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

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Rider on responsibility for report

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Contributions of authors

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

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ABBREVIATIONS

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

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

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

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

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

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

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

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

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

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

3. Critique of the clinical effectiveness evidence submitted

3.1 Summary of company's systematic review methods

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

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

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

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

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

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

3.2.1 Summary of clinical evidence

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

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

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

One RCT of eptinezumab – DELIVER.

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

One RCT of fremanezumab – FOCUS.

Three RCTS of erenumab – LIBERTY, NCT02066415, STRIVE.

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

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

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

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

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

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

3.2.2 Quality assessment

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

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

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

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

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

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

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

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

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

3.2.3 Summary of the ITC methods

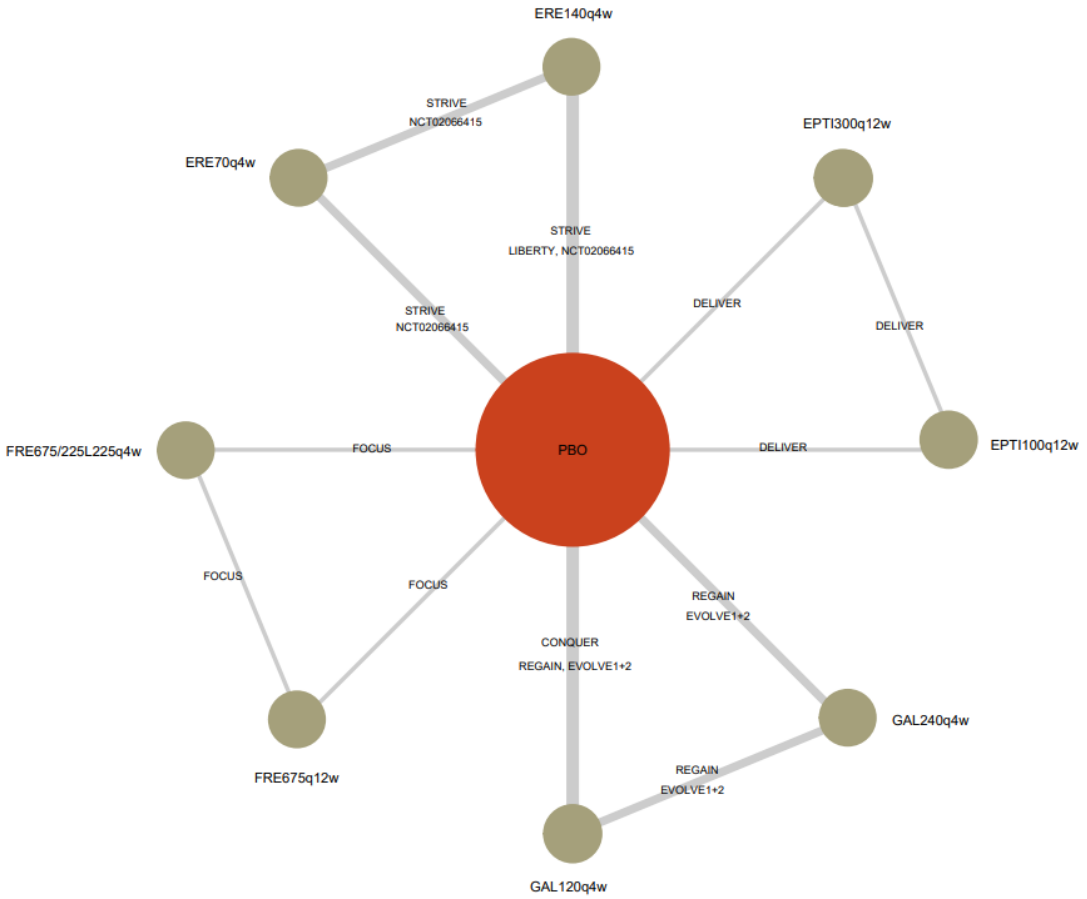
The company identified baseline severity, the number of prior treatment failures and medication overuse headache (MOH) as potential treatment effect modifiers. NMAs were conducted in the subgroups stratified by EM and CM and the prior number of treatment failures (2+ and 3+) to control

