%)								
Males	22 (7.4)	33 (11.3)	35 (11.7)	90 (10.1)	9 (9.7)[2]	10 (10.9)[2]	31 (21.8)[2]	50 (15.3)[2]
Females	277 (92.6)	260 (88.7)	263 (88.3)	800 (89.9)	84 (90.3)	82 (89.1)	111 (78.2)	277 (84.7)[1]
Time since diagnosis	18.4 (11.62)	16.8 (10.91)	17.7 (11.51)	17.6 (11.36)	25.2 (13.2)	24.6 (11.7)	24 (12.9)	NR
Duration of current chronic migraine diagnosis (years)	12.9 (12.06)	10.3 (8.89)	11 (10.91)	11.4 (10.8)	NR	NR	NR	NR
Race, n (%)								
White	288 (96.3)	281 (95.9)	285 (95.6)	854 (96)	NR	NR	NR	NR

	DELIVER				Ashina et al. 2018			
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Erenumab 70 mg (n: 93)	Erenumab 140 mg (n: 92)	Placebo (n: 142)	Total (n: 327)
Other	-	-	2 (0.7)	2 (0.2)	NR	NR	NR	NR
Unknown	11 (3.7)	12 (4.1)	11 (3.7)	34 (3.8)	NR	NR	NR	NR
Ethnicity*, n (%)					NR	NR	NR	NR
Hispanic or Latino	-	1 (0.3)	-	1 (0.1)	NR	NR	NR	NR
Not Hispanic or Latino	1 (0.3)	2 (0.7)	2 (0.7)	5 (0.6)	NR	NR	NR	NR
Not collected	298 (99.7)	290 (99.0)	296 (99.3)	884 (99.3)	NR	NR	NR	NR
Medication overuse headache diagnosis, n (%)	38 (12.7)	35 (11.9)	37 (12.4)	110 (12.4)	45 (48.4)	40 (43.5)	63 (44.4)	NR
Baseline MMDs								
Mean ±SD	13.9 (5.7)	13.8 (5.6)	13.7 (5.4)	-	18 (4.4)	18.8 (4.4)	18.3 (4.5)	NF
Baseline MHDs								
Mean ±SD	14.5 (5.6)	14.4 (5.4)	14.5 (5.8)	-	NR	NR	NR	NR

	DELIVER				Ashina et al. 2018			
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Erenumab 70 mg (n: 93)	Erenumab 140 mg (n: 92)	Placebo (n: 142)	Total (n: 327)
Use of MSM, n (%)	NR	NR	NR	NR	82 (88.2)	84 (91.3)	125 (88)	-
Monthly MSMD	NR	NR	NR	NR	10.5 (7.2)	12.4 (6.2)	11.4 (7.4)	-

[1]The value is calculated by adding the female patients in each treatment group and the percentage is calculated as the proportion of female patients of the total population.[2]Calculated based on proportion of females.

Comparability of patients across studies

In the DELIVER trial and NCT02066415 (published in Ashina et al. 2018), the mean age of the patients ranged between 42.9 and 44.6 years. Both studies have an overweight of female patients (89.9% in DELIVER and 84.7 in NCT02066415). The proportion of male patients is only stated in the DELIVER trial, where it ranged between 7.4% and 11.7%. The mean time since diagnosis varied between 16.8 and 18.4 years in DELIVER and 24 and 25.2 years in NCT02066415, indicating a small difference in mean time since diagnosis across the two studies. Duration of current CM diagnosis is only mentioned in DELIVER, where it ranged between 10.3 and 12.9 years. The patients' race and ethnicity are only stated in DELVER, where the majority of patients were white and their ethnicity was not collected in most cases. The percentage of patients with medication overuse varies between 11.9% and 12.7% in DELIVER and 43.5% and 48.4% in NCT02066415, which is a noticeable difference. In both studies, the baseline number of MMDs is presented, where the mean number of MMDs ranged between 13.7 and 13.9 in DELIVER and 18 and 18.8 in NCT02066415, indicating a minor difference. The number of MHDs is only presented in DELIVER, where the mean value was around 14.5. NCT02066415 stated, as the only study, the patients' use of MSM and monthly MSMD, which ranged between 88% and 91.3% and 10.5 and 12.4, respectively.

Comparability of the study populations with Danish patients eligible for treatment

According to the two clinical experts, the age of an average Danish patient with CM is approximately 45. This is similar in the DELIVER trial and NCT02066415. The majority of the patients with CM are females (around 70% of the Danish patient population), and this was higher in both the DELIVER trial and NCT02066415. The mean time since diagnosis for the Danish patient population is difficult to estimate, and according to the clinical experts, it depends on where in Denmark you look. One of the experts would estimate that his patients had had the diagnosis for an average of 10 years, but said that it was an uncertain estimate. None of their patients had an overuse of medication, since it is Danish practice to stop the overuse before initiating CGRP antibody treatment. For chronic patients in general, approximately 25-40% may overuse medication. In terms of numbers of MMDs and MHD, they informed that in a study they have participated in, patients had approximately 23 headache days where 17 of them were migraine days. This was slightly lower in the DELIVER trial but similar to the mean baseline number of MMDs in NCT02066415. Overall, the patient populations in the DELIVER trial and NCT02066415 correspond well to the Danish patient population with CM.

Table 80: Baseline characteristics of patients in DELIVER and the FOCUS study applied in the comparative analysis of efficacy and safety of eptinezumab and fremanezumab

	DELIVER				The FOCUS study			
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Fremanezumab 225 mg monthly (n: 283)	Fremanezumab 675 mg quarterly (n: 276)	Placebo (n: 279)	Total (n: 838)
Age (years)								
Mean (SD)	44.6 (10.76)	43.1 (10.2)	43.8 (10.83)	43.8 (10.61)	45.9 (11.1)	45.8 (11)	46.8 (11.1)	-
Median (min, max)	46 (18,74)	44 (18, 66)	44 (18,73)	44.5 (18,74)	-	-	-	-
Gender, n (%)								
Males	22 (7.4)	33 (11.3)	35 (11.7)	90 (10.1)	45 (16)	47 (17)	46 (16)	-
Females	277 (92.6)	260 (88.7)	263 (88.3)	800 (89.9)	238 (84)	229 (83)	233 (84)	-
Time since diagnosis	18,4 (11.62)	16.8 (10.91)	17.7 (11.51)	17.6 (11.36)	24 (13.7)	24.3 (12.8)	24.3 (13.6)	-
Duration of current chronic migraine diagnosis (years)	12.9 (12.06)	10.3 (8.89)	11 (10.91)	11.4 (10.8)	NR	NR	NR	NR
Race, n (%)								

	DELIVER				The FOCUS study			
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Fremanezumab 225 mg monthly (n: 283)	Fremanezumab 675 mg quarterly (n: 276)	Placebo (n: 279)	Total (n: 838)
White	288 (96.3)	281 (95.9)	285 (95.6)	854 (96)	262 (94)	262 (95)	263 (93)	-
Black or African-American	-	-	-	-	2 (<1)	2 (<1)	4 (1)	-
Asian	-	-	-	-	1 (<1)	0	3 (1)	-
American Indian or Alaska native	-	-	-	-	0	0	1 (<1)	-
Other	-	-	2 (0.7)	2 (0.2)	1 (<1)	2 (<1)	1 (<1)	-
Not reported	11 (3.7)	12 (4.1)	11 (3.7)	34 (3.8)	13 (5)	10 (4)	12 (4)	-
Ethnicity*, n (%)								
Hispanic or Latino	-	1 (0.3)	-	1 (0.1)	NR	NR	NR	NR

	DELIVER				The FOCUS study			
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Fremanezumab 225 mg monthly (n: 283)	Fremanezumab 675 mg quarterly (n: 276)	Placebo (n: 279)	Total (n: 838)
Not Hispanic or Latino	1 (0.3)	2 (0.7)	2 (0.7)	5 (0.6)	NR	NR	NR	NR
Not collected	298 (99.7)	290 (99.0)	296 (99.3)	884 (99.3)	NR	NR	NR	NR
Medication overuse headache diagnosis, n (%)	38 (12.7)	35 (11.9)	37 (12.4)	110 (12.4)	NR	NR	NR	NR
Baseline MMDs								
Mean (SD)	13.8 (5.6)	13.7 (5.4)	13.9 (5.7)	13.7 (5.4)	-	14.1 (5.6)	14.1 (5.6)	14.3 (6.1)
Baseline MHDs								
Mean (SD)	14.5 (5.6)	14.4 (5.4)	14.5 (5.8)	-	12.7 (5.8)	12.4 (5.8)	12.8 (5.9)	-
Monthly days of use of any acute								

	DELIVER				The FOCUS study			
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Fremanezumab 225 mg monthly (n: 283)	Fremanezumab 675 mg quarterly (n: 276)	Placebo (n: 279)	Total (n: 838)
headache medication at baseline								
Mean (SD)	NR	NR	NR	NR	12.2 (6)	12.8 (6.2)	12.3 (6.3)	-

Comparability of patients across studies

In DELIVER trial and the FOCUS study, the mean age of the patients ranged between 43.1 and 46.8 years. The gender distribution in the DELIVER trial and FOCUS study is similar, with a larger proportion of female patients. The mean time since diagnosis varied between the two studies, as the mean time in the DELIVER trial ranged between 16.8 and 18.4 years and 24 and 24.3 years in the FOCUS study. In both studies, the patients' race are informed and the majority of patients were white, which applied to 93% to 96.3% of them. A minor proportion of the patients did not report their race, and a few patients in the FOCUS study were either black or African American, Asian, American Indian or Alaska native, or other. The DELIVER trial also reported the patients' ethnicity; however this characteristic was in most cases not collected. Medication overuse was only presented in DELIVER, where between 11.9% and 12.7% of patients reported this. The baseline MMDs and MHDs are presented in both the DELIVER trial and the FOCUS study. The MMDs varied between 13.7 and 14.3, and the MHDs varied between 12.4 and 14.5 in the two studies. The number of monthly uses of any acute headache medication at baseline was only stated in the FOCUS study, where it ranged between 12.2 and 12.8.

