CONFIDENTIAL UNTIL PUBLISHED
Evidence Review Group's Report

Galcanezumab for preventing migraine

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Authors	Nick Meader, Research Fellow, CRD Peter Murphy, Research Fellow, CRD Sofia Dias, Professor of Health Technology Assessment, CRD Kath Wright, Information Service Manager, CRD Robert Hodgson, Research Fellow, CRD
Correspondence to	Sofia Dias, Centre for Reviews and Dissemination, University of York, Heslington, York, YO10 5DD
Date completed	20/04/2020

Source of funding

This report was commissioned by the NIHR Systematic Reviews Programme as project number 131017.

Declared competing interests of the authors

None.

Acknowledgements

We would like to thank Dr Gina Kennedy (Consultant Neurologist), City Hospitals Sunderland; and Dr Niranjanan Nirmalananthan (Consultant Neurologist), St George's University Hospitals, for their expert advice.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

This report should be referenced as follows:

Meader N, Murphy P, Dias S, Wright K, Hodgson R. Galcanezumab for preventing migraine: A Single Technology Appraisal. CRD and CHE Technology Assessment Group, University of York, 2020.

Contributions of authors

Nick Meader and Sofia Dias wrote the clinical effectiveness sections of the report. Peter Murphy and Robert Hodgson wrote the cost effectiveness sections and conducted the ERG economic analyses. Kath Wright wrote the search strategy sections. Sofia Dias took overall responsibility for the report.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

Copyright statement

Copyright belongs to the University of York.

Copyright is retained by Eli Lilly for tables 14, 24, 53, 54, 55 and figures 1 to 4.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Table of Contents

Table of Contents 3
List of abbreviations 8
Glossary 9
1 Executive Summary 10
1.1 Critique of the decision problem in the company's submission 10
1.2 Summary of the key issues in the clinical effectiveness evidence 10
1.3 Summary of the key issues in the cost effectiveness evidence 11
1.4 Summary of exploratory and sensitivity analyses undertaken by the ERG 14
1.5 Summary of ERG's preferred assumptions and resulting ICER 17
Evidence Review Group Report 19
2 INTRODUCTION AND BACKGROUND 19
2.1 Introduction 19
2.2 Background 19
2.2.1 Disease Background 19
2.2.2 The technology and the company's anticipated positioning of galcanezumab 20
2.3 Critique of company's definition of decision problem 23
3 CLINICAL EFFECTIVENESS 29
3.1 Critique of the methods of review(s) 29
3.1.1 Searches 29
3.1.2 Inclusion criteria 30
3.1.3 Quality assessment 31
3.1.4 Evidence synthesis 31
3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these) 32
3.2.1 Relevant trials – CONQUER, REGAIN, EVOLVE-1, EVOLVE-2, CGAJ 32
3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison 41
3.3.1 EM population 41
3.3.2 CM population 41
1.1.1.1 Assessment of ITC assumptions 41
3.4 Critique of the indirect comparison and/or multiple treatment comparison 44
3.4.1 CM patients with ≥ 3 prior preventive medication failures 45
3.4.2 CM patients 'all-comers' population 46
3.5 Additional work on clinical effectiveness undertaken by the ERG 47
3.6 Conclusions of the clinical effectiveness section 47
4 COST EFFECTIVENESS 49
4.1 ERG comment on company's review of cost-effectiveness evidence 49

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

4.2 ERG's summary and critique of company's submitted economic evaluation 50
4.2.1 NICE reference case checklist 50
4.2.2 Model structure 51
4.2.3 Population 57
4.2.4 Interventions and comparators 59
4.2.5 Perspective, time horizon and discounting 62
4.2.6 Treatment effectiveness 63
1.1.1.2 Response rate 63
1.1.1.3 Change in monthly migraine headache days: Responders and non-responders 64
1.1.1.4 Discontinuation rate 68
1.1.1.5 Change in monthly migraine headache days for "discontinuers" 69
4.2.7 Health related quality of life 71
4.2.8 Resources and costs 75
1.1.1.6 Disease management 77
5 COST EFFECTIVENESS RESULTS 81
5.1 Company's cost effectiveness results 81
5.1.1 Base case results 81
5.1.2 Probabilistic sensitivity analysis 82
5.1.3 Subgroup analysis of high frequency episodic migraine (HFEM) 84
5.2 Company's sensitivity analyses 85
5.3 Additional scenario analysis requested by the ERG and PFC 87
5.4 Model validation and face validity check 89
6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES 91
6.1 Exploratory analyses undertaken by the ERG 91
6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG 95
6.2.1 Interpreting the results for episodic migraine 96
6.2.2 Interpreting the results for chronic migraine 96
6.3 Conclusions of the cost effectiveness section 102
7 References 105
Appendix 1 108
Appendix 2 110
Appendix 3 113

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Table of Tables

Table 1 Summary of ERG scenario analysis 14
Table 2 Exploratory ERG analyses (episodic migraine) 15
Table 3 Exploratory ERG analyses - Chronic migraine pairwise analyses (separate models for comparison to BSC and botulinum toxin) 15
Table 4 Exploratory ERG analysis - Scenario 11 (chronic migraine) 17
Table 5 ERG Base-case and exploratory analysis (Episodic population) 17
Table 6 ERG Base-case and exploratory analysis (Chronic population) 18
Table 7 Summary of company's decision problem (adapted from CS, Table 1) 23
Table 8 ERG appraisal of evidence identification for the effectiveness review 29
Table 9 Summary of efficacy and safety trials CONQUER, REGAIN, EVOLVE-1, EVOLVE-2 (based on CS, Table 5) 33
Table 10 Clinical effectiveness of galcanezumab versus placebo for key outcomes in patients with ≥ 3 prior preventive medication failures (based on CS Tables 27, 28, 30, 31, 33, 34 and 35) 35
Table 11 Mean difference in health related quality of life mean change from baseline difference: GMB versus placebo in patients with ≥ 3 prior preventive medication failures (based on CS Tables 29, 32, 34) 37
Table 12 Baseline mean migraine headache days in CM patients with ≥ 3 prior preventive medication failures 42
Table 13 Baseline characteristics in CM patients for 'all-comers' population (based on CS table 38, CSR REGAIN[11], and CADTH Report[7]) 42
Table 14 Outcomes for which indirect treatment comparisons were carried out (from CS Table 37) 44
Table 15 Mean difference in change from baseline in mean MHD for CM DTT-3 population: data sources and ITC results 45
Table 16 Percentage of patients with at least 50% reduction in monthly MHD from baseline in the CM 'all-comers' population: data sources and ITC results 46
Table 17 NICE reference case checklist 50
Table 18 Proportion of patient's ineligible for galcanezumab at baseline 56
Table 19 Baseline patient characteristics (adapted from Table 51 CS pg. 117) 58
Table 20 Proportion of responders at the 3-month assessment 63
Table 21 Change from baseline in mean MHDs for responders and non-responders 65
Table 22 Probability of discontinuation (adapted from Table 58 & Table 59 CS pg. 124 & 125) 68
Table 23 Modelled discontinuation parameters 70
Table 24: Utility values for each MHD health state (from Table 61, CS) 72
Table 25: Unit costs of the elements of prophylactic treatment 76
Table 26 Side by side comparison of health state consumption rates (derived from CS Table 65) 79
Table 27 Updated company base case results: Episodic migraine, vs BSC (Table 53, PFC response) 81
Table 28 Updated company base case results: Chronic migraine, vs BSC (Table 54, PFC response) 82
Table 29 Updated company base case results: Chronic migraine, vs botulinum toxin (Table 55, PFC response) 82

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Table 30 Updated company base case results: High frequency episodic migraine, vs BSC 84
Table 31 Utility values from CONQUER in the failed ≥ 3 prior preventative treatment subpopulation 87
Table 32 Scenario analysis using CONQUER pooled with REGAIN and EVOLVE failed ≥3 prior preventative treatment subpopulation 87
Table 33 Scenario analysis using CONQUER inputs only 88
Table 34 Scenario analysis, approximated responder and non-responder MHDs for botulinum toxin A 88
Table 35 Scenario analysis, dissipation of the placebo effect 89
Table 36 Scenario analysis where patients who discontinue galcanezumab and botulinum toxin A return to baseline MHDs over 72 cycles 89
Table 37 General population age decrements 92
Table 38 Alternative treatment effectiveness parameters (response-based model structure) 95
Table 39 Exploratory ERG analyses (episodic migraine) 98
Table 40 Exploratory ERG analyses - Chronic migraine pairwise analyses (separate models for comparison to BSC and botulinum toxin) 98
Table 41 Exploratory ERG analysis - Scenario 11 (chronic migraine) 100
Table 42 ERG base case and exploratory analysis (chronic migraine) 101
Table 43 Quality assessment of included CEA study using Drummond et al. checklist completed by the ERG 110
Table 44 ERG Scenario 11a) Equal effectiveness (ITC) 113
Table 45 ERG Scenario 11b) Response rate differs (ITC) 113
Table 46 ERG Scenario 11c) CFB in MHD differs (ITC) 113
Table 47 ERG Scenario 11d) 11b and 11c combined 113
Table 48 ERG base case 1 (Scenarios 1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11a) 114
Table 49 ERG base case 2 (Scenarios 1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11b) 114
Table 50 ERG base case 3 (Scenarios 1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11c) 114
Table 51 ERG base case 4 (Scenarios 1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11d) – preferred 114
Table 52 ERG preferred base case + 12) Incorporation of natural history 115

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Table of Figures

Figure 1 The Company's anticipated positioning of galcanezumab (reproduced from CS, Figure 2) . 21
Figure 2 Washout data – REGAIN (reproduced from CS, Figure 17) 39
Figure 3 Washout period EVOLVE-2 (reproduced from CS, Figure 16) 40
Figure 4 Model structure (from CS, Figure 11, pg. 107) 53
Figure 5: Cost-effectiveness plane, EM population (vs BSC) ..... **Error! Bookmark not defined.**
Figure 6 Cost-effectiveness plane, CM population (vs BSC) ..... **Error! Bookmark not defined.**
Figure 7 Cost-effectiveness plane, CM population (vs botulinum toxin) ..... **Error! Bookmark not defined.**
Figure 8 DSA: Episodic (vs BSC) ..... **Error! Bookmark not defined.**
Figure 9 DSA: Chronic (vs BSC) ..... **Error! Bookmark not defined.**
Figure 10 DSA Chronic vs botulinum toxin A ..... **Error! Bookmark not defined.**

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

List of abbreviations

AE	Adverse events
BNF	British National Formulary
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost-effectiveness analysis
CFB	Change from baseline
CGRP	Calcitonin Gene-Related Peptide
CI	Confidence interval
CM	Chronic migraine
CMU	Commercial medicine unit
CS	Company submission
CSR	Clinical study report
CV	Cardiovascular
DSA	Deterministic sensitivity analysis
EM	Episodic migraine
EMA	European Medicines Agency
ERG	Evidence review group
GMB	Galcanezumab
HD	Headache days
HFEM	High frequency episodic migraine
HRQoL	Health related quality of Life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intention to treat
MHD	Migraine headache days
MSQ	Migraine-Specific Quality of Life Questionnaire
NA	Not applicable
NHS	National Health Service
NHWS	National Health and Wellness Survey
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory drug
PAS	Patient access scheme

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

PFC	Points for clarification
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal and Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life-year
RCT	Randomised Controlled Trial
SAE	Serious adverse events
SmPC	Summary of Product Characteristics
SR	Systematic Review
TLR	Targeted literature review

Glossary

'All-comers' population	Patients included in the trial regardless of how many previous preventive treatments received for migraine.
DTT-3 population	Difficult to treat population of patients who have failed ≥ 3 previous preventive treatments for migraine.
Intention-to-treat (ITT)	ITT technically requires all data from randomized patients to be included in the analyses whether they completed the trial or not. The company used a modified definition to include all randomized patients who received at least one dose. In addition, patients are analysed according to the group they were randomized whether they received the treatment or not.
Responders	Patients who experienced a predefined (≥ 30% or ≥ 50%) magnitude of reduction from baseline in migraine headache days.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

1 EXECUTIVE SUMMARY

1.1 Critique of the decision problem in the company's submission

The company's decision problem largely matched the NICE scope. The company is positioning galcanezumab as 4th line therapy for patients who have previously failed at least three preventive treatments. The key population of interest is therefore, patients with episodic or chronic migraine who have had at least 3 prior preventive treatment failures (i.e. the difficult to treat, failed three therapies, [DTT-3] population).

Evidence is presented separately for patients with episodic and chronic migraine. Evidence on patients with high frequency episodic migraine (HFEM, a subgroup of episodic migraine) is also presented. However, the Evidence Review Group (ERG) noted some uncertainties:

- Clinical meaningfulness of the HFEM category: there is debate in the literature regarding whether this a clinically distinct patient subgroup (see section 2.2.1 for further details).
- Combining chronic migraine (CM) and HFEM groups in some analyses: the ERG noted that in some analyses data from both groups were combined. This is inconsistent with the decision problem (see section 2.3). However, the ERG is aware that there is significant debate in the literature regarding the distinctiveness of HFEM in comparison with CM and episodic migraine (EM) (see section 2.2.1 for further detail).
- The natural history of the condition is not included in the economic evaluation. This has potential implications for evaluating long-term treatment benefits (see section 2.2.1 for further detail).

1.2 Summary of the key issues in the clinical effectiveness evidence

The key clinical evidence is based on the results of four randomized controlled trials (RCTs) comparing galcanezumab to placebo. The ERG noted three main limitations with the clinical effectiveness data:

- Only limited available data are available for all outcomes on the DTT-3 population: most company trial data for this population was based on small samples sizes and unplanned subgroup analyses (see section 3.2).
- Evidence on long-term efficacy and treatment effect waning after discontinuation covers only a limited time-period (see sections 2.2.1 and 3.2.1).
- Lack of consistency in data synthesis throughout submission: estimates used in the economic model were not always based on all available relevant data (see section 3.1.4).

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

- Concerns about generalisability of the DTT-3 patients included: approximately [redacted] of the participants included in the CONQUER trial had failed at least one treatment not used in the UK including botulinum toxin A, normally only available as 4th line treatment in the National Health Service (NHS, see section 3.2.1).
- Validity of the indirect treatment comparisons (ITC) between galcanezumab and botulinum toxin A is highly uncertain (see sections 3.3 and 3.4 for further discussion).
- Although galcanezumab appears to be well tolerated, safety in pregnancy and for those at risk of cardiovascular events in unknown (see section 3.2.1).

1.3 Summary of the key issues in the cost effectiveness evidence

Model structure

Outcomes used to drive clinical effectiveness

The economic analysis presented by the company adopted an approach based around frequency of migraine headache, which was assumed to drive all differences in both health related quality of life (HRQoL) and costs. While consistent with the previous appraisals of Calcitonin Gene-Related Peptide (CGRP) therapies, the focus on migraine frequency to the exclusion of other trial outcomes, represents a limitation of the present economic analysis (see section 4.2.2).