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

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

3.2.4 Summary of the ITC results

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



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

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

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

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

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

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

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

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

3.3 Critique of company's ITC

3.3.1 Clinical evidence used in the ITC

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

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

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

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

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

3.3.2 Methods used in the ITC

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

3.4 Conclusions of the clinical effectiveness section

Strengths

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

Limitations

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

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

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

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

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

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

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

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

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

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

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

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

Table 5: Assumed costs of administration

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

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

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

6. Additional considerations

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

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8. APPENDICES

Appendix 1 Additional quality assessment tables

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

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

Table 7: Quality assessment results of comparator studies galcanezumab

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

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

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

Table 8: Quality assessment results of comparator study fremanezumab

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

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

Table 9: Quality assessment results of comparator studies erenumab

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

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

Table 10: Quality assessment results of comparator studies botulinum toxin A

Trial number (acronym)	PREEMPT-1 NCT00156910 NICE TA260 ERG report[2] Aurora 2010 [15]	PREEMPT-2 NCT00168428 NICE TA260 ERG report[2] Diener 2010 [16]
Was randomisation carried out appropriately?	Yes Randomisation was stratified based on the frequency of acute headache pain medication intake during the 28-day baseline as yes/no overuse of acute headache pain medications, where medication overuse–yes was defined as intake during baseline of simple analgesics on 15 days, or other medication types or combination of types for 10+ days, with intake 2+ days/week from the category of overuse. [15]	yes Randomisation was stratified based on the frequency of acute headache pain medication use during baseline (designated as ‘‘medication overuse–yes’’ or ‘‘medication overuse–no’’), with treatments balanced in blocks of four within each medication-overuse stratum for each investigator site [16]
Was the concealment of treatment allocation adequate?	yes	yes
Were the groups similar at the outset of the study in terms of prognostic factors?	No patients in the Botox group had at baseline a significantly lower frequency of migraine episodes (11.5 vs 12.7, p=0.006) and frequency of headache episodes (12.3 versus 13.4, p=0.023), and significantly more cumulative hours of headache occurring on headache days (295.7 versus 274.9), p =0.022) compared to those in the placebo group. [2] However primary outcome was “changed to headache days because of new guidelines for the conduct of clinical trials in chronic migraine”[2]	yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes, however Unclear if blinding in patients maintained	Yes, however Unclear if blinding in patients maintained
Were there any unexpected imbalances in dropouts between groups?	no	no
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Partial[2]	Partial[2]

Trial number (acronym)	**PREEMPT-1** **NCT00156910** **NICE TA260 ERG report[2]** **Aurora 2010 [15]**	**PREEMPT-2** **NCT00168428** **NICE TA260 ERG report[2]** **Diener 2010 [16]**
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes N=679 randomised, and in analyses	Yes N=705 randomised and in analysis
Details of any conflicts of interest or funding sources declared by the authors	Company funded	Company funded

Table 11: Quality assessment results eptinezumab supporting studies

Trial number (acronym)	PROMISE-1 NCT02559895 CS assessment CS Appendices Table 31 CSR[29]	PROMISE-1 NCT02559895 ERG assessment Ashina 2020[30] CSR[29] clincaltrialsgov [31]	PROMISE-2 NCT02974153 CS assessment CS Appendices Table 31 CSR[32]	PROMISE-2 NCT02974153 ERG assessment Lipton 2020[33] CSR[32] clinicaltrials.gov [34]
Was randomisation carried out appropriately?	Yes	Unclear from Ashina 2020[30] [redacted] 29	Yes	Unclear from Lipton 2020[33] [redacted] 32
Details of randomisation	Patients were randomly assigned in a 1:1:1:1 ratio to treatment arms. Randomisation was stratified by the number of migraine days recorded during screening.	Randomisation was stratified by the number of migraine days recorded during the screening period (<=9 days vs. >9 days) [30]	Patients were randomly assigned in a 1:1:1 ratio to treatment arms. Stratified permuted block randomisation was used. Stratification was by migraine days during the screening period and prophylactic medication use during the 3 months prior to screening.	Randomisation was stratified by the number of migraine days recorded during the screening period (≤17 vs >17 days) and preventive medication use during the 3 months before screening (use vs no use) [33]
Was the concealment of treatment allocation adequate?	Yes	Unclear from Ashina 2020 [redacted]	Yes	Unclear from Lipton 2020 [33] [redacted] 32