Comparability of the study populations with Danish patients eligible for treatment

According to the two clinical experts, the age of an average Danish patient with CM is approximately 45. This is similar in the DELIVER trial and the FOCUS study. The majority of the patients with CM are females (around 70% of the Danish patient population), and this was higher in both the DELIVER trial and the FOCUS study. The mean time since diagnosis for the Danish patient population is difficult to estimate, and according to the clinical experts, it depends on where in Denmark you look. One of the experts would

estimate that his patients had had the diagnosis for an average of 10 years, but said that it was an uncertain estimate. None of their patients had an overuse of medication, since it is Danish practice to stop the overuse before initiating CGRP antibody treatment. For chronic patients in general, approximately 25-40% may overuse medication. In terms of numbers of MMDs and MHD, they informed that in a study they have participated in, patients had approximately 23 headache days where 17 of them were migraine days. This was slightly lower in both DELIVER and the FOCUS study. Overall, the patient populations in the DELIVER trial and the FOCUS study correspond well to the Danish patient population with CM.

Table 81: Baseline characteristics of patients in DELIVER and REGAIN applied in the comparative analysis of efficacy and safety of eptinezumab and galcanezumab

	DELIVER				REGAIN			
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Galcanezumab 120 mg (n: 278)	Galcanezumab 240 mg (n: 277)	Placebo (n: 558)	Total (n: 1113)
Age (years)								
Mean (SD)	44.6 (10.76)	43.1 (10.2)	43.8 (10.83)	43.8 (10.61)	42.8 (11.3)	42.1 (12.6)	43.9 (11.8)	43.2 (11.9)
Median (min, max)	46 (18,74)	44 (18, 66)	44 (18,73)	44.5 (18,74)	-	-	-	-
Gender, n (%)								
Males	22 (7.4)	33 (11.3)	35 (11.7)	90 (10.1)	23 (8.1)	47 (17.1)	63 (11.3)	138 (12.4)
Females	277 (92.6)	260 (88.7)	263 (88.3)	800 (89.9)	255 (91.9)	230 (82.9)	495 (88.7)	975 (87.6)
Time since diagnosis	18.4 (11.62)	16.8 (10.91)	17.7 (11.51)	17.6 (11.36)	22.6 (13.3)	21.3 (13.4)	24.3 (13.1)	23.1 (13.3)

	DELIVER				REGAIN			
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Galcanezumab 120 mg (n: 278)	Galcanezumab 240 mg (n: 277)	Placebo (n: 558)	Total (n: 1113)
Duration of current chronic migraine diagnosis (years)	12.9 (12.06)	10.3 (8.89)	11 (10.91)	11.4 (10.8)	NR	NR	NR	NR
Race, n (%)								
White	288 (96.3)	281 (95.9)	285 (95.6)	854 (96)	NR	NR	NR	NR
Other	-	-	2 (0.7)	2 (0.2)	NR	NR	NR	NR
Unknown	11 (3.7)	12 (4.1)	11 (3.7)	34 (3.8)	NR	NR	NR	NR
Ethnicity*, n (%)								
Hispanic or Latino	-	1 (0.3)	-	1 (0.1)	NR	NR	NR	NR
Not Hispanic or Latino	1 (0.3)	2 (0.7)	2 (0.7)	5 (0.6)	NR	NR	NR	NR
Not collected	298 (99.7)	290 (99.0)	296 (99.3)	884 (99.3)	NR	NR	NR	NR

	DELIVER				REGAIN			
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Galcanezumab 120 mg (n: 278)	Galcanezumab 240 mg (n: 277)	Placebo (n: 558)	Total (n: 1113)
Medication overuse headache diagnosis, n (%)	38 (12.7)	35 (11.9)	37 (12.4)	110 (12.4)	218 (78.4)	177 (63.8)	377 (67.6)	765 (68.7)
Baseline MMDs								
Mean (SD)	13.9 (5.7)	13.8 (5.6)	13.7 (5.4)	-	NR	NR	NR	NR
Baseline MHDs								
Mean (SD)	14.5 (5.6)	14.4 (5.4)	14.5 (5.8)	-	20 (4.3)	19 (4.9)	19.6 (4.71)	19.5 (4.7)
MHDs per month with acute medication use								
Mean (SD)	NR	NR	NR	NR	16.6 (5.6)	14.7 (5.8)	15.8 (6)	15.7 (5.9)

Comparability of patients across studies

In the DELIVER trial and the REGAIN study, the mean age of the patients ranged between 42.1 and 44.6 years. The gender distribution in the DELIVER trial and REGAIN study is similar, with a greater proportion of female patients. The mean time since diagnosis varied between 16.8 and 18.4 years in the DELIVER trial and 21.3 and 24.3 years in the REGAIN study, indicating a small difference across the two studies. Duration of current CM diagnosis is only mentioned in the DELIVER trial, where it ranged between 10.3 and 12.9 years of duration. The patients' race and ethnicity are only presented in the DELIVER trial, where the majority of patients were white and their ethnicity was not collected for almost every patient. The percentage of patients with medication overuse varies between 11.9% and 12.7% in DELIVER and 63.8% and 78.4% in the REGAIN study, which is a large difference. The number of MMDs is only presented in DELIVER, where the mean value ranged between 13.7 and 13.9. In both studies, the baseline number of MHDs is presented, where the mean number of MHDs was around 14.5 in DELIVER and ranged between 19 and 20 in the REGAIN study, indicating a small difference. The REGAIN study also presents MHDs per month with acute medication use, which varied between 14.7 and 16.6 for the patients.

Comparability of the study populations with Danish patients eligible for treatment

According to the two clinical experts, the age of an average Danish patient with CM is approximately 45. This is similar in the DELIVER trial and the REGAIN study. The majority of the patients with CM are females (around 70% of the Danish patient population), and this was higher in both the DELIVER trial and the REGAIN study. The mean time since diagnosis for the Danish patient population is difficult to estimate, and according to the clinical experts, it depends on where in Denmark you look. One of the experts would estimate that his patients had had the diagnosis for an average of 10 years, but said that it was an uncertain estimate. None of their patients had an overuse of medication, since it is Danish practice to stop the overuse before initiating CGRP antibody treatment. For chronic patients in general, approximately 25-40% may overuse medication. In terms of numbers of MMDs and MHD, they informed that in a study they have participated in, patients had approximately 23 headache days where 17 of them were migraine days. MMDs at baseline were not reported in REGAIN but in DELIVER, where it was slightly lower at baseline. MHDs were lower than 23 in both studies. Overall, the patient populations in the DELIVER trial and the REGAIN study correspond well to the Danish patient population with CM.

Table 82: Baseline characteristics of patients in DELIVER and CONQUER applied in the comparative analysis of efficacy and safety of eptinezumab and galcanezumab

	DELIVER				CONQUER		
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Galcanezumab 120 mg (n: 232)	Placebo (n: 230)	Total (n: 462)
Age (years)							
Mean (SD)	44.6 (10.76)	43.1 (10.2)	43.8 (10.83)	43.8 (10.61)	45.9 (11.3)	45.7 (12.3)	-
Median (min, max)	46 (18,74)	44 (18, 66)	44 (18,73)	44.5 (18,74)	-	-	-
Gender, n (%)							
Males	22 (7.4)	33 (11.3)	35 (11.7)	90 (10.1)	37 (16)	28 (12)	-
Females	277 (92.6)	260 (88.7)	263 (88.3)	800 (89.9)	195 (84)	202 (88)	-
Time since diagnosis	18,4 (11.62)	16.8 (10.91)	17.7 (11.51)	17.6 (11.36)	22.7 (13.2)	23.8 (13.9)	-
Duration of current chronic migraine diagnosis (years)	12.9 (12.06)	10.3 (8.89)	11 (10.91)	11.4 (10.8)	NR	NR	NR
Race, n (%)							
White	288 (96.3)	281 (95.9)	285 (95.6)	854 (96)	183 (79)	182 (79)	-

	DELIVER				CONQUER		
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Galcanezumab 120 mg (n: 232)	Placebo (n: 230)	Total (n: 462)
Asian	-	-	-	-	37 (16)	35 (15)	-
Black or African American	-	-	-	-	3 (1)	2 (1)	-
American Indian	-	-	-	-	0	1 (1)	-
Other	-	-	2 (0.7)	2 (0.2)	1 (<1)	3 (1)	-
Not reported	11 (3.7)	12 (4.1)	11 (3.7)	34 (3.8)	8 (3)	7 (3)	-
Ethnicity*, n (%)							
Hispanic or Latino	-	1 (0.3)	-	1 (0.1)	NR	NR	NR
Not Hispanic or Latino	1 (0.3)	2 (0.7)	2 (0.7)	5 (0.6)	NR	NR	NR
Not collected	298 (99.7)	290 (99.0)	296 (99.3)	884 (99.3)	NR	NR	NR

	DELIVER				CONQUER		
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Galcanezumab 120 mg (n: 232)	Placebo (n: 230)	Total (n: 462)
Medication overuse headache diagnosis, n (%)	38 (12.7)	35 (11.9)	37 (12.4)	110 (12.4)	108 (47)	99 (43)	-
Baseline MMDs							
Mean (SD)	13.9 (5.7)	13.8 (5.6)	13.7 (5.4)	-	13.4 (6.1)	13 (5.7)	-
Baseline MHDs							
Mean (SD)	14.5 (5.6)	14.4 (5.4)	14.5 (5.8)	-	15.3 (6.4)	14.8 (6)	-
Number of monthly days with any acute headache medication use							
Mean (SD)	NR	NR	NR	NR	13.3 (6)	12.4 (6)	-

Comparability of patients across studies

In the DELIVER trial and the CONQUER study, the mean age of the patients ranged between 43.1 and 45.9 years. The gender distribution in the DELIVER trial and the CONQUER study is similar, with a larger proportion of female patients. The mean time since diagnosis varied between 16.8 and 18.4 years in DELIVER and 22.7 and 23.8 years in CONQUER, indicating a small difference across the two studies. Duration of current CM diagnosis is only presented in DELIVER, where it ranged between 10.3 and 12.9 years of duration. The patients' race is informed in both the DELIVER trial and the CONQUER study, where a larger proportion of patients were white. In the CONQUER study, a minor proportion of patients were Asian, African-American or American Indian. In both studies, a small number of patients were categorised as "other" or "not reported". Ethnicity is only presented in DELIVER, where the majority of patients' ethnicity was not collected. The percentage of patients with medication overuse varies between 11.9% and 12.7% in DELIVER and 43% and 47% in CONQUER, which is a noticeable difference. The baseline MMDs and MHDs are presented in both the DELIVER trial and the CONQUER study. The MMDs varied between 13 and 13.9, and the MHDs varied between 14.4 and 15.3 in the two studies. In the CONQUER study, the number of monthly days with any acute headache medication use is presented and ranged between 12.4 and 13.3.