Long-term treatment efficacy

The economic analysis makes strong assumptions about the durability of the treatment effect extrapolating short-term effects observed over a period of 3 months to a 25-year time horizon. This together with the lack of modelling of the effects of natural history means there is substantial uncertainty regarding the long-term benefits of galcanezumab treatment. The ERG considers that there is significant scope for the benefits of galcanezumab treatment to decline with time, either as a result of acquired resistance to the drug or because of the natural reductions in the severity and frequency of migraine. This is particularly problematic when considered in the context of the modelled assumption of lifetime treatment (see section 4.2.2).

Comparison with botulinum toxin A for chronic migraine

While high quality trial evidence is available to support the comparisons to best supportive care (BSC), the comparison of galcanezumab with botulinum toxin A is drawn from an ITC, with significant concerns regarding the validity of the resulting effect estimates. Therefore, the results of the economic analysis for this comparison should be interpreted with caution and are subject to uncertainty not expressed in the probabilistic analysis (see section 4.2.6).

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Treatment sequencing

The economic analysis presented by the company has the significant limitation of only evaluating the cost-effectiveness of specific treatments rather than evaluating alternative treatment sequences. This is an important omission, as the positioning of galcanezumab within the treatment pathway may have important implications for its cost-effectiveness. It is also inconsistent with clinical practice where it is anticipated that galcanezumab would be used as part of a treatment sequence for chronic migraine patients (see sections 2.2.2 and 4.2.4).

Inputs and assumptions

The ERG also identified several issues relating to the inputs and assumption used in the economic analysis. These are outlined in brief below.

Source of utility data

The company base-case uses the utility values from the whole population of the CONQUER trial. This population is broader than the modelled population as it includes patients who have failed fewer than three preventative treatments. It also ignores available HRQoL data from the other pivotal trials. It is the ERG's view that the utility data should align with the modelled population i.e. patients who have failed > 3 preventative treatments and should make maximum use of the available trial data (see section 4.2.7).

Treatment specific utilities

The company's base-case analysis takes the conservative position that utility estimates are the same across treatment groups. This aligns with committee preferences in previous appraisals. However, there is a case for implementing treatment specific utilities. The company presented an analysis showing a strong statistically significant difference in utility values between galcanezumab and placebo. Furthermore, the limitations of the model structure mean there is clinical rationale for such a difference, which would reflect the impact of treatment on migraine severity and the number of non-migraine headache days prevented (see section 4.2.7).

Age related disutility

The utilities used in the company's economic analysis are assumed to remain constant over the 25-year time horizon of the model. There is, however, significant scope for natural history to impact on the underlying severity of headache and migraine, as well as for the effects of aging to impact upon quality-of-life. While the impact of these factors is unknown, it is likely that they will act to moderate the benefits of reducing migraine days reducing the absolute HRQoL benefits of treatment (see section 4.2.7).

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Source of effectiveness data

For both response and the mean change in migraine headache days (MHDs), the company does not use all the available trial evidence, instead relying primarily on the CONQUER trial. This creates several inconsistencies such that pooled values are used in some comparisons, but not in others. The ERG does not consider this selective approach appropriate and considers that, where possible, the company should have sought to use all the available data (see sections 3.1.4 and 4.2.6).

Estimation of treatment effect between galcanezumab and botulinum toxin A

Due to limited data on change in monthly MHDs in a responder population, the company adopts a different model structure from the comparison with BSC. This approach, referred to as the combined population approach, uses data from the ITC of MHDs (DTT-3 population) to approximate the difference in MHDs in responders to galcanezumab and botulinum toxin A. The ERG accepts the need for assumptions to be made for this comparison. However, the company's approach relies on assumptions that cannot hold, and which cause the model to make predictions that do not align with the results of the ITC. Importantly, where the response rate is < 100% the company's approach leads the model to predict a difference in MHDs that are lower than that estimated by the ITC, therefore biasing the ICER in favour of botulinum toxin A (see Section 1.1.1.3).

Furthermore, the use of different model structure means that an incremental analysis in which the cost-effectiveness of galcanezumab, BSC and botulinum toxin A are jointly assessed, cannot be conducted (see section 4.2.2).

Duration of waning period

The company model assumes patients discontinuing treatment will wane back to baseline MHDs. The ERG considers the application of a waning period reasonable in principle, but notes that the data used to model this waning is of very short duration and is not from patients who have discontinued due to adverse events. The ERG is also concerned about the plausibility of the predicted waning periods, noting that very different waning periods are applied in the EM and CM populations. The waning period for galcanezumab is also modelled as being considerably longer than that applied for BSC and botulinum toxin A, without any evidence to justify this assumption (see Section 4.2.6).

Waning of treatment effect in responders to BSC

The company's economic analysis assumes that responses to placebo will not be durable. As such, responders to BSC are assumed to wane back to baseline MHDs. The ERG considers it plausible that responses to placebo will be durable, representing factor such as regression to the mean, natural history and response to tertiary treatment that constitute BSC. Further, the ERG considers the unilateral application of waning unfair, as placebo effects will also be part of the observed response to

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

galcanezumab. The application of waning also means that the modelled benefit of treatment is, in effect, larger than the one observed in the trial (see Section 4.2.6).

Administration costs for galcanezumab

The company's economic analysis assumes all patients will be able to self-administer galcanezumab and as such, no administration costs are included after the first cycle. A proportion of patients may, however, not be able to self-administer due to comorbid physical or mental disabilities. In line with this, the ERG also notes previous committee preference for administration costs to be included for 10% of patients (see Section 4.2.8).

Resource use consumption rates

In contrast to the recent appraisals of erenumab and fremanezumab the company base-case uses a US survey of resource consumption rates to populate the model. The ERG preference is to use the same source as used in previous appraisals which is also more likely to reflect resource use in the NHS (see Section 4.2.8).

1.4 Summary of exploratory and sensitivity analyses undertaken by the ERG

The scenario analysis run by the ERG are summarised in Table 1.

Table 1 Summary of ERG scenario analysis

Scenario 1	Addition of administration cost in 10% of patients
Scenario 2	Resource consumptions rates revised to align with those used in previous appraisals of CGRP's.
Scenario 3	EVOLVE 1, EVOLVE 2, REGAIN and CONQUER used as the source of utility data (DDT3 population only)
Scenario 4	Differential utilities applied for active therapies relative to BSC.
Scenario 5	Age related disutilies applied.
Scenario 6	Waning period in the chronic migraine population set to 13 months, consistent with the episodic populations.
Scenario 7	Waning period for botulinum toxin A set equal to galcanezumab.
Scenario 8	All waning removed – patients revert to baseline after 1 cycle.
Scenario 9	BSC responders assumed to retain response for duration of model time horizon.
Scenario 10a	Patients discontinuing treatment assumed to wane back from responder MHDs
Scenario 10b	10 a, but also assuming rates of discontinuation are common across active treatments.
Scenario 11a	Galcanezumab and botulinum toxin A assumed equally effective.*
Scenario 11b	Response rate modelled using ITC, responder MHD assumed equal.*
Scenario 11c	Response rate assumed equal, responder MHDs estimated from ITC.*
Scenario 11d	11c and 11d combined.

*Response model structure used for both BSC and botulinum toxin A.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Results of the ERG's scenario analysis are presented in Table 2 for the episodic population. Results for chronic population are presented in Table 3 and Table 4. These results are presented inclusive of the patient access scheme (PAS) available for galcaneuzmab, but exclude the commercial medicine unit (CMU) discount for botulinum toxin A. Results including the CMU discount are presented in a confidential Appendix.

Table 2 Exploratory ERG analyses (episodic migraine)

Analysis	Discounted costs		Discounted QALYs		ICER	Change from company base case ICER
	Galcanezumab	BSC	Galcanezumab	BSC		
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	£29,230	-
ERG correction of model errors	[redacted]	[redacted]	[redacted]	[redacted]	£29,313	£83
1) Galcanezumab administration cost for 10% of patients	[redacted]	[redacted]	[redacted]	[redacted]	£29,563	£334
2) Alternative resource consumption rates	[redacted]	[redacted]	[redacted]	[redacted]	£36,049	£6,820
3) Alternative source used to generate HRQoL	[redacted]	[redacted]	[redacted]	[redacted]	£37,149	£7,919
4) Differential utilities for galcanezumab and comparator	[redacted]	[redacted]	[redacted]	[redacted]	£13,232	-£15,998
5) Age-related disutility	[redacted]	[redacted]	[redacted]	[redacted]	£30,247	£1,017
8) Removal of treatment waning	[redacted]	[redacted]	[redacted]	[redacted]	£29,976	£747
9) Dissipation of placebo effect	[redacted]	[redacted]	[redacted]	[redacted]	£36,918	£7,689

BSC, best supportive care; ERG, evidence review group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness analysis; QALY, quality-adjusted life year

Note: All results correspond to deterministic analyses

Table 3 Exploratory ERG analyses - Chronic migraine pairwise analyses (separate models for comparison to BSC and botulinum toxin)

Analysis	Comparator	Discounted Costs		Discounted QALYs		Pairwise	
		Galcanezumab	Comparator	Galcanezumab	Comparator	ICER	Change from company base case
Company base case	**BSC**	[redacted]	[redacted]	[redacted]	[redacted]	**£8,080**	-
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	**£2,560**	-
ERG correction of model errors	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£8,053	-£27
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£4,203	£1,643

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

1) Galcanezumab administration cost for 10% of patients	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£8,243	£163
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£3,255	£694
2) Alternative resource consumption rates	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£14,892	£6,813
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£9,534	£6,974
3) Alternative source used to generate HRQoL	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£10,269	£2,189
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£3,254	£694
4) Differential utilities for galcanezumab and comparator	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£4,456	-£3,624
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£1,185	-£1,375
5) Age-related disutility	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£8,347	£268
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£2,622	£61
6) Consistent waning period between episodic and chronic migraine populations	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£9,602	£1,522
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£25,168	£22,608
7) Consistent waning period between galcanezumab and botulinum toxin A	BSC	n/a	n/a	n/a	n/a	n/a	n/a
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£5,464	£2,904
8) Removal of treatment waning	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£10,068	£1,988
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£42,566	£40,006
9) Dissipation of placebo effect	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£10,239	£2,160
	Botulinum toxin A	n/a	n/a	n/a	n/a	n/a	n/a
10a) Alternative MHDs for patients discontinuing galcanezumab (vs. Botulinum toxin type A)	BSC	n/a	n/a	n/a	n/a	n/a	n/a
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£27,615	£25,054
	BSC	n/a	n/a	n/a	n/a	n/a	n/a

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

10b) Equivalent long-term discontinuation rate for galcanezumab and botulinum toxin (0.44%)	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£11,742	£9,181

BSC, best supportive care; ERG, evidence review group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness analysis; MHDs, migraine headache days; QALY, quality-adjusted life year
Note: All results correspond to deterministic analyses

Table 4 Exploratory ERG analysis - Scenario 11 (chronic migraine)

Analysis	Discounted Costs			Discounted QALYs			Incremental ICER (Galcanezumab)
	BSC	Botulinum toxin A	Galcanezumab	BSC	Botulinum toxin A	Galcanezumab	
11a) Equal effectiveness (ITC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£64,281
11b) Response rate differs (ITC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,167
11c) CFB in MHD differs (ITC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,454
11d) 11b and 11c combined	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,734

BSC, best supportive care; ERG, evidence review group; ICER, incremental cost-effectiveness analysis; ITC, indirect treatment comparison; MHDs, migraine headache days; QALY, quality-adjusted life year
Note: All results correspond to deterministic analyses

1.5 Summary of ERG's preferred assumptions and resulting ICER

The ERG's base case for the episodic population included scenarios 1,2, 3, 4, 5 and 9. Additional scenario analysis was also conducted on the ERG's base case incorporating natural history effects. Results are presented in Table 5. These results are presented inclusive of the PAS available for galcaneuzmab, but exclude the CMU discount for botulinum toxin A. Results including the CMU discount are presented in a confidential Appendix.

Table 5 ERG Base-case and exploratory analysis (Episodic population)

Analysis	Discounted costs		Discounted QALYs		ICER
	Galcanezumab	BSC	Galcanezumab	BSC	
ERG base case (1, 2, 3, 4, 5, 9)	[redacted]	[redacted]	[redacted]	[redacted]	£28,014
Base case + Incorporation of natural history (12)	[redacted]	[redacted]	[redacted]	[redacted]	£66,583

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

BSC, best supportive care; ERG, evidence review group; ICER, incremental cost-effectiveness analysis; ITC, indirect treatment comparison; MHDs, migraine headache days; QALY, quality-adjusted life year
Note: Results based on probabilistic analysis

The ERG's base case in the chronic population included scenarios (1, 2, 3, 4, 5, 6, 7, 10a, 10b, and 11d. Additional scenario analysis was conducted exploring:

- Alternative assumptions regarding the relative treatment effect between galcanezumab and botulinum toxin A.
- The effects of natural history.

Results of these analyses are presented in Table 6. As above these results only include the PAS discount for galcanezumab not the CMU discount for botulinum toxin A.

Table 6 ERG Base-case and exploratory analysis (Chronic population)

Analysis	Discounted Costs			Discounted QALYs			Incremental ICER (Galcanezumab)
	BSC	Botulinum toxin A	Galcanezumab	BSC	Botulinum toxin A	Galcanezumab	
ERG base case 4 (1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11d)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,830
ERG exploratory analysis							
ERG base case 1 (1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11a)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£190,641
ERG base case 2 (1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11b)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,840
ERG base case 3 (1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11c)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,539
ERG preferred base case + Incorporation of natural history (12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,721

BSC, best supportive care; ERG, evidence review group; ICER, incremental cost-effectiveness analysis; ITC, indirect treatment comparison; MHDs, migraine headache days; QALY, quality-adjusted life year
Note: Note: Results based on probabilistic analysis

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

EVIDENCE REVIEW GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

2.2 Background

The company proposes galcanezumab (GMB) as fourth-line therapy for patients with episodic and chronic migraine, after failure of three other preventive therapies, which is appropriate and in line with ERG's clinical advice. However, for patients with chronic migraine who have failed on three previous preventive treatments, botulinum toxin A is an option, so it is possible that some patients might receive GMB as a fifth-line treatment, having previously failed on botulinum toxin A. This option is not considered in the company's submission (CS).

2.2.1 **Disease Background**

The description of the underlying health problem in the company's submission was appropriate and relevant to the decision problem.

The company focused the disease overview appropriately on the impact of migraine headaches. However, our clinical advisor pointed out that migraine patients often experience headaches that do not meet criteria for migraine which additionally impacts on their quality of life.

The CS rightly distinguishes between patients with episodic (<15 headache days per month) or chronic migraine (≥ 15 headache days with ≥ 8 migraine headache days) as distinct clinical populations based on standard clinical criteria. The CS does not mention the group of patients with ≥ 15 headache days but < 8 migraine headache days. However, the ERG's clinical advisor suggested these patients would usually be treated as CM patients in common clinical practice.