Trial number (acronym)	PROMISE-1 NCT02559895 CS assessment CS Appendices Table 31 CSR[29]	PROMISE-1 NCT02559895 ERG assessment Ashina 2020[30] CSR[29] clincaltrialsgov [31]	PROMISE-2 NCT02974153 CS assessment CS Appendices Table 31 CSR[32]	PROMISE-2 NCT02974153 ERG assessment Lipton 2020[33] CSR[32] clinicaltrials.gov [34]
		[redacted] [29]		
Details of treatment allocation concealment	Allocation was reported to be concealed. The clinical study was double-blind. The subjects and site personnel were blinded to treatment assignment, except for the site's unblinded pharmacist or study drug consignee. The study site had a written plan in place to ensure blinding was adequately maintained for the study. If the blind was broken, the date, and reason were recorded. The blind was only to have been broken for reasons		Allocation was reported to be concealed. This clinical study was double-blinded, meaning the subjects and site personnel were blinded to treatment assignment, except for the clinical study site's unblinded pharmacist or designee. The study site had a written Blinding Plan in place to ensure blinding was adequately maintained for the study. If the blind was broken, the date, time, and reason were to be recorded. The blind was only to be	

Trial number (acronym)	PROMISE-1 NCT02559895 CS assessment CS Appendices Table 31 CSR[29]	PROMISE-1 NCT02559895 ERG assessment Ashina 2020[30] CSR[29] clincaltrialsgov [31]	PROMISE-2 NCT02974153 CS assessment CS Appendices Table 31 CSR[32]	PROMISE-2 NCT02974153 ERG assessment Lipton 2020[33] CSR[32] clinicaltrials.gov [34]
	in which knowledge of the study drug was critical to the subject safety or to the study management. The investigator was to report any cases of unblinding to the sponsor within 24 hours of the incident.		broken for reasons in which knowledge of the treatment assignment was critical to subject safety or to the study management. The investigator was to report any cases of unblinding to the Sponsor within 24 hours of the incident.	
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Mostly yes “higher percentage of males in the eptinezumab 100 mg group versus other treatment groups (19.7% vs 11.2–16.2%).” CS Document B	Yes	yes
Details of imbalances in baseline characteristics	Clinical characteristics of migraine appeared well balanced across treatment groups, although there was a higher		Demographics and baseline characteristics were balanced between treatment groups.	

Trial number (acronym)	PROMISE-1 NCT02559895 CS assessment CS Appendices Table 31 CSR[29]	PROMISE-1 NCT02559895 ERG assessment Ashina 2020[30] CSR[29] clincaltrialsgov [31]	PROMISE-2 NCT02974153 CS assessment CS Appendices Table 31 CSR[32]	PROMISE-2 NCT02974153 ERG assessment Lipton 2020[33] CSR[32] clinicaltrials.gov [34]
	percentage of males in the eptinezumab 100 mg group versus other treatment groups (19.7% vs 11.2–16.2%).			
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes	yes	Yes	yes
Details of blinding	The study sites and patients remained blinded to individual treatment assignments until study completion.		All research participants, clinicians, and research personnel were blinded and remained blinded throughout the duration of the clinical trial.	
Were there any unexpected	No	No [29]	No	No[32]

Trial number (acronym)	PROMISE-1 NCT02559895 CS assessment CS Appendices Table 31 CSR[29]	PROMISE-1 NCT02559895 ERG assessment Ashina 2020[30] CSR[29] clincaltrialsgov [31]	PROMISE-2 NCT02974153 CS assessment CS Appendices Table 31 CSR[32]	PROMISE-2 NCT02974153 ERG assessment Lipton 2020[33] CSR[32] clinicaltrials.gov [34]
imbalances in dropouts between groups?				
If so, give details. Were the imbalances explained and adjusted for?	N/A		N/A	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No 31	No	No 34
Details of potentially unreported outcomes	N/A		N/A	
Did the analysis include an	Yes	mITT – all patients randomised and received treatment 898 randomised; 888 received	Yes	mITT “1,121 patients were randomly assigned; 1,072 received treatment and were included in the safety and full