Comparability of the study populations with Danish patients eligible for treatment

According to the two clinical experts, the age of an average Danish patient with CM is approximately 45. This is similar in the DELIVER trial and the CONQUER study. The majority of the patients with CM are females (around 70% of the Danish patient population), and this was higher in both DELIVER and CONQUER. The mean time since diagnosis for the Danish patient population is difficult to estimate, and according to the clinical experts, it depends on where in Denmark you look. One of the experts would estimate that his patients had had the diagnosis for an average of 10 years, but said that it was an uncertain estimate. None of their patients had an overuse of medication, since it is Danish practice to stop the overuse before initiating CGRP antibody treatment. For chronic patients in general, approximately 25-40% may overuse medication. In terms of numbers of MMDs and MHD, they informed that in a study they have participated in, patients had approximately 23 headache days where 17 of them were migraine days. MMDs at baseline were slightly lower in both studies (around 13 days), as well as MHDs which were also lower in both studies. Overall, the patient populations in the DELIVER trial and the CONQUER study correspond well to the Danish patient population with CM.

Table 83: Baseline characteristics of patients in DELIVER and LIBERTY applied in the comparative analysis of efficacy and safety of eptinezumab and erenumab

	DELIVER				LIBERTY		
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Erenumab 140 mg (n: 121)	Placebo (n: 125)	Total (n: 246)
Age (years)							
Mean (SD)	44.6 (10.76)	43.1 (10.2)	43.8 (10.83)	43.8 (10.61)	44.6 (10.5)	44.2 (10.6)	-
Median (min, max)	46 (18,74)	44 (18, 66)	44 (18,73)	44.5 (18,74)	-	-	-
Gender, n (%)							
Males	22 (7.4)	33 (11.3)	35 (11.7)	90 (10.1)	24 (20)	22 (18)	-
Females	277 (92.6)	260 (88.7)	263 (88.3)	800 (89.9)	97 (80)	103 (82)	-
Time since diagnosis	18,4 (11.62)	16.8 (10.91)	17.7 (11.51)	17.6 (11.36)	NR	NR	-
Duration of current chronic migraine diagnosis (years)	12.9 (12.06)	10.3 (8.89)	11 (10.91)	11.4 (10.8)	NR	NR	NR
Race, n (%)							
White	288 (96.3)	281 (95.9)	285 (95.6)	854 (96)	112 (93)	115 (92)	-

	DELIVER				LIBERTY		
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Erenumab 140 mg (n: 121)	Placebo (n: 125)	Total (n: 246)
Non-white	-	-	-	-	9 (7)	10 (8)	
Asian	-	-	-	-	-	-	-
Black or African American	-	-	-	-	-	-	-
American Indian	-	-	-	-	-	-	-
Other	-	-	2 (0.7)	2 (0.2)	-	-	-
Not reported	11 (3.7)	12 (4.1)	11 (3.7)	34 (3.8)	-	-	-
Ethnicity*, n (%)							
Hispanic or Latino	-	1 (0.3)	-	1 (0.1)	9 (7)	5 (4)	-
Not Hispanic or Latino	1 (0.3)	2 (0.7)	2 (0.7)	5 (0.6)	104 (86)	109 (87)	-

	DELIVER				LIBERTY		
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Erenumab 140 mg (n: 121)	Placebo (n: 125)	Total (n: 246)
Not collected	298 (99.7)	290 (99.0)	296 (99.3)	884 (99.3)	-	-	-
Medication overuse headache diagnosis, n (%)	38 (12.7)	35 (11.9)	37 (12.4)	110 (12.4)	NR	NR	NR
Baseline MMDs							
Mean (SD)	13.9 (5.7)	13.8 (5.6)	13.7 (5.4)	-	9.2 (2.6)	9.3 (2.7)	-
Baseline MHDs							
Mean (SD)	14.5 (5.6)	14.4 (5.4)	14.5 (5.8)	-	10.1 (2.8)	10.1 (2.7)	-
Number of monthly days with any acute migraine-specific medication use							
Mean (SD)	NR	NR	NR	NR	4.8 (2.9)	4.4 (2.8)	-

Comparability of patients across studies

In the DELIVER and LIBERTY studies, the mean age of the patients ranged between 43.1 and 44.6 years. Both studies have an overweight of female patients (89.9% in DELIVER and 80-82% in LIBERTY). The proportion of male patients is stated in both studies: it was 10.1% in DELIVER and ranged between 18-10% in LIBERTY. The mean time since diagnosis is only stated in DELIVER, where it is 17.6 years in the total population. Duration of current CM diagnosis is also only mentioned in DELIVER, where it ranged between 10.3 and 12.9 years. The patients' race is stated in both studies, where the majority of patients were white (96% in DELIVER and 92-93% in LIBERTY). In LIBERTY, the remaining patients were categorised as non-white, which was 7-8% of the total population. In DELIVER, 0.2% were categorised as other, and in 3.8% of the cases, race was not reported. In DELIVER, they also state the patients' ethnicity. In the majority of patients, ethnicity was not collected (99.3%), and the remaining patients were either categorised as Hispanic or Latino (0.1%) or not Hispanic or Latino (0.6). The percentage of patients with medication overuse is only stated in DELIVER, where it is the case for 12.4% of the patients. In both studies, the baseline number of MMDs and MHDs is presented. In DELIVER, the MMDs ranged between 13.7-13.9, and in LIBERTY, it ranged between 9.2-9.3, indicating a minor difference. In DELIVER, the MHDs ranged between 14.4-14.5, and in LIBERTY, it was 10.1 in both groups. The number of monthly days with any acute migraine-specific medication use is only stated in LIBERTY, where it ranged between 4.4-4.8 days.

Comparability of the study populations with Danish patients eligible for treatment

According to the two clinical experts, the age of an average Danish patient with CM is approximately 45. This is similar in the DELIVER trial and the LIBERTY study. The majority of the patients with CM are females (around 70% of the Danish patient population), and this was higher in both DELIVER and LIBERTY. The mean time since diagnosis for the Danish patient population is difficult to estimate, and according to the clinical experts, it depends on where in Denmark you look. One of the experts would estimate that his patients had had the diagnosis for an average of 10 years, but said that it was an uncertain estimate. None of their patients had an overuse of medication, since it is Danish practice to stop the overuse before initiating CGRP antibody treatment. For chronic patients in general, approximately 25-40% may overuse medication. In terms of numbers of MMDs and MHD, they informed that in a study they have participated in, patients had approximately 23 headache days where 17 of them were migraine days. MMDs at baseline were slightly lower in both studies (between 9 and 13 days), as well as MHDs, which were also lower in both studies. Overall, the patient populations in the DELIVER trial and the LIBERTY study correspond well to the Danish patient population with CM.

Table 84: Baseline characteristics of patients in DELIVER and STRIVE applied in the comparative analysis of efficacy and safety of eptinezumab and erenumab

	DELIVER				STRIVE			
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Erenumab 70 mg (n: 317)	Erenumab 140 mg (n: 319)	Placebo (n: 319)	Total (n: 955)
Age (years)								
Mean (SD)	44.6 (10.76)	43.1 (10.2)	43.8 (10.83)	43.8 (10.61)	41.1 (11.3)	40.4 (11.1)	41.3 (11.2)	-
Median (min, max)	46 (18,74)	44 (18, 66)	44 (18,73)	44.5 (18,74)	-	-	-	-
Gender, n (%)								
Males	22 (7.4)	33 (11.3)	35 (11.7)	90 (10.1)	49 (15.5)	47 (14.7)	45 (14.1)	-
Females	277 (92.6)	260 (88.7)	263 (88.3)	800 (89.9)	268 (84.5)	272 (85.3)	274 (85.9)	-
Age at migraine onset	NR	NR	NR	NR	21.4 (11)	20.7 (9.9)	21.2 (10.2)	-
Time since diagnosis	18,4 (11.62)	16.8 (10.91)	17.7 (11.51)	17.6 (11.36)	NR	NR	NR	NR
Duration of current chronic migraine diagnosis (years)	12.9 (12.06)	10.3 (8.89)	11 (10.91)	11.4 (10.8)	NR	NR	NR	NR
Race, n (%)								