There is debate in the clinical community about the company's claim that HFEM represents a distinct subgroup of patients. Advice from two Consultant Neurologists specialising in migraine treatment, suggested these patients were a neglected and important clinical subgroup. However, it should also be noted that previous appraisals[1, 2] have judged that HFEM was not a clinically meaningful category. This uncertainty was reflected in the clinical advice received by the ERG. One of our clinical advisors considered little difference between HFEM and CM patients in terms of quality of life impact and disease burden, while another suggested that HFEM and CM patients were clinically distinct.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

The CS correctly states that migraine is associated with a number of social and demographic variables (such as age, gender etc.). For example, prevalence of migraine is highest between ages 25-55 years before declining in middle age. Prevalence of migraine is higher in women than in men (28% vs 15%) and women are more likely to experience longer duration and greater intensity of migraines, with the exception of during pregnancy and after menopause when migraine attacks are less common.[3] However, there was limited discussion of stability of migraine symptoms over time. The CS estimates 2-3% of EM patients go on to meet criteria for chronic migraine annually, although this 'migraine chronification' may partly be accounted for by measurement error.[4]

The CS did not completely capture the relapsing and remitting nature of migraine over time in the background. For example, a 30-year Swiss prospective study[5] found that most patients continued to experience migraine symptoms over the course of the study (86.7% of migraine with aura patients, 75.6% of migraine without aura patients). However, most did not experience migraines continually, only 20% of patients reported migraines for more than half of the follow up period with symptoms remitting and returning over time. On average, migraine with aura patients reported 27.4 migraine MHDs per year and migraine without aura patients reported 33.7 MHDs per year.[5]

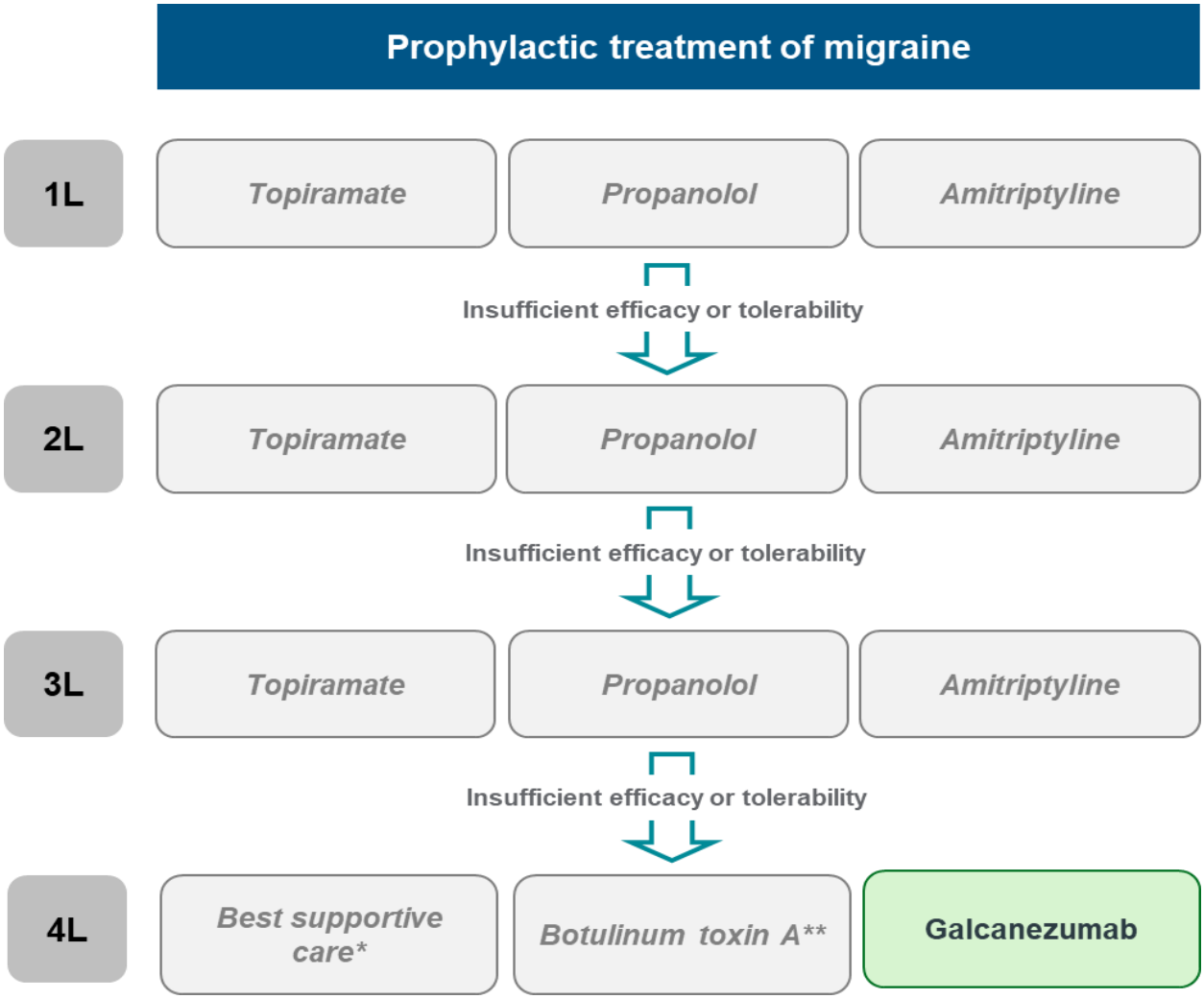
Although available evidence on the natural history of chronic and episodic migraine is sparse, these data have implications for assumptions made about long-term efficacy and potential discontinuation.

2.2.2 **The technology and the company's anticipated positioning of galcanezumab**

Figure 1 summarizes the clinical care pathway for the prophylaxis of migraine (reproduced from Figure 2 in the CS).

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Figure 1 The Company's anticipated positioning of galcanezumab (reproduced from CS, Figure 2)



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

The CS correctly stated that NICE guidance recommends topiramate, propranolol, and amitriptyline as first-, second-, and third-line preventive options. Sequencing is based on patient preference, comorbidities and risk of adverse events. For patients with CM who have failed ≥ 3 oral treatments, botulinum toxin A is recommended as a fourth-line treatment. Since the company submission, fremanezumab has also been recommended by NICE as a fourth-line treatment. Galcanezumab is positioned by the company as an additional fourth-line option. Our clinical advisors agreed this was appropriate. However, they noted that there is a potentially large prevalent population of CM patients who have already received botulinum toxin A as a failed preventive treatment. Therefore, GMB would represent a fifth-line option for these patients. In addition, the clinical advisors suggested there are potentially a range of other sequences that clinicians may consider for prescribing galcanezumab,

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

botulinum toxin A, and fremanezumab based on availability, service capacity and costs, and individual preference.

For patients with EM, botulinum toxin A and fremanezumab have not been recommended. Therefore, if recommended, GMB would be the only fourth line treatment option for this patient group.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

2.3 Critique of company's definition of decision problem

Table 7 Summary of company's decision problem (adapted from CS, Table 1)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with migraine	Adults with migraine who have ≥4 migraine headache days (MHDs) per month, who have a history of ≥3 prior preventive treatment failures. Two populations considered: • Patients with chronic migraine (≥15 headache days per 30-day period, of which ≥8 are MHDs) • Patients with episodic migraine (4-14 MHDs and <15 headache days per 30-day period)	The population is aligned to the marketing authorisation granted to galcanezumab in the UK, which restricts its use as prophylaxis of migraine in adults who have at least 4 MHDs per month. In addition, current clinical practice within the NHS, and feedback from clinicians suggests that galcanezumab is most suitable for use in patients who have a history of ≥3 prior preventive treatment failures.	The clinical evidence submitted largely matches the patient population. However, clinical parameters are used in the economic model which are informed by data on patient populations falling outside of the described populations. The ERG also notes analyses are conducted in which HFEM and chronic migraine are combined. This is a deviation from the two distinct patient populations outlined in the scope.
Intervention	Galcanezumab	Galcanezumab	NA	NA
Comparator(s)	Oral preventive treatments;	The following comparators are considered:	Comparators selected were based on final appraisal	Based on clinical advice and given the proposed positioning,

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

	botulinum toxin A; erenumab (subject to ongoing NICE appraisal); fremanezumab (subject to ongoing NICE appraisal); and best supportive care (BSC)	• Episodic migraine: BSC (represented by placebo) • Chronic migraine: BSC (placebo) and botulinum toxin A.	document of erenumab for preventing migraine.[6] Most people with migraine who have a history of ≥3 prior preventive treatment failures would either use botulinum toxin A or BSC. Clinical trials compared galcanezumab to placebo (used to represent BSC in CS) At the time of submission, erenumab and fremanezumab were not recommended as preventive treatment by NICE. As a result, they are not relevant comparators within the scope of this appraisal.	the ERG is satisfied with the selected comparators and the reason for the exclusion of fremanezumab and erenumab from any analyses.
Outcomes	The outcome measures to be considered include: • frequency of headache days per month • frequency of migraine days per month	The outcome measures to be considered include: • frequency of headache days per month	The outcome measures to be considered include: • frequency of headache days per month • frequency of migraine days per month	The outcomes considered in the clinical evidence submission are: • Improvement in MHDs • Improvement in HDs

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

	• severity of headaches and migraines • number of cumulative hours of headache or migraine on headache or migraine days • reduction in acute pharmacological medication • adverse effects of treatment • health-related quality of life	- overall mean change from baseline in mean monthly headache days • frequency of MHDs per month - overall mean change from baseline in mean monthly MHDs - percentage of patients with episodic migraine with ≥50% reduction from baseline in mean monthly MHDs - percentage of patients with chronic migraine with ≥30% reduction from baseline in mean monthly MHDs • number of cumulative hours of headache or migraine on headache or migraine headache days - Overall mean change from baseline in number of monthly migraine headache hours	• severity of headaches and migraines • number of cumulative hours of headache or migraine on headache or migraine days • reduction in acute pharmacological medication • adverse effects of treatment • health-related quality of life	• Response to treatment • Adverse events • Health related quality of life (captured by MSQ) • Acute medication use The economic model limits the outcomes considered to change in monthly MHD rather than both MHDs and HDs. The economic model does not consider adverse events, rather it captures discontinuation. The ERG notes that the severity of MHDs and HDs is not captured in the economic model.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

		• reduction in acute pharmacological medication - Overall mean change from baseline in the number of monthly migraine headache days with acute headache medication use • Analysis of treatment-emergent adverse events • health-related quality of life Changes from baseline to month 3 in: • MSQ v2.1 total score, Role Function-Restrictive, Role Function-Preventive and Emotional Function domain scores • EQ-5D-5L		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	As per scope	NA	NA

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.			
Subgroups	If the evidence allows, subgroups considered: • People with chronic or episodic migraine • Number of previous preventive treatments • Frequency of episodic migraine.	The following subgroups are considered in the CS: • People with HFEM who suffer 8 -14 MHDs per month (with <15 headache days in a 30-day period) • Pooled analysis of people with HFEM and chronic migraine, to allow review of patients in whom chronic migraine is defined as ≥8 MHDs per month	The base case analysis has been presented separately for patients with chronic and episodic migraine in patients who have a history of ≥3 prior preventive treatment failures. The company consider the subgroup of patients experiencing ≥8 MHDs per month (i.e. chronic and HFEM) to be a clinically meaningful subgroup.	The ERG understands the rationale for combining chronic and HFEM patients, however this is inconsistent with previous migraine appraisals.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Special considerations including issues related to equity or equality	None	None	NA	NA

Abbreviations: BSC, best supportive care; EQ-5D-5L : 5 level EuroQol 5 dimensions 5 level; HFEM: high-frequency episodic migraine; MHD, migraine headache days; MSQ-v2.1, Migraine-Specific Quality of Life Questionnaire Version 2.1; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS: Personal Social Services.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS included a systematic review (SR) of GMB and relevant comparators. Overall, there were no concerns with searches. However, the ERG noted limitations with the inclusion criteria. Trials that did not report separate data for patients who had failed previous preventive medications were excluded. This limited the comprehensiveness of the analyses conducted by the company on an 'all-comers' population (i.e. data from patients included in analyses regardless of how many previous failed preventive treatments). In addition, evidence synthesis methods sometimes lacked consistency and comprehensiveness in application. For example, in some analyses only data from CONQUER were used when similar data were available from other company trials (see section 3.1.4 for further details).

3.1.1 **Searches**

Table 8 summarises the ERG's comments on the company's search strategy for clinical effectiveness literature.

Table 8 ERG appraisal of evidence identification for the effectiveness review

Topic	ERG response	Note
Is the report of the search clear and comprehensive?	Yes	1. Originally there was no PRISMA flow chart. This was submitted after the Points for Clarification stage 2. The original submission referred to SR1/SR2/SR3/SR4. After Points for Clarification it was clear that this was one SR updated on 3 occasions
Were appropriate sources searched?	Yes	The search used: 1. bibliographic databases (MEDLINE, Embase, Cochrane CDSR, Cochrane CENTRAL) 2. Trial Registers (ClinicalTrials.gov) 3. Conference Proceedings (as listed) 4. HTA repositories (as listed)
Was the timespan of the searches appropriate?	Yes	1. The original search was conducted in 2017 and covered from database inception to December 2017.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

		2. Three subsequent updates covered Dec 2017 -Oct 2018/Oct 2018 - Aug 2019/Aug 2019 - Oct 2019
Were appropriate parts of the PICOS included in the search strategies?	Yes	The search strategies combine terms for migraine (P) with terms for Galcanezumab and comparators (I) and terms for RCTs (S)
Were appropriate search terms used?	Yes	1. The full search strategies are provided for each of the databases. 2. In line with best practice, these combine thesaurus terms with free text terms and drug registry numbers
Were any search restrictions applied appropriate?	NA	
Were any search filters used validated and referenced?	Yes	1. RCT search filters are applied in both the MEDLINE and Embase searches 2. The filter used in the MEDLINE search is the Cochrane Highly Sensitive Search filter 3. The filter used in the Embase search is referred to as being the Cochrane RCT filter. 4. The Cochrane RCT filter was only published in 2019 and is not the same as the one being used here

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE (NA)
ERG, evidence review group; RCT, randomised controlled trial; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; HTA, health technology assessment.

3.1.2 **Inclusion criteria**

Full details of inclusion criteria are provided in Table 8, Appendix D of the CS. Phase II, III, and IV randomised controlled trials (RCTs) examining the safety and effectiveness of either GMB or botulinum toxin A were eligible for inclusion in the systematic review. These criteria were appropriate and reflected the decision problem.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Trials that did not include separate data for patients who had failed previous preventive medications were excluded. These criteria limit the comprehensiveness of the 'all comers' (includes all patients regardless of how many previous failed medications) ITC analyses (see CS section B.2.8.2.1.1). The ERG identified a Cochrane review that included a number of additional potentially relevant studies to inform the 'all comers' ITC (see points for clarification [PFC] question A15 for further details). The company responded that the 'all comers' analyses were not central to the submission and therefore they chose not to include these studies. However, the ERG notes that results from the ITC on the 'all-comers' population are presented in the CS and they have been used to inform parameters in the ERG's economic model and ERG base case (see section 1.1.1.2).