Trial number (acronym)	PROMISE-1 NCT02559895 CS assessment CS Appendices Table 31 CSR[29]	PROMISE-1 NCT02559895 ERG assessment Ashina 2020[30] CSR[29] clincaltrialsgov [31]	PROMISE-2 NCT02974153 CS assessment CS Appendices Table 31 CSR[32]	PROMISE-2 NCT02974153 ERG assessment Lipton 2020[33] CSR[32] clinicaltrials.gov [34]
intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		treatment and included in analyses [30]		analysis populations" [33]
Details of analysis methods	Patients were analysed according to the assigned treatment group. Normalisation was used to address missing migraine data in the primary efficacy analysis. If the eDiary was completed for ≥ 21 days of a 4-week interval, the observed frequency was normalised to 28 days by		All patients who received study medication were included in the safety and efficacy populations. For the safety analyses, patient results were summarised within the group representing the treatment they received; if they received 2 different doses, they were summarised in the treatment arm of	

Trial number (acronym)	PROMISE-1 NCT02559895 CS assessment CS Appendices Table 31 CSR[29]	PROMISE-1 NCT02559895 ERG assessment Ashina 2020[30] CSR[29] clincaltrialsgov [31]	PROMISE-2 NCT02974153 CS assessment CS Appendices Table 31 CSR[32]	PROMISE-2 NCT02974153 ERG assessment Lipton 2020[33] CSR[32] clinicaltrials.gov [34]
	multiplying by the inverse of the completion rate. If the eDiary was completed for < 21 days of a 4-week interval, the results were a weighted function of the observed data for the current interval and the results from the previous interval, with the weight proportional to how many days the eDiary had been completed.		the highest dose received. For the efficacy population, patients' results were summarised within the treatment group to which they were randomly assigned. Summary statistics were reported based upon observed data except for the eDiary data and HIT-6 results. Additionally, if the start date of an AE or concomitant medication was incomplete or missing, it was assumed to have occurred on or after the infusion of study drug, except if an incomplete date (e.g., month and year) clearly	

Trial number (acronym)	PROMISE-1 NCT02559895 CS assessment CS Appendices Table 31 CSR[29]	PROMISE-1 NCT02559895 ERG assessment Ashina 2020[30] CSR[29] clincaltrialsgov [31]	PROMISE-2 NCT02974153 CS assessment CS Appendices Table 31 CSR[32]	PROMISE-2 NCT02974153 ERG assessment Lipton 2020[33] CSR[32] clinicaltrials.gov [34]
			indicated that the event started prior to treatment.	
Details of study funding	H. Lundbeck A/S, Copenhagen, Denmark	Funded by the company	H. Lundbeck A/S, Copenhagen, Denmark	Funded by the company

Appendix 2: Results of the company's ITC

Table 12: Fixed effect NMA results in patients with ≥3 treatment failures (adapted from CS, Table 20, and Table 21)

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

155-195q 12w		[redacted]				[redacted]								

Key: CrI, credible interval; ERE140q4w, erenumab 140 mg (q4w); FRE675q12w, fremanezumab 675 mg (q12w); FRE675/225/225q4w, fremanezumab 675/225/225 mg (q4w); GAL 120q4w, galcanezumab 120 mg (q4w); BOT155-195q12w, botulinum toxin A 155-195 mg (q12w); MMD, monthly migraine days; PBO, placebo; EM, episodic migraine; CM, chronic migraine.

Notes: Change from baseline in MMDs and MMDs with use of acute medication: mean differences in change from baseline with 95% CrIs, where results < 0 favour the comparator, results > 0 favour eptinezumab 100 mg.

Change from baseline in MSQ subscores: mean differences in change from baseline with 95% CrIs, where results > 0 favour the comparator and results < 0 favour eptinezumab 100 mg.

50% and 75% migraine response rate results: odds ratios with 95% CrIs, where results > 1 favour the comparator, results < 1 favour eptinezumab 100 mg.

Table 13: Fixed effect NMA results for pooled CM and EM in patients with ≥3 treatment failures (adapted from CS, Table 22)

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

Key: CrI, credible interval; ERE140q4w, erenumab 140 mg (q4w); FRE675q12w, fremanezumab 675 mg (q12w); FRE675/225/225q4w, fremanezumab 675/225/225 mg (q4w); GAL 120q4w, galcanezumab 120 mg (q4w); HIT-6, 6-item Headache Impact Test; MMD, monthly migraine days; PBO, placebo.

Notes: 50% and 75% migraine response rate results: odds ratios with 95% CrIs, where results > 1 favour the comparator, results < 1 favour eptinezumab 100 mg.