	DELIVER				STRIVE			
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Erenumab 70 mg (n: 317)	Erenumab 140 mg (n: 319)	Placebo (n: 319)	Total (n: 955)
White	288 (96.3)	281 (95.9)	285 (95.6)	854 (96)	NR	NR	NR	NR
Asian	-	-	-	-	NR	NR	NR	NR
Black or African American	-	-	-	-	NR	NR	NR	NR
American Indian	-	-	-	-	NR	NR	NR	NR
Other	-	-	2 (0.7)	2 (0.2)	NR	NR	NR	NR
Not reported	11 (3.7)	12 (4.1)	11 (3.7)	34 (3.8)	NR	NR	NR	NR
Ethnicity*, n (%)								
Hispanic or Latino	-	1 (0.3)	-	1 (0.1)	NR	NR	NR	NR
Not Hispanic or Latino	1 (0.3)	2 (0.7)	2 (0.7)	5 (0.6)	NR	NR	NR	NR

	DELIVER				STRIVE			
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Erenumab 70 mg (n: 317)	Erenumab 140 mg (n: 319)	Placebo (n: 319)	Total (n: 955)
Not collected	298 (99.7)	290 (99.0)	296 (99.3)	884 (99.3)	NR	NR	NR	NR
Medication overuse headache diagnosis, n (%)	38 (12.7)	35 (11.9)	37 (12.4)	110 (12.4)	NR	NR	NR	NR
Baseline MMDs								
Mean (SD)	13.9 (5.7)	13.8 (5.6)	13.7 (5.4)	-	8.3 (2.5)	8.3 (2.5)	8.2 (2.5)	-
Baseline MHDs								
Mean (SD)	14.5 (5.6)	14.4 (5.4)	14.5 (5.8)	-	9.1 (2.6)	9.3 (2.5)	9.3 (2.6)	-
Acute headache medication use, n (%)								
Migraine-specific	NR	NR	NR	NR	179 (56.5)	192 (60.2)	191 (59.9)	-
Non-migraine-specific	NR	NR	NR	NR	243 (76.7)	256 (80.3)	244 (76.5)	-

	DELIVER				STRIVE			
	Eptinezumab 100 mg (n: 299)	Eptinezumab 300 mg (n: 293)	Placebo (n: 298)	Total (n: 890)	Erenumab 70 mg (n: 317)	Erenumab 140 mg (n: 319)	Placebo (n: 319)	Total (n: 955)
Migraine-preventive medication use, n (%)								
No current or previous use	NR	NR	NR	NR	175 (55.2)	187 (58.6)	178 (55.8)	-
Previous use only	NR	NR	NR	NR	133 (42)	124 (38.9)	131 (41.1)	-
Current use	NR	NR	NR	NR	9 (2.8)	8 (2.5)	10 (3.1)	-

Comparability of patients across studies

In the DELIVER and STRIVE study, the mean age of the patients ranged between 40.4 and 44.6 years. Both studies have an overweight of female patients (89.9% in DELIVER and 84.5-85.9% in STRIVE). The proportion of male patients is stated in both studies, where 10.1% of patients are men in DELIVER and between 14.1-15.5% of patients in the three groups are men in STRIVE. In DELIVER, the mean time since diagnosis is 17.6 years. In STRIVE, they present the patients' age at migraine onset, which ranged between 20.7-21.4 years. In DELIVER, they also present the duration of current CM diagnosis, which ranged between 10.3 and 12.9 years. The race and ethnicity is only stated in DELIVER. Here, the majority of patients are white (96%), and the other patients are categorised as other (0.2%) or not reported (3.8%). The ethnicity is in most cases not collected (99.3%), and if collected, 0.1% of patients are Hispanic or Latino, and 0.6% are not Hispanic or Latino. The percentage of patients with medication overuse is only stated in DELIVER, where it is the case for 12.4% of the patients. In both studies, the baseline number of MMDs and MHDs is presented. In DELIVER, the MMDs ranged between 13.7-13.9 and in STRIVE, it ranged between 8.2-8.3, indicating a minor difference. In DELIVER, the MHDs ranged between 14.4-14.5, and in STRIVE, it ranged between 9.1-9.3. The percentage of patients with acute headache medication use (migraine-specific or non-migraine-specific) and migraine-preventive medication use (no current or previous use, previous use only or current use) is only stated in STRIVE. The percentage of patients with migraine-specific and non-migraine-specific medication ranged between 56.5-60.2% and 76.5-80.3%, respectively. The

percentage of patients with no current or previous use, previous use only or current use of migraine-preventive medication use ranged between 55.2-58.6%, 38.9-42% and 22.5-3.1%, respectively.

Comparability of the study populations with Danish patients eligible for treatment

According to the two clinical experts, the age of an average Danish patient with CM is approximately 45. This is similar in the DELIVER trial and the STRIVE study. The majority of the patients with CM are females (around 70% of the Danish patient population), and this was higher in both DELIVER and STRIVE. The mean time since diagnosis for the Danish patient population is difficult to estimate, and according to the clinical experts, it depends on where in Denmark you look. One of the experts would estimate that his patients had had the diagnosis for an average of 10 years, but said that it was an uncertain estimate. None of their patients had an overuse of medication, since it is Danish practice to stop the overuse before initiating CGRP antibody treatment. For chronic patients in general, approximately 25-40% may overuse medication. In terms of numbers of MMDs and MHD, they informed that in a study they have participated in, patients had approximately 23 headache days where 17 of them were migraine days. MMDs at baseline were slightly lower in both studies (between 8 and 13 days), as well as MHDs which were also lower in both studies. Overall, the patient populations in the DELIVER trial and the STRIVE study correspond well to the Danish patient population with CM.

Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

In Table 85, an overview of all outcomes included in the assessment of the efficacy and safety of eptinezumab compared to erenumab, fremanezumab and galcanezumab is presented. In addition, the table includes a description of the validity and clinical relevance of each outcome.

Table 85: Definition, validity and clinical relevance of each outcome included in the assessment of the efficacy and safety of eptinezumab

Outcome measure	Definition	Validity	Clinical relevance
Frequency of migraine	CfB in MMD	MMD is a valid outcome measure, as one of the primary treatment goals of preventive migraine treatment is to reduce the frequency of monthly migraine days. All included studies had MMD as an outcome, and there was a general consistency in definition of migraine days across studies: Migraine days were consistently defined as a day with a headache with features meeting the ICHD criteria for a migraine.	MMD is a clinically relevant outcome measure, as one of the primary treatment goals of preventive migraine treatment is to reduce the frequency of monthly migraine days. In addition, MMD has been used as a critical outcome in all previous DMC evaluations of CGRP antibodies (53–55). The expert committee states in their evaluation of the CGRP antibody galcanezumab, that studies on erenumab and fremanezumab in chronic migraine patients who have failed previous preventive treatments have showed a mean reduction in MMDs of approximately 25%. A clinically relevant difference of 10 percentage points between two CGRP antibodies was stated in the galcanezumab evaluation (55).
Frequency of migraine	Proportion of patients who achieves ≥50 reduction in monthly migraine days	We regard 50% MRR as a valid outcome, as this outcome has been used by the DMC in all previous evaluations of CGRP antibodies. All included studies had 50% MRR as an outcome.	Response rate of ≥50% is a clinically relevant outcome, as migraine and migraine symptoms can be highly disabling for patients. Moreover, complete freedom of symptoms are mostly not possible without the patient being too affected by AEs. In addition, 50% response rate has been used as an important outcome in all previous DMC evaluations of CGRP antibodies (53–

Outcome measure	Definition	Validity	Clinical relevance
			55). The expert committee states in their evaluation of the CGRP antibody galcanezumab, that studies on erenumab and fremanezumab in chronic migraine patients who have failed previous preventive treatments have showed that 35% of patients achieve at least 50% reduction in their migraine frequency. A clinically relevant difference of 5 percentage points between two CGRP antibodies was stated in the galcanezumab evaluation (55).
Quality of life	CfB in HIT-6	The validity of HIT-6 in CM has been assessed by Houts et al. 2021 (56).	QoL is a critical outcome in migraine due to the high disease burden of migraine and the high impact of migraine on patients' QoL. In the DMC evaluation of erenumab, the expert committee states that a clinically relevant difference in HIT-6 for patients with chronic migraine is -2.3 points (57,58).
Quality of life	CfB in MSQ	The validity of MSQ in migraine was assessed by Bagley et al. 2012 and Martin et al. 2000 (42,59).	QoL is a critical outcome in migraine due to the high disease burden of migraine and the high impact of migraine on patients' QoL. MSQ is one of the most frequently applied disease specific tools for evaluating HRQoL in migraine patients. The expert committee states in their evaluation of the CGRP antibody galcanezumab, the clinically relevant differences for each subscale of the MSQ (RF-R, EF and RF-P) are 5 points, 5 points and 8 points, respectively (60).
Severity	MMDs with acute medication use	The validity of this outcome has not been assessed.	It is difficult to estimate the severity of a migraine attack directly, as it depends on when during the migraine attack the patient reports how severe the attack is. Traditionally, use of acute medication has been used as a surrogate measure that indicates that the severity of an attack is at least moderate. The use of

Outcome measure	Definition	Validity	Clinical relevance
			pain-relieving medication is also a clinically relevant outcome, as the use of this type of medication can cause AEs and MOH. The expert committee states in their evaluation of the CGRP antibody galcanezumab, that studies on erenumab and fremanezumab in chronic migraine patients who have failed previous preventive treatments have showed a reduction of approximately 30-35% after 12 weeks of treatment (30,31). The expert committee further stated that a difference of 10 percentage points in the number of days per month where acute medication are used is clinically relevant.

Results per study

In the following tables, we present the results per study from the trials included in the NMA. In the tables, it is stated how the results should be interpreted. Continuous outcomes includes CfB in MMD, HIT-6 and MSQ domains. For CfB in MMDs and HIT-6, results <0 favour the comparator, results >0 favour the reference treatment because a decrease in MMD or HIT-6 indicates a clinical improvement. For MSQ domains, results >0 favour the comparator, results <0 favour the reference because an increase in each MSQ domain indicates a clinical improvement.