3.1.3 Quality assessment

Included studies were critically appraised using the Cochrane risk of bias tool (v1). The judgements from these assessments were summarised in Appendix D of the CS: Table 12 (for trials included in the ITC), Table 13 (trials in EM patients), Table 14 (trials in CM patients), Table 15 (trials in mixed EM and CM patient populations), Table 16 (trials in unspecified migraine populations). The key trials that informed the submission were mainly judged to be at low risk of bias. The company's REGAIN trial was judged low risk of bias for all components of the risk of bias tool. Appendix D originally judged the company's CONQUER trial to be at an unclear risk of bias. But in response to PFC question A9, the company clarified these judgements were based on publicly available material. When taking into account data reported in the company submission, they judged the trial to be at low risk of bias. Risk of bias assessments were not reported for EVOLVE-1 or EVOLVE-2.

The two included trials on botulinum toxin A (PREEMPT-1 and PREEMPT-2) were judged to be at low risk of bias or most categories, but judged to be at high risk of outcome reporting bias, since limited baseline characteristics were available for patients with ≥ 3 previous failed preventive treatments. This judgement was based on a report by the Canadian Agency for Drugs and Technologies in Health (CADTH)[7] that conducted subgroup analyses in this population.

However, since these subgroup analyses were conducted by a national technology assessment centre, the ERG considered it unlikely the lack of available data was due to outcome reporting bias. However, the ERG agrees that the lack of information on baseline characteristics for this subgroup is an important source of uncertainty (see section 1.1.1.1 for further discussion).

3.1.4 Evidence synthesis

The CS focused on a subgroup of patients with ≥ 3 prior preventive medications included in the company trials: CONQUER, REGAIN, EVOLVE-1 and EVOLVE-2. However, the CS also summarised data not specific to patients who had failed ≥ 3 prior preventive medications from

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

CONQUER on the effectiveness of GMB compared with placebo. These data were reported in combined CM and EM populations; as well as separately for CM, HFEM, and EM patients. These trial data are summarised in more detail in section 3.2.

The company pooled baseline monthly MHDs for CM patients using both arms of the CONQUER study (GMB and Placebo) to inform the economic model (see Sections 1.1.1.3 and 1.1.1.1). However, the company did not use similar available data from REGAIN which would likely have increased precision of these estimates.

Data on patient counts from REGAIN and CONQUER were naively pooled to inform the 50% response rate (i.e. ≥ 50% reduction in baseline monthly MHDs) for patients who had failed ≥ 3 prior preventive medications in the economic model (see section 1.1.1.2). This was done by adding the number of responders and the number of included patients in the trial arms and calculating proportions. However, these data could have been formally meta-analysed on an appropriate scale (e.g. log-odds) resulting in more valid estimates with a more appropriate characterisation of the underlying uncertainty.

The baseline monthly MHD for EM was pooled from both arms of the CONQUER study (GMB and Placebo) to inform the economic model (see section 4.2.3). However, data from EVOLVE-1 and EVOLVE-2 were available but were not pooled with the baseline data from CONQUER which would have increased precision of the estimate.

Indirect treatment comparison analyses were also conducted comparing the effectiveness of GMB with botulinum toxin A. These analyses are discussed in more detail in sections 3.3 and 3.4.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The following sections summarise and critique the company trial data. The main concerns identified by the ERG were the limited available data on all outcomes for the key DTT-3 population (i.e. patients with ≥ 3 prior preventive treatment failures), and generalisability of the trial data to the NHS. For example, [redacted] of DTT-3 patients in CONQUER had failed on treatments not routinely used in the UK. The European Medicines Agency (EMA) identified some uncertainties in the safety of GMB for pregnant women and patients with cardiovascular risks which should be taken into account.

3.2.1 **Relevant trials – CONQUER, REGAIN, EVOLVE-1, EVOLVE-2, CGAJ**

The key clinical evidence in the CS is based on subgroup analyses of patients with ≥ 3 prior preventive treatment failures in four randomized controlled trials (RCTs). All subgroup analyses were unplanned, with the exception of data from CONQUER. Trials are summarized in Table 9.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

The CS presented data from CONQUER showing that GMB was more effective than placebo in the joint (CM and EM) population. Subgroup analyses that considered CM and EM patients separately found that GMB was more effective than placebo in both populations.

Table 9 Summary of efficacy and safety trials CONQUER, REGAIN, EVOLVE-1, EVOLVE-2 (based on CS, Table 5)

Study	CONQUER	REGAIN	EVOLVE-1	EVOLVE-2	CGAJ
Study design	Phase III, randomised, multicentre, double blind, placebo-controlled. double blinded treatment + 3 months + 3 months open-label treatment	Phase III, randomised, multicentre, double blind, placebo-controlled. double blinded treatment + 3 months + 9 months open-label treatment + 4 months post-treatment follow up	Phase III, randomised, multicentre, double blind, placebo-controlled. double blinded treatment + 6 months + 4 months post-treatment follow up	Phase III, randomised, multicentre, double blind, placebo-controlled. double blinded treatment + 6 months + 4 months post-treatment follow up	Phase III, multicentre, randomised open-label study 12 months open-label treatments and 4 months post-treatment follow-up
Population	ICHD-3 criteria for a diagnosis of migraine with or without aura or chronic migraine, and **who have previously failed 2 to 4 standard-of-care treatments** (categories) for migraine prevention	ICHD-3 beta criteria for chronic migraine	Episodic migraine, ICHD-3 criteria 1.1 or 1.2	Episodic migraine, ICHD-3 criteria 1.1 or 1.2	Episodic or chronic migraine ICHD-3 criteria (1.1, 1.2, or 1.3)
Intervention(s)	Galcanezumab (120 mg/month) with Galcanezumab 240 mg loading dose	Galcanezumab (120 mg/ month) with Galcanezumab 240 mg loading dose Galcanezumab 240 mg/month	Galcanezumab (120 mg/ month) with Galcanezumab 240 mg loading dose Galcanezumab 240 mg/month	Galcanezumab (120 mg/ month) with Galcanezumab 240 mg loading dose Galcanezumab 240 mg/month	Galcanezumab (120 mg/ month) with Galcanezumab 240 mg loading dose Galcanezumab 240 mg/month
Comparator(s)	Placebo for 3 months	Placebo for 3 months	Placebo for 6 months	Placebo for 6 months	-

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Study	CONQUER	REGAIN	EVOLVE-1	EVOLVE-2	CGAJ
Outcomes assessed in trial and relevant to decision problem	**Primary outcome:** Overall mean change from baseline in monthly MHDs **Other outcomes informing cost-effectiveness model:** Proportion of patients with episodic migraine with ≥50% reduction in mean monthly MHDs from baseline Proportion of patients with chronic migraine with ≥30% reduction in mean monthly MHDs from baseline	**Primary outcome:** Overall mean change from baseline in monthly MHDs **Other outcomes informing cost-effectiveness model:** NA	**Primary outcome:** Overall mean change from baseline in monthly MHDs **Other outcomes informing cost-effectiveness model:** Proportion of patients with episodic migraine with ≥50% reduction in mean monthly MHDs from baseline	**Primary outcome:** Overall mean change from baseline in monthly MHDs **Other outcomes informing cost-effectiveness model:** Proportion of patients with episodic migraine with ≥50% reduction in mean monthly MHDs from baseline	Outcomes do not inform the economic model

MHD=migraine headache days, ICHD=International Classification of Headache Disorders, NA=not applicable

ERG comments on design and generalisability

The ERG noted that subgroups of patients who had failed ≥ 3 prior preventive medications were the appropriate population to address questions on the efficacy of GMB, given the company's positioning. The outcomes were also judged to be relevant and appropriate. Unfortunately, the length of the placebo-controlled period in all trials was limited to either three (CONQUER, REGAIN) or six (EVOLVE-1 and EVOLVE-2) months. Therefore, it is challenging to judge the long-term effectiveness of GMB compared with placebo or best supportive care, as the company assumes patients will experience these benefits over a 25-year period (CS section B.3.3.2.4). Similar uncertainties in long-term effectiveness have been raised for similar treatments in earlier appraisals (see section 4.2.2 for further discussion)[1]

The ERG identified a few factors that may impact on generalisability of the GMB trial populations to the NHS context. First, for some patients, the prior preventive medication failures were for treatments not routinely used in the UK. This was particularly the case for patients with ≥ 3 prior preventive medication failures. In this subgroup of the CONQUER trial, [redacted] in the placebo group and [redacted] in the GMB group had failed on medication not used in the UK (see Table 8, company response to ERG PFC letter). Information about the most common preventive medications in the CONQUER trial not routinely used in the UK was only provided for the combined EM and CM study populations. The company's response to question A4 of the ERG's PFC letter indicated that, in the CONQUER trial, the most common medication failures not available in the UK were for valproate ([redacted]), flunarizine ([redacted]) and medications locally approved ([redacted]

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

[redacted]). Similar data were not provided for other trials conducted by the company.

Second, patients could have received botulinum toxin A prior to galcanezumab as one of their earlier treatment failures ([redacted] in the CONQUER trial, company response to question A4 of the PFC), which does not reflect the company's positioning of GMB and may also not reflect standard clinical practice in the UK should GMB be approved.

Primary and key secondary outcomes

Table 10 summarises clinical effectiveness for the subgroup of patients with 3-4 preventive medication failures from CONQUER, REGAIN, EVOLVE-1, and EVOLVE-2 considered by the company to be the most clinically relevant population to inform clinical and cost-effectiveness of GMB.

Table 10 Clinical effectiveness of galcanezumab versus placebo for key outcomes in patients with ≥ 3 prior preventive medication failures (based on CS Tables 27, 28, 30, 31, 33, 34 and 35)

Study	Outcome	CM: Effect (95% CI)	EM: Effect (95% CI)	HFEM: Effect (95% CI)
CONQUER	**Change from baseline in mean migraine headache days**	[redacted]	[redacted]	[redacted]
	Change from baseline in mean headache days	[redacted]	[redacted]	[redacted]
	≥ 50% reduction from baseline in migraine headache days	[redacted]	[redacted]	[redacted]
	≥ 30% reduction from baseline in migraine headache days	[redacted]	-	[redacted]
REGAIN	**Change from baseline mean migraine headache days**	[redacted]	-	-
	Change from baseline mean headache days	-	-	-
	≥ 50% reduction from baseline in migraine headache days	[redacted]	-	-
	≥ 30% reduction from baseline in	-	-	-

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Study	Outcome	CM: Effect (95% CI)	EM: Effect (95% CI)	HFEM: Effect (95% CI)
	migraine headache days			
EVOLVE 1 and 2 pooled	**Change from baseline mean migraine headache days**	-	-	-
	Change from baseline mean headache days	-	-	-
	≥ 50% reduction from baseline in migraine headache days	-	[redacted]	-
	≥ 30% reduction from baseline in migraine headache days	-	-	-

GMB 120mg was associated with a greater mean change in monthly MHD compared with placebo for all patient subgroups. Chronic migraine patients experienced approximately [redacted] extra migraine free days compared with placebo (CONQUER: [redacted]; REGAIN: [redacted]) than for episodic migraine (CONQUER: [redacted]) or high frequency episodic migraine patients (CONQUER: [redacted]).

A similar pattern was found with mean headache days (HDs). There was a reduction in monthly HDs for all patient groups compared with placebo and [redacted].

In the CONQUER trial, the proportion of GMB patients with ≥ 50% reduction from baseline in MHDs days (CS, Table 28) were similar for CM ([redacted]), EM ([redacted]), and HFEM ([redacted]) patients. REGAIN, which included only CM patients, found lower response rates for GMB ([redacted]) than in CONQUER. Differences with placebo were [redacted] for CM (CONQUER: [redacted]) than EM (CONQUER: [redacted]) and HFEM (CONQUER: [redacted]) patients largely due to the [redacted] placebo response rates in the latter subgroups.

The proportion of GMB patients with ≥ 30% reduction from baseline in MHDs was available only for CM patients in CONQUER. As above, GMB patients ([redacted]) were [redacted] likely to respond than placebo ([redacted]) ([redacted]).

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Excluding prior botulinum toxin A failures

As noted above, NHS patients would be unlikely to receive botulinum toxin A as one of their ≥ 3 prior preventive medication failures at the point of eligibility for GMB. Table 6 of the Company's response to PFC reported data that excluded these patients from the analyses. However, these data are limited because the Company did not report separate estimates for CM, EM and HFEM patients.

The difference in mean change in monthly MHDs was slightly [redacted] when excluding patients with prior botulinum toxin A failure ([redacted]) compared with all patients with ≥ 3 prior preventive medication failure ([redacted]). The odds ratios for achieving 30% and 50% response (ie reduction from baseline in monthly MHDs at month 3) were [redacted] when excluding patients with prior botulinum toxin A failure (OR=[redacted] and OR=[redacted], respectively) compared with all patients with ≥ 3 prior preventive medication failure ([redacted] and [redacted]).

Quality of life

Table 11 shows all patient subgroups receiving GMB experienced improvements in quality of life compared with placebo. All differences were [redacted], except for Migraine Specific Quality of Life Questionnaire (MSQ) role restrictive subscale in HFEM patients. Mean differences with placebo met criteria for minimally important differences[8] (3.2 points on role-restrictive function and 7.5 points on emotional function for group differences) in all patient groups and therefore were likely to be clinically meaningful.

For EM and HFEM patients, CIs for differences in quality of life measures were wide, with lower bounds close to zero. Estimates for CM patients were more precise with lower and upper CIs suggesting a clinically meaningful effect.

Table 11 Mean difference in health related quality of life mean change from baseline difference: GMB versus placebo in patients with ≥ 3 prior preventive medication failures (based on CS Tables 29, 32, 34)

Study	Outcome	Chronic migraine	Episodic Migraine	High frequency episodic migraine
CONQUER	MSQ total	[redacted]	[redacted]	[redacted]
	MSQ role function-restrictive	[redacted]	[redacted]	[redacted]
	MSQ role function-emotional	[redacted]	[redacted]	-
REGAIN	MSQ total	-	-	-
	MSQ role function-restrictive	[redacted]	-	-

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

	MSQ role function-emotional	-	-	-

CI: confidence interval; MSQ: Migraine Specific Quality of Life Questionnaire

Discontinuation

Discontinuation was low in all the company conducted trials. For example, in the 3-month double blind phase of CONQUER, [redacted] of patients discontinued for any reason in the GMB group and [redacted] in the placebo group (CS, Figure 4). Only [redacted] discontinued due to adverse events in the GBM group and [redacted] discontinued in the placebo group (CS, Figure 4).