For the binary outcome 50% reduction in MRRs, results >1 favour the comparator, results <1 favour the reference. The discontinuation outcomes are rate-outcomes where results <1 favour the comparator, results >1 favour the reference. To calculate the relative risk based on the OR for the 50% reduction in MRR outcome and the absolute difference based on the RR or HR (for the discontinuation outcome), placebo was used as the reference in the comparisons between placebo and the four CGRP antibodies. In the comparisons of the other CGRP antibodies and eptinezumab, eptinezumab 100 mg was used as the reference. In the comparisons of the two erenumab doses, erenumab 140 mg was used as the reference and for fremanezumab, the monthly dose was used as the reference.

Table 86: Results per study from DELIVER

Results of DELIVER, NCT04418765										
				Estimated absolute difference in effect		Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference (95% CrI)**	***P* value**	**Difference**	**95% CI**	***P* value**		
Mean CfB in MMD	Eptinezumab 100 mg	[redacted]	[redacted]	[redacted]	Not reported				Mean difference in CfB	CSR on DELIVER (data on file)
	Eptinezumab 300 mg	[redacted]	[redacted]	[redacted]		NA	NA	NA		CSR on DELIVER (data on file)
	Placebo	[redacted]	[redacted]							CSR on DELIVER (data on file)
Proportion with 50% MRR	Eptinezumab 100 mg	[redacted]	[redacted]	[redacted]	Not reported	[redacted]		Not reported	Relative difference presented as a RR calculated based on the OR from the NMA (appendix 2 in DMC guideline). Absolute difference calculated	CSR on DELIVER (data on file)
	Eptinezumab 300 mg	[redacted]	[redacted]	[redacted]		[redacted]				CSR on DELIVER (data on file)

Results of DELIVER, NCT04418765									
	Placebo	[redacted]	[redacted]	[redacted]				based on RR with the method from DMC guideline (appendix 5 in DMC guideline).	CSR on DELIVER (data on file)
Mean CfB in HIT-6	Eptinezumab 100 mg	[redacted]	[redacted]	Not reported				Mean difference presented	CSR on DELIVER (data on file)
	Eptinezumab 300 mg	[redacted]	[redacted]		NA	NA	NA		CSR on DELIVER (data on file)
	Placebo	[redacted]	[redacted]						CSR on DELIVER (data on file)
Mean CfB in RF-R MSQ	Eptinezumab 100 mg	[redacted]	[redacted]	Not reported				Mean difference presented	CSR on DELIVER (data on file)
	Eptinezumab 300 mg	[redacted]	[redacted]		NA	NA	NA		CSR on DELIVER (data on file)
	Placebo	[redacted]	[redacted]						CSR on DELIVER (data on file)

Results of DELIVER, NCT04418765									
Mean CfB in EF MSQ	Eptinezumab 100 mg	[redacted]	[redacted]	[redacted]	Not reported				Mean difference presented	CSR on DELIVER (data on file)
	Eptinezumab 300 mg	[redacted]	[redacted]			NA	NA	NA		CSR on DELIVER (data on file)
	Placebo	[redacted]	[redacted]							CSR on DELIVER (data on file)
Mean CfB in RF-P MSQ	Eptinezumab 100 mg	[redacted]	[redacted]	[redacted]	Not reported				Mean difference presented	CSR on DELIVER (data on file)
	Eptinezumab 300 mg	[redacted]	[redacted]			NA	NA	NA		CSR on DELIVER (data on file)
	Placebo	[redacted]	[redacted]							CSR on DELIVER (data on file)
Mean CfB in acute	Eptinezumab 100 mg	[redacted]	[redacted]	[redacted]	Not reported	NA	NA	NA	Mean difference presented	CSR on DELIVER (data on file)

Results of DELIVER, NCT04418765									
medication use	Eptinezumab 300 mg	[redacted]	[redacted]	[redacted]					CSR on DELIVER (data on file)
	Placebo	[redacted]	[redacted]						CSR on DELIVER (data on file)

Table 87: Results per study from FOCUS

Results from the FOCUS study, NCT03308968									
				Estimated absolute difference in effect		Estimated relative difference in effect		Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference (95% CI)**	***P* value**	**Difference (95% CI)**	***P* value**		
Mean CfB in MMD	Fremanezumab 675/225/225 mg	173	-4.5 (-5.38, -3.62)	[redacted]	Not reported			Mean difference presented from NMA	NMA (data on file)
	Fremanezumab 675 mg	169	-3.9 (-4.80, -3.00)			NA	NA	NA	NMA (data on file)
	Placebo	167	-0.7 (-1.62, 0.22)						NMA (data on file)

Results from the FOCUS study, NCT03308968									
50% MRR	Fremanezumab 675/225/225 mg	173	29.5% (22.7%, 36.3%)	[redacted]	Not reported	[redacted]	Not reported	Relative difference presented as a RR calculated based on OR (appendix 2 in DMC guideline). Absolute difference calculated based on RR with method from the DMC guideline (appendix 5).	NMA (data on file)
	Fremanezumab 675 mg	169	27.2% (20.5%, 33.9%)						NMA (data on file)
	Placebo	166	8.4% (4.2%, 12.7%)						NMA (data on file)

Table 88: Results per study from NCT02066415 (Study 295)

Results from NCT02066415										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference (95% CI)**		***P* value**		
Mean CfB in MMD	Erenumab 140 mg	92	-7.00 (-8.16, -5.84)	[redacted]		Not reported	NA	NA	NA	Mean difference presented from NMA	NMA (data on file)
	Erenumab 70 mg	93	-5.4 (-6.60, -4.20)								NMA (data on file)

Results from NCT02066415									
	Placebo	142	-2.7 (-3.66, -1.74)	[redacted]					NMA (data on file)
50% MRR	Erenumab 140 mg	92	41.3% (31.2%, 51.4%)	[redacted]	Not reported	[redacted]	Not reported	Relative difference presented as a RR calculated based on OR (appendix 2). Absolute difference calculated based on RR with method from the DMC guideline (appendix 5).	NMA (data on file)
	Erenumab 70 mg	93	35.5% (25.8%, 45.2%)						NMA (data on file)
	Placebo	142	14.1% (8.4%, 19.8%)						NMA (data on file)
Mean CfB in HIT-6	Erenumab 140 mg	91	-5.2 (-6.45, -3.95)	[redacted]	Not reported			Mean difference presented from NMA	NMA (data on file)
	Erenumab 70 mg	86	-5.4 (-6.69, -4.11)			NA	NA	NA	NMA (data on file)
	Placebo	134	-1.5 (-2.56, -0.44)						NMA (data on file)
Mean CfB in acute	Erenumab 140 mg	92	-5.4 (-6.28, -4.52)		Not reported	NA	NA	NA	Mean difference presented from NMA	NMA (data on file)

Results from NCT02066415								
medication use	Erenumab 70 mg	93	-4.1 (-5.00, -3.20)	[redacted]				NMA (data on file)
	Placebo	142	-1.3 (-2.05, -0.56)					NMA (data on file)

Table 89: Results per study from CONQUER

Results of CONQUER, NCT03559257									
				Estimated absolute difference in effect			Estimated relative difference in effect		Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference (95% CI)**	***P* value**		
Mean CfB in MMD	Galcanezumab 120 mg	95	-6.00 (-7.18, -4.82)	[redacted]		Not reported	NA	NA	Mean difference presented from NMA	NMA (data on file)
	Placebo	98	-2.20 (-3.38, -1.02)							NMA (data on file)
50% MRR	Galcanezumab 120 mg	95	31.6% (22.2%, 40.9%)	[redacted]		Not reported	[redacted]	Not reported	Relative difference presented as a RR	NMA (data on file)

Results of CONQUER, NCT03559257										
	Placebo	98	8.2% (2.7%, 13.6%)						calculated based on OR. Absolute difference calculated based on RR with method from the DMC guideline	NMA (data on file)
Mean CfB in RF-R MSQ	Galcanezumab 120 mg	95	20.61 (16.59, 24.63)	[redacted]	Not reported	NA	NA	NA	Mean difference presented from NMA	NMA (data on file)
	Placebo	98	6.71 (2.81, 10.61)							NMA (data on file)
Mean CfB in EF MSQ	Galcanezumab 120 mg	95	24.38 (19.23, 29.54)	[redacted]	Not reported	NA	NA	NA	Mean difference presented from NMA	NMA (data on file)
	Placebo	98	11.09 (6.05, 16.13)							NMA (data on file)
Mean CfB in RF-P MSQ	Galcanezumab 120 mg	95	15.27 (11.59, 18.96)	[redacted]	Not reported	NA	NA	NA	Mean difference presented from NMA	NMA (data on file)
	Placebo	98	5.37 (1.78, 8.96)							NMA (data on file)
Mean CfB in acute medication use	Galcanezumab 120 mg	95	-5.40 (-6.58, -4.22)	[redacted]	Not reported	NA	NA	NA	Mean difference presented from NMA	NMA (data on file)
	Placebo	98	-1.6 (-2.78, -0.42)							NMA (data on file)

Table 90: Results per study from the REGAIN study

Results of REGAIN, NCT02614261												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference (95% CI)**		***P* value**		
Mean CfB in MMD	Galcanezumab 120 mg	72	-5.35 (-6.72, -3.98)	[redacted]		Not reported				Mean difference presented from NMA	NMA (data on file)
	Placebo	174	-1.01 (-1.99, -0.03)				NA	NA	NA		NMA (data on file)
											NMA (data on file)
50% MRR	Galcanezumab 120 mg	72	29.2% (18.7%, 39.7%)	[redacted]		Not reported	[redacted]		Not reported	Relative difference presented as a RR calculated based on OR (appendix 2). Absolute difference calculated based on RR with method from the DMC guideline (appendix 5).	NMA (data on file)
	Placebo	174	9.2% (4.9%, 13.5%)								NMA (data on file)
											NMA (data on file)
Mean CfB in RF-R MSQ	Galcanezumab 120 mg	64	19.13 (13.51, 24.76)	[redacted]		Not reported				Mean difference presented from NMA	NMA (data on file)
	Placebo	160	10.67 (6.52, 14.83)				NA	NA	NA		NMA (data on file)

Results of REGAIN, NCT02614261										
										NMA (data on file)
Mean CfB in acute medication use	Galcanezumab 120 mg	72	-5.80 (-7.17, -4.43)	[redacted]	Not reported				Mean difference presented from NMA	NMA (data on file)
	Placebo	174	-1.4 (-2.38, -0.42)			NA	NA	NA		NMA (data on file)
			-							NMA (data on file)

Appendix E Safety data for intervention and comparator(s)

In the following tables, we present safety data from the studies used to inform the NMA presented in section 7.3.