Longer term evidence of discontinuation for GMB is provided in CGAJ (12 month open label study), the open-label phase of CONQUER (data up to 6 months), and the open-label phase of REGAIN (data up to 12 months). Discontinuation due to adverse events was [redacted] in REGAIN [redacted] clinical study report [CSR] CGAI section 12.2.1.2), followed by CONQUER ([redacted] CS section B.3.2.2.6.3) and CGAJ ([redacted] CS section B.3.2.2.6.3).

Four month washout periods were used to assess the impact of discontinuation from GMB in four trials (REGAIN, CGAJ, EVOLVE-1, EVOLVE-2).

For CM patients, the REGAIN trial found that at month 16 of the post-treatment (washout) period, patients had experienced a waning in reduction from baseline of [redacted] monthly MHD compared with month 12 after treatment discontinuation [redacted] compared to [redacted], Table 52, Company response to PFCs and Figure 2 below); that is, patients' improvement reduced by [redacted] over the four month period.

The ERG notes that the company's extrapolation of these waning treatment effects in the economic model is highly uncertain. The company extrapolated from this four-month post-treatment (washout) period to assume monthly change in MHDs for patients who had responded to GMB would continue to wane at the same rate back to baseline frequency of monthly MHDs over a period of [redacted] months after discontinuation of treatment (see section 4.2.6 for further details). However, Figure 2 does not support the assumption of a linear waning effect even within the four-month post-treatment (washout) period. It is possible that the waning effect has a complex, unknown, form beyond the observation period and that larger reductions in effectiveness may have occurred after the 4-month washout period of REGAIN. The implications of these assumptions to the economic model are discussed in more detail in section 4.2.6.

Although study CGAJ also included CM patients, the ERG were unable to find similar data reported for this study. Appropriate pooling of wash out data from REGAIN and CGAJ, taking into account

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

the non-linear nature of the waning effect after discontinuation, may have provided more plausible estimates. It would have also enabled an assessment of heterogeneity of waning effects across trials.

Figure 2 Washout data – REGAIN (reproduced from CS, Figure 17)

Figure 3 illustrates the quadratic function fitted to the waning data from EVOLVE-2 for MHDs in EM patients. This is a more sophisticated approach than used for CM patients, and is likely to better account for the non-linear nature of the waning effects observed. The company extrapolated from this four-month period assuming that monthly change in MHDs would continue to wane at the same rate back to baseline frequency of monthly MHDs. Based on these data, the company assumed the treatment effect would wane back to baseline monthly MHDs over a period of [redacted] months after discontinuation of treatment. The ERG were unable to find similar data for EVOLVE-1. The CS reported that when data from EVOLVE-1 and EVOLVE-2 were pooled this led to implausible predictions. It is unclear from the CS the extent to which waning effects differed between trials of EM patients. For a more detailed discussion of the implications for the economic model see section 4.2.6.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Figure 3 Washout period EVOLVE-2 (reproduced from CS, Figure 16)

Safety

The CS reported no deaths and relatively few serious adverse events (SAEs) (see CS section B.2.9 for further details). There do not appear to be any additional safety issues identified for GMB in comparison with other currently recommended treatments for patients with ≥ 3 prior preventive medication failures.

In the CONQUER study, two patients in the GMB group and two in the placebo group experienced SAEs. The most frequently reported adverse effects across all GMB trials were injection site pain (injection site reaction ( ), vertigo ( ), constipation ( ) and pruritus ( ).

The EMA identified some uncertainties about the safety of GMB. First, there is very limited data on safety in pregnancy as pregnant women were excluded from clinical trials of GMB. This is an important uncertainty as the majority of migraine patients are females of child bearing age.[9]

Second, in common with other CGRP antagonists, GMB could theoretically aggravate ischemic events such as stroke, transient ischaemic attack and myocardial infarction. This is because CGRP is thought to have a protective effect on cardiovascular health. Clinical trials have not found meaningful differences between GMB and placebo groups on cardiovascular (CV) related outcomes. However, as noted by the EMA, higher risk (i.e. with recent acute CV events and/or serious CV risk) and older age (> 65 years) patients were excluded from clinical trials. Therefore, potential CV risks cannot be ruled out at this stage.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

3.3.1 EM population

No indirect comparisons were carried out for EM as BSC is the comparator of interest for which the Placebo arm of GMB trials was taken as a proxy.

3.3.2 CM population

Due to the lack of direct RCT evidence comparing GMB to botulinum toxin A in CM patients, the company conducted ITCs to compare the two treatments. Two studies of botulinum toxin A with data available for the population of patients who have failed at least 3 previous therapies were identified and included: PREEMPT-1 and PREEMPT-2 (data for this subgroup were available in a report by CADTH[7]). However, no data on the proportion of responders were available for botulinum toxin A in the target patient population, so ITC in the 'all-comers' CM population were conducted to supplement the results. However, the ERG notes that whilst the SR was appropriate for studies reporting outcomes for CM patients who failed ≥ 3 preventive treatments, it was not sufficiently inclusive for the 'all-comers' CM population (see Section 3.1.2). Therefore, the 'all-comers' population results should be interpreted with caution as they may only include a subset of the relevant studies.

1.1.1.1 Assessment of ITC assumptions

The key assumption for ITC is that patient populations are comparable across all included studies (i.e. the consistency, or transitivity, assumption) which implies that the studies included in the indirect comparison do not differ with respect to the distribution of known treatment effect modifiers. Results of the ITC will still hold when study characteristics differ if they are not treatment effect modifiers.

Baseline patient characteristics

Baseline patient characteristics of CM patients who have previously been unsuccessfully treated with at least 3 prior preventive migraine treatments were similar in the REGAIN and CONQUER trials (CS, Table 38). For further discussion, see section 3.2.1.

Full baseline characteristics for CM patients who have previously been unsuccessfully treated with at least 3 prior preventive migraine treatments were not reported for the botulinum toxin A trials (PREEMPT-1 and -2).[7] Although these values have been considered in a previous NICE TA,[10] they are redacted and were not made available to the ERG. Only baseline MHD data for this subgroup of patients in the PREEMPT-1 and -2 studies were available[7] and are presented in Table 12 along with comparable values for CONQUER and REGAIN. The populations appear to be comparable across the trials on this characteristic, although it is not possible to draw conclusions about the comparability

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

between the galcanezumab subgroups of REGAIN and CONQUER and the PREEMPT subgroups on other potential effect modifying characteristics.

Table 12 Baseline mean migraine headache days in CM patients with ≥ 3 prior preventive medication failures

	BSC/Placebo			Galcanezumab			Botulinum toxin A		
Study	**N**	**Mean**	**SD**	**N**	**mean**	**SD**	**N**	**mean**	**SD**
CONQUER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
REGAIN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
PREEMPT-1[a]	109	19.7	4.05	-	-	-	107	19.5	4.03
PREEMPT-2[a]	139	19.2	4.30	-	-	-	124	19.3	3.8

[a] monthly values based on 28 day month; BSC, best supportive care; CM, chronic migraine; N, number of patients included; SD, standard deviation.

Detailed baseline characteristics for CM patients in the 'all-comers' population were available for REGAIN (GMB vs placebo, see CSR for REGAIN[11] for further details) and PREEMPT-1 and -2 (botulinum toxin A vs placebo)[7] (see also CS, Table 38). Populations appeared comparable across these studies on baseline characteristics, including on potential effect modifiers such as baseline MHD, age and gender (see Table 13) and values are similar to those in the DTT-3 population (Table 12). The only substantial difference between trials was the proportion of DTT-3 patients in the analyses (REGAIN range [redacted] PREEMPT-1 31-32%; PREEMPT-2 36-39%). The proportion of DTT-3 patients could be an effect modifier as differences between GMB and placebo in pre-planned subgroup analyses were highest in patients with ≥ 2 failed preventive treatments, followed by patients with ≥ 1 failed preventive treatments, and then on the all-comers population.[9] If the proportion of included DTT-3 patients is an effect modifier, this can present problems for the consistency assumption in the 'all-comers' population ITC. Although this would likely result in conservative estimates of the relative treatment effect of GMB compared to botulinum toxin A, i.e. favouring botulinum toxin A.

Table 13 Baseline characteristics in CM patients for 'all-comers' population (based on CS table 38, CSR REGAIN[11], and CADTH Report[7])

Study	Age: Years (SD)	Gender: % females	Proportion of DTT-3 patients at baseline	Baseline MHDs: mean (SD)	Baseline HDs: mean (SD)
REGAIN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

PREMPT-1[a]	**Botulinum toxin A:** 41.2 (10.49) **Placebo:** 42.1 (10.46)	**Botulinum toxin A:** 89.1% **Placebo:** 85.8%	**Botulinum toxin A:** 31.38% (107/341) **Placebo:** 32.25% (109/338)	**Botulinum toxin A:** 19.10 (4.04), n=341 **Placebo:** 19.10 (4.05), n=338	**Botulinum toxin A:** 20.0 (3.73), n=341 **Placebo:** 19.8 (3.71), n=338
PREMPT-2[a]	**Botulinum toxin A:** 41.0 (10.39) **Placebo:** 40.9 (10.82)	**Botulinum toxin A:** 86.2% **Placebo:** 84.6%	**Botulinum toxin A:** 35.73% (124/347) **Placebo:** 38.82% (139/358)	**Botulinum toxin A:** 19.2 (3.94), n=347 **Placebo:** 19.8 (3.71), n=358	**Botulinum toxin A:** 19.9 (3.63), n=341 **Placebo:** 19.7 (3.65), n=358

[a] monthly values based on 28 day month; CM, chronic migraine; DTT-3, difficult to treat population failed on 3 previous therapies; GMB, galcanezumab; MHD, migraine headache days; HD, headache days; n, number of patients included; SD, standard deviation.

Study characteristics

In addition, the studies of GMB and botulinum toxin A differed in the following characteristics, which may affect the estimated relative effects:

- definition of headache/migraine headache – galcanezumab: ≥30 minutes duration; botulinum toxin A: ≥ 4 continuous hours;
- statistical methods for calculating treatment effects – galcanezumab: mixed model repeated measures; botulinum toxin A: analysis of covariance;
- double blind treatment periods - galcanezumab trials: 3 months; botulinum toxin A: 24 weeks;
- the placebo is different in GMB (REGAIN two injections at each dosing visit, CONQUER two injections at visit 3 and one injection thereafter) and botulinum toxin A studies (31-39 injections sites).

As noted by the company, the placebo response in the all-comers population in the PREEMPT trials is higher than that in REGAIN or CONQUER, which may be partly explained by the perception of stronger efficacy related to a more invasive treatment.[12, 13] However, it is unclear whether this is an effect modifier and how much this will impact the reliability of the ITC in patients with ≥ 3 prior preventive medication failures. Nevertheless, using different types of placebo interventions as the common link for an ITC can lead to a violation of the consistency assumption required for ITC.[14]

For the PREEMPT trials, limited evidence was available for outcomes at week 12 and all ITC used data at 24 weeks. The low number of included studies is another limitation with at most two studies per direct comparison and four studies per network. The sample size of the individual study groups, for the treatment resistant patient population was also small and this is reflected in the uncertainty of the estimates and the width of the 95%CIs.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

ERG comment

Given the limitations outlined above, it is unclear whether the included trials are sufficiently homogeneous to satisfy the consistency assumption and the results of the ITCs must be interpreted with caution.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The methods used for ITC are adequate: the Bucher method was used to compare GMB to botulinum toxin A via the placebo common comparator. Fixed and random effects meta-analyses were used to pool REGAIN and CONQUER studies to obtain effects for GMB vs Placebo and PREEMPT-1 and -2 to obtain results of botulinum toxin A vs placebo prior to applying the Bucher method for ITC. However, there is not enough information to estimate between-study heterogeneity (only 2 studies per comparison) hence results of fixed and random effects meta-analyses are very similar. The fixed effect model results were chosen to perform the ITC, which the ERG considers appropriate.

Although CM patients with ≥ 3 prior preventive medication failures were the population of interest for comparison between GMB and botulinum toxin A, ITC were also carried out in the 'all-comers' population, defined as including patients regardless of how many previous treatment failures they had experienced (see Table 14). Evidence for this population is obtained from REGAIN and the botulinum toxin A studies (PREEMPT-1 and -2), but not from the CONQUER study which only included patients with 2-4 prior treatment failures (see Table 9).

No data were available from the PREEMPT studies on the proportion of patients with 30% or greater reduction in MHD, which is of most relevance for the CM population so this outcome could not be considered in an ITC. There were also no data on adverse events (AE), so no ITC were conducted.

Table 14 Outcomes for which indirect treatment comparisons were carried out (from CS Table 37)

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

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

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

3.4.1 CM patients with ≥ 3 prior preventive medication failures

ITCs to compare GMB to botulinum toxin A for CM patients with ≥ 3 prior preventive medication failures were carried out for the following outcomes: mean change from baseline (CFB) in the number of monthly MHD and HD, and three domains of the Migraine-Specific Quality of Life Questionnaire (Role Function-Restrictive, Role Function-Preventive and Emotional Function). Results are summarised in the CS (Table 41) and show that [redacted]. Results of the ITC for this outcome were used in both the company's and ERG's economic models, and are therefore presented in detail below along with the ERG's comments.

Change from baseline in mean MHD

Data for the subgroup of patients with ≥ 3 prior preventive medication failures (DTT-3 population) from the CONQUER, REGAIN and PREEMPT-1 and -2 trials were used to derive an indirect comparison of GMB vs botulinum toxin A, using the placebo arm as the common comparator. Table 15 shows the data sources and ITC results. The ITC indicates that GMB [redacted] mean MHD from baseline by [redacted] days compared to botulinum toxin A (Table 15) and the result [redacted].

Table 15 Mean difference in change from baseline in mean MHD for CM DTT-3 population: data sources and ITC results

	GMB vs Placebo				Botulinum toxin A vs Placebo			
Source	**N Placebo**	**N active**	**mean difference**	**95% CI**	**N Placebo**	**N active**	**mean difference**	**95% CI**
CONQUER*	42	42	[redacted]	[redacted]				
REGAIN*	[redacted]	36	[redacted]	[redacted]				
Pooled	[redacted]	[redacted]	[redacted]	[redacted]				
PREEMPT 1					109	107	-2.1	-3.89 to -0.31
PREEMPT 2					139	124	-3.5	-5.04 to -1.96
Pooled					248	231	-2.9	-4.07 to -1.74
ITC GMB vs Botulinum toxin A (fixed effect model)			[redacted]	[redacted]				

* CI for mean change from baseline across months 1- 3 for GMB and Placebo used in the ITC is wider than in company's main analyses (presented in Tables 27 and 33 of the company submission) as it does not account for the repeated nature of the measurements.

CI, confidence interval; GMB, galcanezumab; ITC, indirect treatment comparison; MHD, migraine headache days; N, number of patients included.

ERG comment

Precision in this ITC could have been increased if the variance of the mean difference in the changes from baseline in MHD calculated accounting for repeated measures over time for the CONQUER and REGAIN studies had been used (as reported in Tables 27 and 33 of the CS). Instead, the variance for the mean difference between GMB and placebo calculated for the purposes of the ITC did not account

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

for the repeated nature of the measurements, leading to slightly wider CIs in Table 15 and consequently less precision in the ITC results. However, this is unlikely to have a meaningful impact on model results.

3.4.2 CM patients 'all-comers' population

ITCs to compare GMB to botulinum toxin A for the general population of CM patients regardless of prior treatment failures ('all-comers') were carried out for the following outcomes: proportion of patients with at least 50% reduction in monthly MHD, mean change from baseline in the number of monthly MHD and HD, and three domains of the Migraine-Specific Quality of Life Questionnaire (Role Function-Restrictive, Role Function-Preventive and Emotional Function). Results are summarised in CS Tables 39 and 40 and show that [redacted].

The ERG notes that the SR was not sufficiently inclusive for the 'all-comers' CM population (see Section 3.1.2 and 3.3). Therefore, results should be interpreted with caution as they may only include a subset of the relevant studies.

None of these ITCs were used by the company in their economic model. However, the ERG used the ITC of GMB with botulinum toxin A for the proportion of patients with at least 50% improvement in MHD in scenario analysis and the in the ERG's base-case see Section 6.1. Therefore, data sources and results for this ITC are presented in detail below along with the ERG's comments.

Proportion of patients with at least 50% reduction in monthly MHD (Responders - 50%)

Data for the 'all-comers' population from the REGAIN and PREEMPT-1 and -2 trials were used to derive an indirect comparison of GMB vs botulinum toxin A, using the placebo arm as the common comparator. Table 16 shows the data sources and ITC results.

The ITC indicates that the odds of patients achieving a 50% or greater reduction in monthly MHD are [redacted] in patients receiving GMB compared to botulinum toxin A (Table 16) [redacted].

Table 16 Percentage of patients with at least 50% reduction in monthly MHD from baseline in the CM 'all-comers' population: data sources and ITC results

	GMB vs Placebo				Botulinum toxin A vs Placebo			
Source	**n/N (proportion) Placebo**	**n/N (proportion) active**	**Odds ratio**	**95% CI**	**n/N (proportion) Placebo**	**n/N (proportion) active**	**Odds ratio**	**95% CI**
REGAIN*	[redacted]	[redacted]	[redacted]	[redacted]				
Pooled	[redacted]	[redacted]	[redacted]	[redacted]				

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

PREEMPT 1					98/261 (0.375)	104/294 (0.354)	1.38	0.97 to 1.96
PREEMPT 2					104/294 (0.354)	142/279 (0.509)	1.89	1.35 to 2.65
Pooled					260/539	202/555	1.63	1.28 to 2.07
ITC GMB vs Botulinum toxin A (fixed effect model)			[redacted]	[redacted]				

* odds ratio calculated from simple proportion for ITC, CI is wider than if using categorical, pseudo-likelihood-based repeated measures analysis in company's main analyses presented in page 25 of the company submission (odds ratio 2.09 95%CI 1.56 to 2.80).

CI, confidence interval; GMB, galcanezumab; ITC, indirect treatment comparison; MHD, migraine headache days; n, number of responders; N, number of patients included.

ERG comment

Precision in the ITC could have been increased if the odds ratio which accounted for the repeated measures over time in the REGAIN study had been used (as reported in page 25 of the CS). Instead, an odds ratio between GMB and placebo based on simple proportions was calculated for the purposes of the ITC, leading to slightly wider CIs for the comparisons of GMB to Placebo Table 16 and consequently less precision in the ITC results. However, this is unlikely to have a meaningful impact on model results. The fact that other relevant studies may not have been included is likely to have a greater impact on the uncertainty in these analyses (Section 3.3).

The REGAIN and PREEMPT studies included both treatment naïve and previously treated patients. The CONQUER study included patients with 2-4 previous treatment failures which is a subset of the types of patients included in REGAIN and PREEMPT. An argument could be made to also include results from the full CONQUER population in the ITC for 'all-comers'. However, the company's choice to exclude this study is also defensible and is a more conservative option (i.e. will lead to less precise results and ensures the populations are, in principle, more homogeneous across GMB and botulinum toxin A studies).

3.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG verified the company's ITC methods and code and were able to reproduce all the results. No additional analyses were carried out.

3.6 Conclusions of the clinical effectiveness section

The CS included a systematic review of GMB and relevant comparators. Overall, there were no concerns with the searches. However, the ERG noted inconsistencies in how the resulting data were synthesised. For example, estimates used in the economic model were not always based on all available relevant data (see Sections 4.2.3, 1.1.1.5 and 4.2.7 for more details).

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

The CS rightly focused on the DTT-3 population (i.e. patients with ≥ 3 prior preventive treatment failures) as the most relevant data to inform the decision problem. However, there were limited available data for all outcomes in this population. In addition, there were concerns about the generalisability of included participants since most DTT-3 patients in CONQUER had failed on a treatment not used in the UK.

Differences in effectiveness between GMB and botulinum toxin A were informed by ITCs using placebo as the common comparator. The company acknowledged a number of limitations with these analyses. First, there were a small number of participants included in only four relevant trials. Second, there were differences in trial methods including definition of headache/migraine headache, statistical methods for calculating treatment effects, and double-blind treatment periods. Third, substantially higher placebo response rates were observed in PREEMPT-1 and PREEMPT-2 compared with placebo response rates in REGAIN and CONQUER (although it is unclear whether placebo response rates are an effect modifier). In addition, the ERG notes that the SR may not have been sufficiently inclusive for the 'all-comers' CM population (see Sections 3.1.2 and 3.3). These limitations make the conclusions from the indirect comparisons highly uncertain.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

4 COST EFFECTIVENESS

This section focuses on the economic evidence submitted by the company and the additional information provided in response to the points for clarification. The submission was subject to a critical review on the basis of the company's report and by direct examination of the electronic version of the economic model.

4.1 ERG comment on company's review of cost-effectiveness evidence

The company performed a targeted literature review (TLR) to identify cost-effectiveness evaluations of prophylactic interventions used to treat people with migraine. The inclusion and exclusion criteria are provided in Table 22 in Appendix G of the CS. In brief, studies were included in the review if they assessed the cost-effectiveness of any preventative treatments for migraine. A broad range of studies were considered for inclusion. These included cost-effectiveness, cost-utility, and cost-minimisation, cost studies and utility studies.

In total, sixteen studies were considered to meet the eligibility criteria for the review. These studies are summarised in Appendix G of the CS. No published cost-effectiveness studies of galcanezumab were identified.

The CS outlines that the structure of the economic model presented in the CS was based on the approach described in the NICE TAs of erenumab and fremanezumab,[15, 16] as well as four of the sixteen studies identified in the TLR: three studies assessing erenumab in episodic and chronic migraine[17-19] and one study assessing fremanezumab in episodic and chronic migraine.[20]

The ERG notes the potential importance of one study in the TLR, which was not considered when developing the company's model structure. This was a US study published by the Institute for Clinical and Economic Review[21] which reported on the cost effectiveness of erenumab and fremanezumab compared to no treatment for episodic migraine, and to botulinum toxin A for chronic migraine. Importantly, unlike the company's model, this model considered not only frequency of migraine, but also severity, with severity of headache/migraine categorised as either mild, moderate or severe. The company provided a short summary and critique of the Institute for Clinical and Economic Review study in Appendix G, Section G.1.3.2 and highlighted the incorporation of severity as a strength of the study.

In response to clarification questions the company outlined a number of reasons for the exclusion of severity from the economic model including: considerable increase in the model complexity; a lack of data to inform the granularity that would be required to incorporate severity within the current health

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

states of the model; the difficulty in capturing severity given its subjectivity; and the lack of severity included in previous NICE TAs.[2, 6, 22]

Despite this, the ERG considers the approach of incorporating migraine severity to be relevant. A brief summary of the Institute for Clinical and Economic Review study is reported in Appendix G, Section G.1.3.2. Further details of the relevance of incorporating migraine severity in the economic model are provided in Section 4.2.2 and Section 4.2.7.

The ERG is otherwise satisfied with the company's review of the cost-effectiveness literature.

4.2 ERG's summary and critique of company's submitted economic evaluation

The company presented a *de novo* analysis based on a Markov model. The ERG notes that the model structure appears similar to the structures used in the economic evaluations identified in the cost-effectiveness review (Section 4.1)

4.2.1 NICE reference case checklist

A summary of the company's *de* novo economic evaluation is presented in Table 17 with comment on the similarity of the analysis to the NICE reference case.

Table 17 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The model considered QALY benefits to treated individuals.
Perspective on costs	NHS and PSS	Costs considered were NHS and PSS.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Fully incremental cost–utility analysis.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The economic model used a time horizon of 25 years – sufficient to capture important differences.
Synthesis of evidence on health effects	Based on systematic review	Systematic review was conducted for evidence of health effects. Indirect treatment comparison was conducted to combine relevant clinical trial data. This is potentially appropriate but there is inconsistency between the use of results from an individual trial and

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

		all of the available data for relevant populations.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects were presented in QALYs. Measured directly from patients in the trials. Utility data was mapped from MSQ to EQ-5D-3L. Disutility associated with number of monthly migraine headache days.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Utilities were populated using Migraine-Specific Quality of Life Questionnaire (MSQ) data collected by patients in the CONQUER trial.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	UK population valuation set used within mapping, described in Gillard, 2012. [23]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No special weighting undertaken.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs considered were NHS and PSS. Resource use was taken from a US survey but priced using prices relevant to the NHS and PSS.

NHS, national health service; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.

4.2.2 **Model structure**

The company developed a *de novo* cost-effectiveness model in Microsoft Excel to evaluate the cost-effectiveness of galcanezumab versus relevant comparators in two parallel analyses, separating episodic migraine (including a separate subgroup of HFEM) from chronic migraine. Both analyses were conducted with a dedicated set of input parameters. For both episodic and chronic migraine patients, galcanezumab was compared to BSC; an additional analysis comparing galcanezumab to botulinum toxin A was conducted for chronic migraine.

Within the model, the impact of migraine is captured by 30 health states representing the frequency of migraine headache per 30-day model cycle. This is used to drive differences in HRQoL and costs in the model, with quality adjusted life-years (QALYs) and costs generated for each state and then combined as a weighted average according to the proportion of patients in each state. Within each separate state, and for each model cycle, the distribution of patients across the range of monthly MHD

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

(ranging from 0 to 30 per cycle/month) is estimated by fitting a parametric distribution to trial data on the frequency of MHD. The choice of distribution was based on goodness of fit analyses. For the EM population, a negative binomial distribution was fitted to data from the all-comers population from the EVOLVE-1 and EVOLVE-2 trials. For the CM population a beta binomial distribution was fitted to data for the all-comers population of the REGAIN trial (see CS, Appendix S, pg. 122).

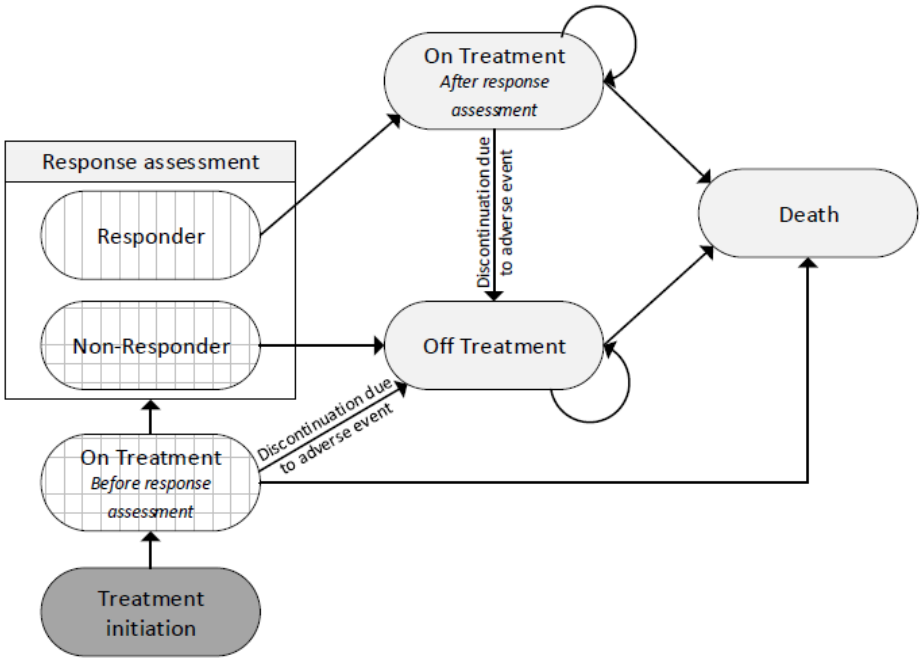
To account for the impact of treatment, the model shifts these distributions through changes in mean monthly MHD for different groups of patients, with differing mean monthly MHDs assumed according to the treatment received and whether patients are classified as responders, non-responders or have discontinued due to AEs. The treatment effect in the model therefore has two dimensions: i) the distribution of patients across different categories i.e. how many patients are classified as responders, non-responders and discontinuers and ii) the assumed mean monthly MHD within categories i.e. being classified as responder on galcanezumab implies a different mean monthly MHD to being classified as responder on BSC.

Response in the model is assessed following three model cycles (90 days). Following assessment of response, non-responders are assumed to discontinue treatment. The response threshold applied was a reduction of 50% in monthly MHDs in the EM population and 30% reduction in monthly MHDs in the CM populations respectively. Patients may also discontinue treatment at any time, with separate discontinuation rates applied in the period prior to and post assessment of response. Patients discontinuing treatment, either due to non-response or adverse events are assumed to rebound to baseline monthly MHDs over varying time horizons.

A schematic of the model structure can be seen in Figure 4.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Figure 4 Model structure (from CS, Figure 11, pg. 107)



Costs and utilities per monthly MHD are identical for galcanezumab and comparators in both episodic and chronic migraine (see Sections 4.2.7 and 4.2.8 for more information). Differences in total costs and utilities across the modelled galcanezumab and comparator arms are therefore driven by the difference in mean MHD (and the corresponding distribution of population monthly MHD).

ERG comment

The ERG considers the Markov model submitted by the company to be restrictive in its simplicity, as it does not account for several important aspects of migraine. These include a focus on migraine frequency to the exclusion of other indicators of migraine severity and the omission of the natural history of migraine. Despite this, the ERG does acknowledge the similarity of the model structure to the models used in the NICE technology appraisals of erenumab[15] and fremanezumab[16]; that is, they are driven by response rate and the mean change in MHDs. The ERG, however, also notes important differences in the company's approach to modelling the distribution of monthly MHDs. A more detailed exposition of these issues is presented below.