Table 91: Safety results per study from DELIVER

Safety results from DELIVER									
				Estimated absolute difference in effect		Estimated relative difference in effect		Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference (95% CI)**	***P* value**	**Difference (95% CI)**	***P* value**		
All-cause discontinuation (pooled EM/CM)	Eptinezumab 100 mg	[redacted]	[redacted]	[redacted]	Not reported	[redacted]	Not reported	Absolute difference calculated based on the HR with the method from appendix 6 in DMC guideline. The relative differences presented are hazard ratios from the NMA.	NMA (data on file)
	Eptinezumab 300 mg	[redacted]	[redacted]						
	Placebo	[redacted]	[redacted]						
Discontinuation due to AEs	Eptinezumab 100 mg	299	**0.0% (0.0%, 1.8%)***	Eptinezumab 300 mg vs eptinezumab 100 mg: -0.30%% (-0.30%, -0.05%)	Not reported	[redacted]	Not reported	Absolute difference calculated based on the HR with the method from appendix 6 in DMC guideline. The relative	Ashina et al. 2022 (29) and NMA (data on file)
	Eptinezumab 300 mg	294	2.0% (0.4%, 3.7%)						

Safety results from DELIVER									
	Placebo	298	0.0% (0.0%, 1.9%)*	Eptinezumab 100 mg vs placebo: -0.02% (-0.30%, 66.29%) Eptinezumab 300 mg vs placebo: -0.30% (-0.30%, -0.06%)		[redacted]		differences presented are hazard ratios from the NMA.	
Proportions with at least one AE	Eptinezumab 100 mg	299	42.5% (36.9%, 48.1%)	Eptinezumab 100 mg vs eptinezumab 300 mg: 1.7% (-6.3%, 9.6%) Eptinezumab 100 mg vs placebo: 2.5% (-5.4%, 10.4% Eptinezumab 300 mg vs placebo: 0.9% (-7.0%, 8.8%)	Not reported	RR eptinezumab 100 mg vs eptinezumab 300 mg: 1.04 (0.86, 1.26) RR eptinezumab 100 mg vs placebo: 1.06 (0.88, 1.29) RR vs eptinezumab 300 mg and placebo: 1.02 (0.84, 1.24)	Not reported	Absolute difference in proportions presented. The relative differences presented are risk ratios.	Ashina et al. 2022 (29)
	Eptinezumab 300 mg	294	40.8% (35.2%, 46.4%)						
	Placebo	298	39.9% (34.4%, 45.5%)						
Proportions with at least one SAE	Eptinezumab 100 mg	299	1.7% (0.2%, 3.1%)	Eptinezumab 100 mg vs eptinezumab 300 mg: -0.7% (-3.0%, 1.6%) Eptinezumab 100 mg vs placebo: 0.3% (-1.6%, 2.3%) Eptinezumab 300 mg vs placebo: 1.1% (-1.1%, 3.2%)	Not reported	RR eptinezumab 100 mg vs eptinezumab 300 mg: 0.70 (0.23, 2.19) RR eptinezumab 100 mg vs placebo: 1.25 (0.34, 4.59) RR eptinezumab 300 mg vs placebo: 1.77 (0.53, 6.00)	Not reported	Absolute difference in proportions presented. The relative differences presented are risk ratios.	Ashina et al. 2022 (29)
	Eptinezumab 300 mg	294	2.4% (0.6%, 4.1%)						
	Placebo	298	1.3% (0.0%, 2.6%)						

*Confidence intervals estimated with the Clopper-Pearson exact method.

Table 92: Results per study from LIBERTY (applied in pooled EM/CM analysis of discontinuation)

Results of LIBERTY, NCT03096834									
				Estimated absolute difference in effect		Estimated relative difference in effect		Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference (95% CI)**	***P* value**	**Difference (95% CI)**	***P* value**		
All-cause discontinuation	Erenumab 140 mg	121	2.0% (1.0%, 7.0%)*	Erenumab 140 vs placebo: -0.29% (-2.00%, 47.45%)	Not reported	[redacted]	Not reported	Absolute difference calculated based on the HR with the method from appendix 6 in DMC guideline. The relative differences presented are hazard ratios from the NMA.	Reuter et al. 2018 and NMA (data on file)
	Placebo	125	2.0% (0.0%, 7.0%)*						
Discontinuation due to AEs	Erenumab 140 mg	121	0.0% (0.0%, 3.0%)*	Erenumab 140 vs placebo: -0.97% (-1.00%, 11.59%)	Not reported	[redacted]	Not reported	Absolute difference calculated based on the HR with the method from appendix 6 in DMC guideline. The relative differences presented are hazard ratios from the NMA.	Reuter et al. 2018 and NMA (data on file)
	Placebo	125	1.0% (0.0%, 4.0%)*						

*Confidence intervals estimated with the Clopper-Pearson exact method.

Table 93: Results per study from STRIVE (applied in pooled EM/CM analysis of discontinuation)

Results of STRIVE, NCT02456740									
				Estimated absolute difference in effect		Estimated relative difference in effect		Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference (95% CI)**	***P* value**	**Difference (95% CI)**	***P* value**		

Results of STRIVE, NCT02456740									
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference (95% CI)**	***P* value**	**Difference (95% CI)**	***P* value**		
Discontinuation due to AEs	Erenumab 140 mg	58	6.9% (0.4%, 13.4%)	Erenumab 70 mg vs erenumab 140 mg: 21.56% (-6.72%, 78.28%) Erenumab 140 mg vs placebo: not estimable due to an incidence rate of 0 in placebo arm Erenumab 70 mg compared to placebo: not estimable due to an incidence rate of 0 in placebo arm	Not reported	[redacted]	Not reported	Absolute difference calculated based on the HR with the method from appendix 6 in DMC guideline. The relative differences presented are hazard ratios from the NMA.	Goadsby et al. 2017 and NMA (data on file)
	Erenumab 70 mg	49	2.0% (0.0%, 1.1%)*						
	Placebo	54	0.0% (0.0%, 7.0%)*						

*Confidence intervals estimated with the Clopper-Pearson exact method.

Table 94: Results per study from NCT02066415

Results of NCT02066415 (Study 295)									
				Estimated absolute difference in effect		**Estimated relative difference in effect**		**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference (95% CI)**	***P* value**	**Difference (95% CI)**	***P* value**		
	Erenumab 140 mg	92	0.0% (0.0%, 4.0%)*	Erenumab 70 mg vs erenumab 140 mg: not estimable due to	Not reported	[redacted]	Not reported	Absolute difference calculated based on the HR with the	Ashina et al. 2018 and

Results of NCT02066415 (Study 295)									
Discontinuation due to AEs	Erenumab 70 mg	92	0.0% (0.0%, 4.0%)*	an incidence rate of 0 in erenumab 140 arm. Erenumab 140 mg vs placebo: -0.97% (-1.00%, 11.59%) Erenumab 70 mg vs placebo: 1.19% (-1.00%, 62.10%)		[redacted]		method from appendix 6 in DMC guideline. The relative differences presented are hazard ratios from the NMA.	NMA (data on file)
	Placebo	141	1.0% (0.0%, 4.0%)*						
Proportion of patients with at least one AE	Erenumab 140 mg	92	57.6% (47.5%, 67.7%)	Erenumab 140 mg vs erenumab 70 mg: 15.2% (0.9%, 29.5%) Erenumab 140 mg vs placebo: 13.6% (0.6%, 26.6%) Erenumab 70 mg vs placebo: -1.58% (-14.6%, 11.4%)	Not reported	Erenumab 140 mg vs erenumab 70 mg: 1.4 (1.0, 1.8) Erenumab 140 mg vs placebo: 1.3 (1.0, 1.7) Erenumab 70 mg vs placebo: 1.0 (0.7, 1.3)	Not reported	Absolute difference in proportions presented. The relative differences presented are relative risks.	Ashina et al. 2018
	Erenumab 70 mg	92	42.4% (32.3%, 52.5%)						
	Placebo	141	44.0% (35.8%, 52.2%)						
Proportion of patients with at least one SAE	Erenumab 140 mg	92	1.0% (0.0%, 6.0%)*	Erenumab 140 mg vs erenumab 70 mg: -2.7% (-6.4%, 2.0%) Erenumab 140 mg vs placebo: -1.8% (-5.2%, 1.7%) Erenumab 70 mg vs placebo: 0.4% (-4.1%, 5.0%)	Not reported	Erenumab 140 mg vs erenumab 70 mg: 0.3 (0.0, 3.1) Erenumab 140 mg vs placebo: 0.4 (0.0, 3.4) Erenumab 70 mg vs placebo: 1.1 (0.3, 5.0)	Not reported	Absolute difference in proportions presented. The relative differences presented are relative risks.	Ashina et al. 2018
	Erenumab 70 mg	92	3.0% (1.0%, 9.0)*						
	Placebo	141	2.8% (0.1%, 5.6%)						

*Estimated with the Clopper-Pearson exact method.

Table 95: Results per study from the FOCUS study

Results of the FOCUS study, NCT03308968									
				Estimated absolute difference in effect		Estimated relative difference in effect		Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference (95% CI)**	***P* value**	**Difference (95% CI)**	***P* value**		
All-cause discontinuation	Fremanezumab 675/225/225 mg monthly	283	3.9% (1.6%, 6.1%)	Fremanezumab quarterly vs fremanezumab monthly: 28.23% (-0.47%, 70.78%) Fremanezumab monthly vs placebo: 3.20% (-4.36%, 28.56%) Fremanezumab quarterly vs placebo: 36.50% (3.20%, 73.60%)	Not reported	[redacted]	Not reported	Absolute difference calculated based on the HR with the method from appendix 6 in DMC guideline. The relative differences presented are hazard ratios from the NMA.	Ferrari et al. 2019 and NMA (data on file)
	Fremanezumab quarterly, 675 mg	276	1.4% (0.0%, 2.9%)						
	Placebo	279	4.7% (2.2%, 7.1%)						
Discontinuation due to AEs	Fremanezumab 675/225/225 mg monthly	283	1.4%% (0.4%, 3.6%)*	Fremanezumab quarterly vs fremanezumab monthly: 25.30% (-0.97%, 90.20%) Fremanezumab monthly vs placebo: -0.74%% (-1.00%, 22.99%) Fremanezumab quarterly vs placebo: 17.20%% (-1.00%, 86.10%)	Not reported	[redacted]	Not reported	Absolute difference calculated based on the HR with the method from appendix 6 in DMC guideline. The relative differences presented are hazard ratios from the NMA.	Ferrari et al. 2019 and NMA (data on file)
	Fremanezumab quarterly, 675 mg	276	0.4% (0.0%, 2.0%)*						
	Placebo	277	1.0% (0.0%, 3.0%)*						

Results of the FOCUS study, NCT03308968									
Proportion of patients with at least one AE	Fremanezumab 675/225/225 mg monthly	285	45.3% (39.5%, 51.0%)	Fremanezumab monthly vs fremanezumab quarterly: -9.5% (-17.7%, -1.2%) Fremanezumab monthly vs placebo: -3.1% (-11.4%, 5.1%) Fremanezumab quarterly vs placebo: 6.3% (-2.0%, 14.6%)	Not reported	Fremanezumab monthly vs fremanezumab quarterly: 0.8 (0.7, 1.0) Fremanezumab monthly vs placebo: 0.9 (0.8, 1.1) Fremanezumab quarterly vs placebo: 1.1 (1.0, 1.3)	Not reported	Absolute difference in proportions presented. The relative differences presented are relative risks.	Ferrari et al. 2019
	Fremanezumab quarterly, 675 mg	276	54.7% (48.8%, 60.6%)						
	Placebo	277	48.4% (42.5%, 54.3%)						
Proportion of patients with at least one SAE	Fremanezumab 675/225/225 mg monthly	285	1.4% (0.0%, 2.8%)	Fremanezumab monthly vs fremanezumab quarterly: 0.7% (-1.0%, 2.4%) Fremanezumab monthly vs placebo: 0.0% (-2.0%, 1.9%) Fremanezumab quarterly vs placebo: -0.7 (-2.4%, 1.0%)	Not reported	Fremanezumab monthly vs fremanezumab quarterly: 1.9 (0.4, 10.5) Fremanezumab monthly vs placebo: 1.0 (0.2, 3.8) Fremanezumab quarterly vs placebo: 0.5 (0.1, 2.7)	Not reported	Absolute difference in proportions presented. The relative differences presented are relative risks.	Ferrari et al. 2019
	Fremanezumab quarterly, 675 mg	276	1.0% (0.0%, 3.0%)						
	Placebo	277	1.4% (0.0%, 2.8%)						

*Estimated with the Clopper-Pearson exact method.

Table 96: Results per study from the CONQUER study

Results of CONQUER, NCT03559257									
				Estimated absolute difference in effect		Estimated relative difference in effect		Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference (95% CI)**	***P* value**	**Difference (95% CI)**	***P* value**		
All-cause discontinuation	Galcanezumab 120 mg	232	3.0% (0.8%, 5.2%)	-1.64% (-1.706%, 9.38%)	Not reported	[redacted]	Not reported	Absolute difference calculated based on the HR with the method from appendix 6 in DMC guideline. The relative differences presented are hazard ratios from the NMA.	Mulleners et al. 2020 and NMA.
	Placebo	230	1.7% (0.0%, 3.4%)						
Discontinuation due to AEs	Galcanezumab 120 mg	232	0.0% (0.0%, 2.0%)*	Not estimable due to an incidence rate of 0 in the placebo arm.	Not reported	[redacted]	Not reported	Absolute difference calculated based on the HR with the method from appendix 6 in DMC guideline. The relative differences presented are hazard ratios from the NMA.	Mulleners et al. 2020 and NMA.
	Placebo	230	0.0% (0.0%, 2.0%)*						
Proportion of patients with at least one AE	Galcanezumab 120 mg	232	51.3% (44.9%, 57.7%)	-1.8% (-10.9%, 7.4%)	Not reported	1.0 (0.8, 1.2)	Not reported	Absolute difference in proportions presented. The relative differences presented are relative risks.	Mulleners et al. 2020
	Placebo	230	53.0% (46.6%, 59.5%)						
Proportion of patients with	Galcanezumab 120 mg	232	1.0% (0.0%, 3.0%)*	0.0% (-1.7%, 1.7%)	Not reported	1.0 (0.1, 7.0)	Not reported	Absolute difference in proportions presented. The	Mulleners et al. 2020
	Placebo	230	1.0% (0.0%, 3.0%)*						

Results of CONQUER, NCT03559257	
at least one SAE	relative differences presented are relative risks.

*Estimated with the Clopper-Pearson exact method.

Appendix F Comparative analysis of efficacy and safety

Comparator data from seven RCTs included in the NMA via a literature search conducted in January 2022. The RCTs identified in the search were included in the NMA if they investigated interventions that were preventative CGRP antibodies in CM (LIBERTY and STRIVE in EM included to be used in pooled analyses of discontinuation) and if they reported on patients who failed at least two prior treatments (either as subgroup results or as ITT populations). Only dosages as per the SPC or expected to be within label for eptinezumab were included as eligible interventions in the NMA. Outcomes of interest were CfB in MMD, 50% MRR (and 75% MRR), CfB in MMD with use of acute medication, HRQoL outcomes such as CfB in HIT-6, CfB in RF-R, EF and RR-P MSQ v2.1 domains and safety outcomes (discontinuation due to AEs and all-cause discontinuation). A feasibility assessment was conducted to assess the availability of these outcomes across studies for an NMA, with the primary timepoint of interest being week 12. The feasibility assessment also assessed heterogeneity across studies in terms of effect-modifying baseline characteristics.

The NMAs were conducted within a Bayesian generalised linear model (GLM) framework using arm-level data (e.g., number of patients achieving a 50% MRR by week 12) captured by the literature search or from the DELIVER clinical trial. Contrast-level data (e.g., ORs comparing CGRP antibodies versus placebo for 50% MRR) were also captured by the SLR but were not deemed necessary include in the analysis due to sufficient availability of arm-level data. Each treatment regimen (and dosage level) was treated as a separate intervention in the NMA. Fixed effect NMA models were fitted to the data with model specifications as per recommendations from the NICE DSU TSD 2. Random effect models were fitted for the priority outcomes of interest: CfB in MMD, and 50% MRR. However, due to there being few studies per treatment comparison, fixed effect models were deemed to be more suitable for the networks analysed; hence, fixed effect models were prioritised. All models were fitted using Markov chain Monte Carlo (MCMC) simulation, which was implemented in the open-source software OpenBUGS.

For the 50% reduction in MRR outcome and the discontinuation outcomes, absolute differences were calculated based on either the RR or the HR. In the calculations, eptinezumab 100 mg was used as the reference.

Table 97: Comparative analysis of eptinezumab 100 mg and erenumab

Comparative analysis of eptinezumab 100 mg and erenumab							
Outcome	**Studies included in the analysis**	**Absolute difference in effect**		**Relative difference in effect**		**Method used for quantitative synthesis**	**Result used in the health economic analysis?**
		Difference (95% CI)	***P* value**	**Difference (95% CI)**	***P* value**		
Mean CfB in MMD	DELIVER and NCT02066415	**Eptinezumab 100 mg vs** [redacted]	Not reported	NA	NA	Mean difference from NMA presented (placebo-adjusted results). Results <0 favour the comparator, results >0 favour the reference because a decrease in MMD indicates a clinical improvement)	No
50% MRR	DELIVER and NCT02066415	[redacted]	Not reported	[redacted]	Not reported	The RRs of eptinezumab 100 mg compared to each erenumab dose were calculated based on the ORs, in accordance with the method suggested in the Appendix in the DMC guideline (44). Absolute difference calculated based on RR.	No
Mean CfB in HIT-6	DELIVER and NCT02066415	**Eptinezumab 100 mg vs** [redacted]	Not reported	NA	NA	Mean difference from NMA presented (placebo-adjusted results). Results <0 favour the comparator, results >0 favour the reference because a decrease in HIT indicates a clinical improvement)	No