Durability of the treatment effect

An implicit assumption of the economic analysis is that effects of treatment as observed at 90 days are extrapolated throughout the time horizon of the model. The company justifies this assumption on the basis of long-term data from the REGAIN and CGAJ studies. The company also notes that this is consistent with assumptions made in the appraisal of erenumab and fremanezumab. The ERG, however notes that these studies provide only limited follow up (maximum 1 year) and that neither

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

study provides comparative evidence. As such these studies provide only limited evidence to support the assumption of a durable treatment effect. Further, the ERG highlights concerns raised in the previous appraisals regarding the plausibility of extrapolating the short-term comparative evidence over long periods of time and that this has been identified as a significant source of uncertainty.

The ERG, concurs with these previous assessments and considers the assumption of an ongoing durable treatment effect to represent a significant source of uncertainty. However, the ERG also highlights that this uncertainty may be mitigated if patients are regularly monitored with a view to discontinuing treatment where it is no longer beneficial.

Omission of migraine severity and headache frequency

A limitation of the economic model structure is that it focuses on frequency of migraine and does not account for other dimensions of the condition which may impact on both HRQoL and costs. Specifically, the model does not account for changes in either migraine severity or the frequency of headache that is not classified as a migraine. Clinical advice received by the ERG highlighted that both migraine severity and headache frequency are aspects that are important in determining the overall burden of the disease. Further comments from the ERG's clinical advisor suggest that an effective treatment (such as galcanezumab) would likely impact upon both these aspects as well as migraine frequency.

With regards to severity of migraine, the ERG notes the US economic evaluation highlighted in Section 4.1, where both migraine frequency and severity were included in the model structure using a tripartite classification of mild, moderate and severe migraine. In response to the ERG's clarification questions, the company outlined several reasons why this structure was not adopted in its *de novo* model. These included the lack of appropriate data to inform the granularity that would be required to incorporate severity in the model. The ERG accepts that some assumptions may have been made to incorporate severity into the model but considers that these may have been appropriate in the context of providing a richer economic analysis better able to reflect the benefits of treatment. In this regard, the ERG also notes that scenario analyses presented assuming differential utilities between treatment arms may allow the model to capture these other dimensions of migraine – see Section 4.2.7 for further discussion.

Omission of natural history

The CS acknowledges that a limitation of the presented model is the exclusion of natural history. The company justifies this exclusion in their clarification response and outlined that this was due to lack of data on the long-term effects of migraine and in particular how this might impact upon active treatments.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

The ERG considers this an important omission and notes that one important consequence of this exclusion is that mean monthly MHDs remain constant for all patients through the entire 25-year time horizon. The only exception to this being the initial treatment effect and waning of this effect assumed after discontinuing active treatment. This assumption of near constant monthly MHDs lacks face validity and is counter to the available evidence on natural history. For example, a 30-year prospective Swiss study[5] identified by the ERG found that the frequency of migraine fluctuated significantly within individual patients, with a substantial proportion of patients showing complete remission of symptoms by the end of the 30 year follow up period. Other studies also offer similar findings and suggest a pattern of decreasing frequency and remission of headache and migraine symptoms with increased age. [24-26] In this regard it has been observed that symptoms in female patients will tend towards resolution post menopause (women comprise about 75% of migraine patients[27]).

This reduction in the severity of migraine over time is likely to have important consequences for the cost-effectiveness of any active treatment, particularly when considered in the context of the assumption of continued lifetime treatment. This is because natural history will tend to erode the benefits of treatment, rending continued treatment increasingly less cost-effective. Given this effect, the ERG emphasises the importance of clinicians complying with the summary of product characteristics (SmPC) recommendation that patients be regularly reviewed to assess the need for continued treatment.[28] This will ensure that patients only continue to receive treatment where it is both beneficial and cost-effective.

The ERG also notes scenario analyses presented in the appraisal of erenumab[15] and fremanezumab[16] which attempt to model positive discontinuation (discontinuation as a result of treatment success). Such scenarios align better with the SmPCs issued for the CGRP treatments in that they attempt to account for the need to continually assess the ongoing need for treatment. However, interpretation of such scenarios is problematic due to the lack of long-term evidence on the duration of treatment and durability of any continued benefits post discontinuation. Further, where such scenarios omit the role of natural history, they are likely to overestimate the benefits of treatment as they attribute remission of symptoms solely to receipt of an active therapy. The potential impact of this natural decline in severity of migraine in older patients is explored in scenario analysis in Section 6.

While the tendency for patient symptoms to resolve in older adulthood is well established, there is also evidence to suggest that patients with episodic migraine will often progress to develop chronic migraine. This phenomenon was highlighted in the company's clarification response when asked to comment on the impact of natural history. In their response, the company highlighted that the omission of natural history and the tendency for some patients to migrate from episodic to chronic migraine was likely to lead to the company model underestimating the cost-effectiveness of galcanezumab in the EM population. The ERG, however, disagrees with this assertion as it assumes

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

that CM patients do not have access to active therapies; both fremanezumab and botulinum toxin A are approved in the CM population.

Distribution of migraine headache days – ineligible patients

The ERG is concerned with the company's approach to modelling the distribution of MHDs. The model makes predictions about the distribution of monthly MHDs that are inconsistent with the licence and described modelled populations. This is particular apparent at baseline where the model predicts that a proportion of patients will start with < 4 MHDs per month despite this being inconsistent with the licenced indication and company positioning. Furthermore, when the EM population is modelled, it predicts that a proportion of patients will start with > 15 MHDs per month, which would be classified as CM. Similarly, when the CM population is modelled it predicts that a proportion of patients will start with < 8 MHDs per month. The extent of these inconsistencies is described in Table 18.

Table 18 Proportion of patient's ineligible for galcanezumab at baseline

	Mean MHDs at baseline	Proportion with < 4 MHDs according to company fitted distribution at baseline	Proportion < 8 MHDs at baseline	Proportion > 15 MHDs at baseline	Total proportion ineligible for treatment at baseline
Chronic (vs BSC)	[redacted]	[redacted]	[redacted]	N/A	[redacted]
Chronic (vs botulinum toxin A)	[redacted]	[redacted]	[redacted]	N/A	[redacted]
Episodic (vs BSC)	[redacted]	[redacted]	N/A	[redacted]	[redacted]
HFEM (vs BSC)	[redacted]	[redacted]	N/A	[redacted]	[redacted]

BSC, best supportive care; HFEM, high frequency episodic migraine; MHDs, migraine headache days.

Considering the impact of this issue on model predictions, the ERG expects that this will lead to some inaccuracy in the predicted distribution of monthly MHDs throughout the time horizon of the model, but that this will not impact significantly on model results because model outputs (costs and QALYs) are largely a linear function of monthly MHDs; the distribution of MHD is only important when model outputs are non-linearly related to monthly MHDs. This, however, remains a source of uncertainty in the model and the ERG considers that it may have been more appropriate to have modelled truncated distributions. This would have ensured model predictions retained face validity and would have improved model accuracy.

Distribution of migraine headache days – responder/non-responder distributions

The ERG notes a point of difference between the company's approach to modelling the distribution of monthly MHDs and the NICE TAs of fremanezumab[16] and erenumab.[15] In the previous appraisals the distribution of monthly MHDs was modelled separately for responders and non-responders i.e.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

different distribution were fitted to each. In contrast, the company's model fits a single pooled distribution to all patients. While both are potentially valid approaches, the former has the advantage that it allows for differences in the distribution of monthly MHDs between responders and non-responders to be reflected in the model and may therefore more accurately reflect the overall distribution of monthly MHDs.

In the response to clarification questions, the company stated this approach was undertaken because at the time of model finalisation, the CONQUER trial was still ongoing and there were concerns regarding the appropriateness of the distributions, given low patient numbers. Following a request from the ERG, the company assessed the estimated distributions to responders and non-responders, and visually compared the estimated pooled distributions to the fitted responder/non-responder distributions, concluding that both approaches produced similar predicted distributions of monthly MHDs.

The ERG expects that this simplification will likely lead to some inaccuracies in the predicted distribution of monthly MHDs. As with the previous issue, the ERG, however, does not expect this to impact significantly on model results because model outputs (costs and QALYs) are largely a linear function of monthly MHDs.

Inability to conduct incremental analysis

While the broad structure of the economic analysis is common across both EM and CM populations, the company utilises different inputs to model the monthly change in MHDs for galcanezumab depending upon whether the comparator is BSC or botulinum toxin A. This is implemented because data on the change in MHD stratified by response is not available for botulinum toxin A. The consequence of this inconsistency is that a fully incremental analysis, in which the cost-effectiveness of BSC, galcanezumab and botulinum toxin A are compared together, cannot be conducted. The ERG considers this a significant limitation of the model and, while the limitations in the available data are recognised, does not consider this a reasonable approach. See Section 1.1.1.3 for a full exploration of this issue.

4.2.3 **Population**

Galcanezumab is licensed for the prophylaxis of migraine in adults who have at least 4 migraine days per month. The economic analysis presented in the CS covers the narrower subpopulation of patients who both have at least 4 migraine days per month and have failed ≥ 3 prior prophylactic treatments.

Within the economic analysis, this population is divided into three sub populations; episodic migraine, high frequency episodic migraine (a subgroup of episodic migraine) and chronic migraine. Episodic migraine is defined as patients with fewer than 15 headache days per month, with at least 4 being

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

migraine days. High frequency episodic migraine is defined as patients with fewer than 15 headache days per month and 8 to 14 migraine days. Chronic migraine is defined as patients who experience 15 or more headache days per month of which at least 8 or more are migraine days. This division of the population was implemented to reflect the provision of botulinum toxin A which is restricted to patients with chronic migraine. In line with the marketing authorisation all scenarios excluded patients with fewer than 4 migraine days per month.

The modelled baseline characteristics were age, sex and mean MHD, which were drawn from the relevant subgroups of the CONQUER trial. These are summarised in Table 19.

Table 19 Baseline patient characteristics (adapted from Table 51 CS pg. 117)

	Age (years)	Gender (% Female)	Mean MHD
Episodic	[redacted]	[redacted]	[redacted]
High frequency episodic migraine	[redacted]	[redacted]	[redacted]
Chronic - Failed at least 3 preventive treatments	[redacted]	[redacted]	[redacted]

MHD, migraine headache days

ERG comment

The ERG considers the modelled populations to be broadly reflective of those treated in practice but notes that the clinical data used in the model are drawn from the sub-population of patients who have received 3 or more previous prophylactic therapies including patients who have previously failed botulinum toxin A (Section 3.2.1). This is inconsistent with provision of botulinum toxin A in the NHS and the expected positioning of galcanezumab. The episodic and HFEM populations are currently ineligible for botulinum toxin A on the NHS and therefore are unlikely to have previously failed botulinum toxin A. In the CM population, galcanezumab is likely to displace botulinum toxin A as the preferred treatment for patients who have failed ≥ 3 prior prophylactic treatments and therefore the incident population will be naïve to botulinum toxin A. The ERG requested at the PFC stage that the company present revised analyses limiting the population to patients who had not previously received botulinum toxin A. To consider the current population of patients who have already failed botulinum toxin A, the ERG further requested that the company consider the relevance of this population in relation to the positioning of galcanezumab. In response, the company stated that galcanezumab would only be considered at a 5th line position after patients have cycled through 3 oral preventatives and botulinum toxin A.. The company's response also included additional results excluding patients who had failed botulinum toxin A and showed that galcanezumab was similarly effective compared with placebo, though point estimates for several key outcomes were slightly

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

smaller. The company, however, did not provide scenario analyses in the botulinum toxin A failure population. .

The ERG notes that the company based the baseline characteristics used in the model on the CONQUER trial, while clinical data used to model treatment effects was drawn from all four trials (CONQUER, REGAIN, EVOLVE-1 and -2). This represents an inconsistency in the economic analysis. Exploratory analyses carried out by the ERG, however, demonstrated that this has very limited impact on cost-effectiveness (results not reported). Moreover, the ERG notes that the modelled population is likely to be a more reasonable reflection of the prevalent population who would be eligible for galcanezumab. The modelled population may, however, be less reflective of the incident population, who are likely to be younger with a mean age under 40.[29, 30] This may impact on the appropriateness of the modelled time horizon of 25 years. It may also have further consequences when considering the potential impact of natural history as patients' age will be a significant factor in determining the rate at which patients experience any age-related decline in the severity and frequency of migraine.[5, 30] This is explored in scenario analysis in Section 6.

4.2.4 Interventions and comparators

Galcanezumab was modelled as a self-administered subcutaneous injection using a pre-filled pen, with an initial loading dose of 240mg followed by a single monthly injection at a dose of 120mg. Patients receiving galcanezumab were assumed to use acute headache or migraine medication and healthcare resources associated with migraine in line with the mean MHD frequency, see Section 4.2.8.

The EMA authorisation of galcanezumab recommends that treatment benefit should be assessed within three months after initiation of treatment, and evaluation of the need to continue treatment is recommended regularly thereafter.[28] In the economic analysis, initial response to treatment was therefore assessed at the end of cycle 3 (day 90). This initial assessment aligned with the effectiveness evidence available from the CONQUER trial. In line with the model structure presented in Section 4.2.2, patients who did not meet the response criteria in the 90-day assessment period were assumed to discontinue treatment. Discontinuation was applied for the proportion failing to reduce mean MHDs by ≥ 50% versus baseline in the episodic migraine analysis; and ≥ 30% mean MHDs in the chronic migraine analysis. Responders to treatment were assumed to remain on treatment for the lifetime of the model, with a "negative" discontinuation rate applied to account for discontinuation resulting from AEs, see 1.1.1.4 for further discussion.

Comparators assessed in the economic evaluation were dependent upon the population under consideration. In the episodic migraine population, galcanezumab was compared with BSC. Best supportive care was assumed to consist of acute management of migraine using simple analgesics (i.e.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

ibuprofen, aspirin or paracetamol), a triptan with or without paracetamol or a non-steroidal anti-inflammatory drug (NSAID). Like the prophylactic strategies, BSC was also modelled in terms of response and non-response. However, response to BSC was assumed to be temporary, such that responders returned to baseline MHD after a period of 12 months.

In the CM population galcanezumab was compared with BSC, as well as botulinum toxin A. Dosing of botulinum toxin A, was 200mg every 12 weeks or 84 days. Response for botulinum toxin A was assessed after 3 months in line with the assessment period for galcanezumab and BSC. Note this differs from the length of the assessment period used in the appraisal of botulinum toxin A which used a period of 24 weeks, but is likely a reasonable reflection of actual pracctice.[10] Scenario analysis was presented assuming an assessment period of 6 cycles (180 days), which is approximately equivalent to an assessment period of 24 weeks. The results of this scenario analysis show this assumption has no material impact on the ICER.

The two other CGRP therapies, erenumab[15] and fremanezumab,[16] were not included in the company's base-case, nor were they included as comparators explored in any scenario analysis. The company also did not present a comparison versus other preventative treatments topiramate, propranolol, amitriptyline or gabapentin, which is in line with their recommendation as earlier options in the treatment pathway.