Comparative analysis of eptinezumab 100 mg and erenumab							
Mean CfB in MSQ RF-R	DELIVER	NA	NA	NA	NA	MSQ not available for correct patient population in NCT02066415	No
Mean CfB in MSQ EF	DELIVER	NA	NA	NA	NA	MSQ not available for correct patient population in NCT02066415	No
Mean CfB in MSQ RF-P	DELIVER	NA	NA	NA	NA	MSQ not available for correct patient population in NCT02066415	No
Mean CfB in MMDs with acute medication use	DELIVER and NCT02066415	**Eptinezumab 100 mg vs** [redacted]	Not reported	NA	NA	Mean difference from NMA presented (placebo-adjusted results). Results <0 favour the comparator, results >0 favour the reference because a decrease in MMD indicates a clinical improvement)	No
All-cause discontinuation	DELIVER and LIBERTY	[redacted]	Not reported	[redacted]	NA	Absolute difference calculated based on hazard ratio in accordance with DMC guideline.	No

Comparative analysis of eptinezumab 100 mg and erenumab							
Discontinuation due to AEs	DELIVER and LIBERTY, STRIVE and NCT02066415	[redacted]	Not reported	[redacted]	Not reported	Absolute difference calculated based on hazard ratio in accordance with DMC guideline.	No
Proportion with at least one AE	DELIVER and NCT02066415	**Eptinezumab 100 mg vs** Erenumab 70 mg: 0.08% (-11.5%, 11.6%) Erenumab 140 mg: -15.13% (-26.7%, -3.6%)	Not reported	Erenumab 70 mg RR: 1.00 (0.76, 1.32) Erenumab 140 mg RR: 0.74 (0.59, 0.92)	Not reported	Absolute difference in proportions presented. Relative difference presented as RRs	No
Proportion with at least one SAE	DELIVER and NCT02066415	**Eptinezumab 100 mg vs** Erenumab 70 mg: -1.59% (-5.5%, 2.3%) Erenumab 140 mg: 0.59% (-2.0%, 3.2%)	Not reported	Erenumab 70 mg RR: 0.51 (0.13, 2.11) Erenumab 140 mg RR: 1.54 (0.18, 13.00)	Not reported	Absolute difference in proportions presented. Relative difference presented as RRs	No

Table 98: Comparative analysis of eptinezumab 100 mg and fremanezumab

Comparative analysis of eptinezumab 100 mg and fremanezumab				
Outcome		**Absolute difference in effect**	**Relative difference in effect**	**Method used for quantitative synthesis**

Comparative analysis of eptinezumab 100 mg and fremanezumab							
	Studies included in the analysis	**Difference (95% CI)**	***P* value**	**Difference (95% CI)**	***P* value**		**Result used in the health economic analysis?**
Mean CfB in MMD	DELIVER and FOCUS	**Eptinezumab 100 mg vs** [redacted]	Not reported	NA	NA	Mean difference from NMA presented (placebo-adjusted results). Results <0 favour the comparator, results >0 favour the reference because a decrease in MMD indicates a clinical improvement)	No
50% MRR	DELIVER and FOCUS	[redacted]	Not reported	[redacted]	Not reported	The RRs of eptinezumab 100 mg compared to each fremanezumab dosing regimens were calculated based on the ORs, in accordance with the method suggested in the Appendix in the DMC guideline (44). Absolute difference calculated based on RR.	No
Mean CfB in HIT-6	DELIVER	NA	NA	NA	NA	HIT-6 not available for correct patient population in the FOCUS study	No
Mean CfB in MSQ RF-R	DELIVER	NA	NA	NA	NA	MSQ not available for correct patient population in the FOCUS study	No

Comparative analysis of eptinezumab 100 mg and fremanezumab							
Mean CfB in MSQ EF	DELIVER	NA	NA	NA	NA	MSQ not available for correct patient population in the FOCUS study	No
Mean CfB in MSQ RF-P	DELIVER	NA	NA	NA	NA	MSQ not available for correct patient population in the FOCUS study	No
Mean CfB in MMDs with acute medication use	DELIVER	NA	Not reported	NA	NA	CfB in MMDs with acute medication use not available for correct patient population in the FOCUS study	No
All-cause discontinuation	DELIVER and FOCUS	[redacted]	Not reported	[redacted]	NA	Absolute difference calculated based on hazard ratio in accordance with DMC guideline.	No
Discontinuation due to AEs	DELIVER and FOCUS	[redacted]	Not reported	[redacted]	Not reported	Absolute difference calculated based on hazard ratio in accordance with DMC guideline.	No

Comparative analysis of eptinezumab 100 mg and fremanezumab							
Proportion with at least one AE	DELIVER and FOCUS	**Eptinezumab 100 mg vs** Fremanezumab 675 mg: -12.24% (-20.4%, -4.1%) Fremanezumab 675/225/225 mg: -2.79% (-10.8%, 5.3%)	Not reported	Fremanezumab 675 mg: RR: 0.78 (0.66, 0.92) Fremanezumab 675/225/225 mg: RR: 0.94 (0.78, 1.13)	Not reported	Absolute difference in proportions presented. Relative difference presented as RRs	No
Proportion with at least one SAE	DELIVER and FOCUS	**Eptinezumab 100 mg vs** Fremanezumab 675 mg: 0.95% (-0.8%, 2.7%) Fremanezumab 675/225/225 mg: 0.27% (-1.7%, 2.3%)	Not reported	Fremanezumab 675 mg: RR: 2.31 (0.45, 11.80) Fremanezumab 675/225/225 mg: RR: 1.19 (0.32, 4.39)	Not reported	Absolute difference in proportions presented. Relative difference presented as RRs	No

Table 99: Comparative analysis of eptinezumab and galcanezumab

Comparative analysis of eptinezumab and galcanezumab							
Outcome		**Absolute difference in effect**		**Relative difference in effect**		**Method used for quantitative synthesis**	**Result used in the health economic analysis?**
	Studies included in the analysis	**Difference (95% CI)**	***P* value**	**Difference (95% CI)**	***P* value**		

Comparative analysis of eptinezumab and galcanezumab							
Mean CfB in MMD	DELIVER and REGAIN and CONQUER	**Eptinezumab 100 mg vs** [redacted]	Not reported	NA	NA	Mean difference from NMA presented (placebo-adjusted results). Results <0 favour the comparator, results >0 favour the reference because a decrease in MMD indicates a clinical improvement)	No
50% MRR	DELIVER and REGAIN and CONQUER	[redacted]	Not reported	[redacted]	Not reported	The RR of eptinezumab 100 mg compared to galcanezumab was calculated based on the ORs, in accordance with the method suggested in the Appendix in the DMC guideline (44). Absolute difference calculated based on RR. Galcanezumab 120 mg N's and number of response/non-response events were pooled from CONQUER and REGAIN.	No
Mean CfB in HIT-6	DELIVER	NA	NA	NA	NA	HIT-6 not available for correct patient population in the REGAIN or CONQUER studies.	No
Mean CfB in MSQ RF-R	DELIVER and REGAIN and CONQUER	[redacted]	Not reported	NA	NA	Mean difference from NMA presented (placebo-adjusted results). Results <0 favour the comparator, results >0 favour the reference because a decrease in MSQ indicates a clinical improvement)	No

Comparative analysis of eptinezumab and galcanezumab							
Mean CfB in MSQ EF	DELIVER and CONQUER	**Eptinezumab 100 mg vs** [redacted]	NA	NA	NA	Mean difference from NMA presented (placebo-adjusted results). Results <0 favour the comparator, results >0 favour the reference because a decrease in MSQ indicates a clinical improvement)	No
Mean CfB in MSQ RF-P	DELIVER and CONQUER	**Eptinezumab 100 mg vs** [redacted]	NA	NA	NA	Mean difference from NMA presented (placebo-adjusted results). Results <0 favour the comparator, results >0 favour the reference because a decrease in MSQ indicates a clinical improvement)	No
Mean CfB in MMDs with acute medication use	DELIVER and REGAIN and CONQUER	**Eptinezumab 100 mg vs** [redacted]	Not reported	NA	NA	Mean difference from NMA presented (placebo-adjusted results). Results <0 favour the comparator, results >0 favour the reference because a decrease in MMDs with acute medication use indicates a clinical improvement)	No
All-cause discontinuation	DELIVER and CONQUER	[redacted]	Not reported	[redacted]	NA	Absolute difference calculated based on hazard ratio in accordance with DMC guideline.	No
Discontinuation due to AEs	DELIVER and CONQUER	[redacted]	Not reported	[redacted]	Not reported	Absolute difference calculated based on hazard ratio in accordance with DMC guideline.	No

Comparative analysis of eptinezumab and galcanezumab							
Proportion with at least one AE	DELIVER and CONQUER	**Eptinezumab 100 mg vs** Galcanezumab 120 mg: -8.82% (-17.3%, -0.3%)	Not reported	RR: 0.83 (0.69, 0.99)	Not reported	Absolute difference in proportions presented. Relative difference presented as RRs	No
Proportion with at least one SAE	DELIVER and CONQUER	**Eptinezumab 100 mg vs** Galcanezumab 120 mg: 0.81% (-1.1%, 2.7%)	Not reported	RR: 1.94 (0.38, 9.91)	Not reported	Absolute difference in proportions presented. Relative difference presented as RRs	No

Appendix G Extrapolation

We did not include any efficacy in the model, because eptinezumab is as effective as the current CGRP antibodies which justifies a cost-minimisation analysis.

Appendix H – Literature search for HRQoL data

The health economic analysis presented in the current application was a cost-minimisation analysis. Therefore, we did not search for any HRQoL data.

Appendix I – Mapping of HRQoL data

Not applicable.

Appendix J – Probabilistic sensitivity analyses

No PSA were conducted in the current application, because the health economic analysis consisted of a cost-minimisation analysis and costs were the only parameter in the analysis. Therefore, it does not make sense to conduct; instead, we conducted deterministic sensitivity analyses.