ERG comment

Omission of other CGRPs as comparators

The ERG considers that the model comparators are consistent with the NICE scope, but is concerned about the omission of erenumab and fremanezumab. As of the date of the CS neither erenumab nor fremanezumab had received a NICE recommendation and both were subject to ongoing appraisals. Fremanezumab has, however, since received a recommendation for use in patients with chronic migraine who have failed ≥ 3 prior preventative treatment failures. The appraisal of erenumab is ongoing. The approval of fremanezumab means it is likely to rapidly become standard of care in the relevant chronic migraine population and therefore represents a relevant comparator for galcanezumab.

Reflecting the ERG's concerns about the omission of erenumab and fremanezumab as comparators the ERG requested, at the PFC stage, that the company consider the impact of erenumab and fremanezumab becoming relevant comparators in the near future. The company's response noted recent approval in patients with chronic migraine, and agreed that fremanezumab would represent a potential comparator in this population. The company's response, however, highlighted that neither erenumab nor fremanezumab had received a NICE recommendation when the company received its

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

invitation to participate in the NICE appraisal process and that fremanezumab was not standard of care at the time of the company's submission.

The ERG recognises that at the time of the CS neither erenumab nor fremanezumab represented standard care and that any comparison of erenumab or fremanezumab with galcanezumab may have been speculative at the time of the production of the CS. The ERG, however, emphasises the importance of considering the relative cost-effectiveness of all CGRPs to ensure that the most cost-effective CGRP treatment is used in the NHS and to ensure continued efficient use of scarce NHS resources.

Sequential therapy

The company's economic model does not consider the potential for sequential treatment with active therapies i.e. the possibility that botulinum toxin A and galcanezumab may be used in sequence either as botulinum toxin A followed by galcanezumab or galcanezumab followed by botulinum toxin A. In a full economic analysis, it is appropriate not only to consider active therapies as direct comparators, but also to consider the comparative cost-effectiveness of alternative treatment sequences. This allows the optimum positioning of active treatments to be established. For example, it may be more cost-effective to use galcanezumab as a 5th line treatment following use of the cheaper botulinum toxin A, than to use it as 4th line treatment. Partial precedent for the evaluation of treatment sequences rather than simple comparisons of active treatments can be observed in many of the recent appraisals of biologics for the treatment of psoriasis,[31-33] where it is typically assumed that patients will cycle through 3 or more active treatments.

Regarding the plausibility of sequential treatment, the ERG notes the successful appeal in the appraisal of erenumab[34] which upheld that the committee should have considered eremumab as a 5th line therapy for patients who had failed botulinum toxin A. Clinical advice received by the ERG concurs that 5th line positioning of CGRPs is a plausible treatment sequence and noted that this would be the effective treatment sequence for the large prevalent population of patients who have failed of botulinum toxin A. Our clinical advisor, however, caveated this by noting that due to the limited availability of botulinum toxin A and the more burdensome administration associated with it, the preferred position for galcanezumab and other CGRPs in the incident population would be as a 4th treatment, with botulinum toxin A positioned as a 5th line treatment. In this regard the ERG notes that there is nothing in the NICE recommendation for botulinum toxin A that precludes prior use of CGRPs. The ERG does not present analysis including these additional comparators due to the significant resource required to conduct these analyses, but considers this an important issue that should be addressed.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Life-time treatment

The ERG questions the plausibility of the assumption that patients responding to galcanezumab remain on therapy for the lifetime of the model. The ERG notes that the SmPC for galcanezumab[28] states that evaluation of the need to continue treatment is recommended regularly following initial assessment of response. Advice from the ERG's clinical advisor suggests that continued lifetime treatment with galcanezumab is unlikely and that in practice it is likely that patients would periodical discontinue treatment. The clinical advisor to the ERG, however, also highlighted that such discontinuation of treatment may be temporary and that the majority of patients who discontinue treatment are likely to subsequently resume treatment.

The ERG further highlights that the assumption of continued treatment is very important when considering the relative cost-effectiveness of active therapies, including galcanezumab, to BSC because natural history data suggest that migraine severity and prevalence decline with age. This implies that the benefits of continuous treatment with an active therapy may diminish over time, with important consequences for cost-effectiveness. See Section 4.2.2 for a detailed exploration of this issue.

4.2.5 **Perspective, time horizon and discounting**

The analyses assumed the perspective of the NHS and Personal Social Services (PSS), and future costs and benefits were discounted at 3.5% per annum.

The time horizon of the base case analyses was 25 years and was considered to represent a lifetime time horizon. Two scenario analyses considering time horizons of 10 and 45 years were also presented. The company justified the choice of a 25-year time horizon noting committee preferences in the appraisal of eremumab and fremanezumab for a lifetime time horizon. The company describes that a 25-year time horizon is sufficiently long for all benefits and costs to be accounted for and that the uncertainty from short-term clinical trial data would inherently make any long-term estimates unreliable. The company also noted that the prevalence of migraine reduces significantly with age and particularly after the menopause.[35]

The ERG considers the company's choice of a 25-year time horizon reasonable in the context of the modelled cohort with an average age of [redacted]. As noted in Section 4.2.3 a longer time horizon may, however be more appropriate if considering an incident population with a younger mix of patients. The ERG, further notes that the absence of long-term data on the effectiveness of galcanezumab and comparator therapies means that projections over such long-time horizons are subject to significant uncertainty. A long time horizon also exacerbates the problems associated with not modelling natural history and in the view of the ERG this represents a significant weakness in the presented model with

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

potentially important implications for the estimated cost-effectiveness of galcanezumab. See Section 4.2.2 for further discussion.

4.2.6 **Treatment effectiveness**

As described in Section 4.2.2, migraine frequency is captured using probability distributions which describe the proportion of patients across the 30 migraine health states. The treatment effect in the model operates by shifting these distributions through mean monthly MHD, with separate distributions modelled for responders, non-responders, and those who discontinue treatment. The effectiveness of a specific treatment is determined by the proportion of patients classified as a responder, non-responder or "discontinuer" as well as the mean monthly MHDs for each of these groups. The following sections describe the data and assumptions made by the company to populate the proportion of patients classified as responders, non-responders, and discontinuers, as well as what being in each of these groups means in terms of migraine frequency (monthly MHDs).

1.1.1.2 Response rate

The response rate is assessed at 3 months (90 days) for all treatments. Response was defined as the proportion of patients achieving a ≥ 50% or ≥ 30% reduction in mean monthly MHDs for episodic or chronic migraine, respectively.

In the episodic migraine setting, the response rate was estimated using data from the DTT-3 subpopulation of EVOLVE-1 and -2, and CONQUER. In the HFEM subgroup analysis the response rate was obtained from the DTT-3 population of the CONQUER trial.

For the chronic migraine population, response rates were drawn from the DTT-3 population of the CONQUER trial with the response rate for botulinum toxin A assumed to be equivalent to galcanezumab. This assumption of equivalent response rates was justified on the basis of the ITC for 'all-comers' and 50% response rate, which found no evidence of statistically significant difference in response rates. The modelled response rates and their respective sources are shown in Table 20.

Table 20 Proportion of responders at the 3-month assessment

Analysis	Galcanezumab	Comparator	Source
Episodic (vs. BSC) – 50%	[redacted]	[redacted]	Naïve pooled response rate from the DTT-3 population from EVOLVE-1, -2 and CONQUER
Chronic (vs. BSC) – 30%	[redacted]	[redacted]	CONQUER, DDT-3
Chronic (vs. botulinum toxin type A) – 30%	[redacted]	[redacted]	CONQUER, DTT-3

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

High Frequency Episodic Migraine (vs. BSC) – 50%	[redacted]	[redacted]	CONQUER, DTT-3

BSC, best supportive care; DTT-3, difficult to treat population who have failed on ≥ 3 previous therapies.

ERG comment

Source of response data

The company appears to take a selective approach to modelling the proportion of responders. In the episodic migraine population data is drawn from a naïve pooling of all relevant studies, while in the chronic migraine population the company selects only the CONQUER trial when relevant data are also available from REGAIN. Because response data at the 30% threshold in the DTT-3 population is not reported for REGAIN in the CS, the ERG is unclear of the impact of this omission.

Assumption of equal response rates for galcanezumab and botulinum toxin

The company cites the reason for rejecting the ITC results and assuming equal response rates for galcanezumab and botulinum toxin A, to be the lack of a statistically significant difference in response rates based on the ITC of the 50% response rate in the 'all-comers' population. The ERG does not agree that this is a valid reason to exclude the results of the ITC, a non-statistically significant finding only suggests uncertainty regarding the magnitude of the difference and a properly specified model should account for this uncertainty. The ERG however, does consider there to be a degree of validity to the assumption of equal response rates given the data available. Data on response for botulinum toxin A patients is limited to the 50% criteria (and not available for the more relevant 30% cut-off) and is only available for the 'all-comers' population. Modelling of treatment effect on response therefore would require assumptions to be made regarding the generalisability of the results of the ITC to both a different population and outcome measure. There are also a number of other issues identified with the ITC regarding the comparability of the patient populations, completeness of data, as well as notable differences in the proportion of placebo responders which may further justify rejecting the estimates obtained from the ITC (see Section 3.4.2). Regarding this specific assumption the ERG, however, notes that similar assumptions were accepted in the appraisal of fremanezumab.[16]

The ERG also notes that we are asked to accept the results of a similar ITC for the outcome change from baseline in monthly MHDs. While this analysis is subject to fewer limitations than the ITC for response, due to data being available for the same outcome and in the DTT-3 population, other limitations of the ITC remain. This is a potential inconsistency and if we are to accept the results of the ITC of MHDs then arguably we should do this so for all outcomes. In Section 6 alternative assumptions are explored by the ERG regarding how to incorporate the results of the ITCs.

1.1.1.3 Change in monthly migraine headache days: Responders and non-responders

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Following the assessment of response in the model, responders and non-responders experience a change in mean monthly MHDs. The magnitude of the change is dependent upon the population under consideration, the treatment received and in the case of chronic migraine the comparison being made.

For all comparisons between galcanezumab and BSC (EM, HFEM and CM populations) the magnitude of the change in monthly MHDs was based on the relevant DTT-3 subpopulation of the CONQUER trial.

In the comparison between galcanezumab and botulinum toxin A (CM population only) evidence on the respective size of the change in monthly MHDs for botulinum toxin A responders is not available. The company therefore approximates the change in MHDs using data from an ITC of MHDs implemented in the DTT-3 population. Importantly, this ITC does not distinguish between responders and non-responders and is for the whole DTT-3 population i.e. responders and non-responders combined. The company therefore makes a number of assumptions about the change in monthly MHDs for responders and non-responders. For galcanezumab responders, the change in monthly MHDs is estimated based on a pooled analysis of the REGAIN and CONQUER trials, using data on change in monthly MHDs for the whole population i.e. responders and non-responders combined. For botulinum toxin A responders, the change is estimated relative to galcanezumab using the results of the ITC on change in MHDs, which reports a reduction of [redacted] MHDs per month. For both galcanezumab and botulinum toxin non-responders, the change in MHDs is derived by pooling the placebo arms of REGAIN and CONQUER. A summary of the change in MHDs for each population and comparison is present in Table 21.

Table 21 Change from baseline in mean MHDs for responders and non-responders

Analysis	Galcanezumab	Comparator	Source
Episodic (vs. BSC)			
Responders	[redacted]	[redacted]	CONQUER DTT-3 population
Non-responders	[redacted]	[redacted]	CONQUER DTT-3 population-
Chronic (vs. BSC)			
Responders	[redacted]	[redacted]	CONQUER DTT-3 population
Non-responders	[redacted]	[redacted]	CONQUER DTT-3 population
Chronic (vs. botulinum toxin type A)			
Responders	[redacted]	[redacted]	GMB values from GMB arms of REGAIN and CONQUER (DTT-3), botulinum toxin A

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

			calculated relative to GMB based on ITC
Non-responders	[redacted]	[redacted]	Pooled Placebo arms of REGAIN and CONQUER (DTT-3)
High Frequency Episodic Migraine (vs. BSC)			
Responders	[redacted]	[redacted]	CONQUER DTT-3 population
Non-responders	[redacted]	[redacted]	CONQUER DTT-3 population

BSC, best supportive care; DTT-3, difficult to treat population who have failed on ≥ 3 pervious therapies; GMB, galcanezumab; MHD, migraine headache days.

Responders to active therapies are assumed to retain their change in monthly MHDs for the duration of the model time horizon. Responders to BSC are assumed to wane back to baseline monthly MHDs over a period of 12 cycles. Non-responders are assumed to discontinue treatment following response assessment, at which point they wane back to baseline MHDs over time. The duration of this waning varies according to the treatment received and the population considered. See Section 1.1.1.5, Table 23 for a summary of the respective waning assumptions.

ERG Comment

The ERG has concerns with the sources used to generate the CFB in MHDs, the assumption of waning in responders to BSC, the approach used to generate values in the botulinum toxin A comparison, and the use of the ITC for the botulinum toxin A comparison. These are discussed below.

Sources of data used

As with the response data used in the model, the company appears to have taken a selective approach regarding which data sources to use in the model.

In the episodic population the company have omitted to use relevant data from EVOLVE-1 and -2, despite the fact that data on response are taken from a pooled analysis of the EVOLVE trials (1 and 2) and CONQUER. In the chronic migraine BSC comparison, the CONQUER trial is used, omitting data available from REGAIN. This is consistent with the response data used but stands in contrast to the botulinum toxin A comparison where values are sourced from both the CONQUER and REGAIN trials.

The reasons for this inconsistent approach are not clear. In general an approach based on using all available data would be more rational and would act to reduce uncertainty. Similar to the response outcome, the impact of the company's selective approach is unknow because relevant values were not reported as part of the CS.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Waning of response in BSC patients

The company's base-case assumes that any response to BSC is not durable and that patients wane back to baseline MHDs over a period of 12 months. Underlying this assumption is the fact that response to BSC is based on the placebo arm of the relevant trial evidence and therefore does not reflect the benefit of therapy but rather the combination of factors that constitute the placebo effect.

The contention that placebo effects are not durable is, however, a debatable issue and unknown given the lack of longer-term comparative evidence. Placebo effects may plausibly reflect several factors that would lead to persistent response. These could include the effects of regression to the mean, natural history and response to 4th line preventive treatments that would comprise BSC. The assumption that these effects wane is therefore subject to uncertainty.

Further, even if one accepts the underlying assumption that the placebo effect is not durable, the ERG questions whether unilateral application of waning is appropriate. This is because the effects of galcanezumab as observed in the supporting trial evidence will also include a placebo effects (this is one reason why relative treatment effects are measured relative to placebo and not to baseline). The waning of the placebo effects would therefore act on both treatment arms equally, such that a proportion of responders to galcanezumab will also wane back to baseline.

Given these uncertainties regarding the persistence of placebo effects, the ERG considers a series of scenarios in Section 6 exploring alternative assumptions regarding the response to BSC and the persistence of the placebo effect.

Inconsistent approach to modelling of botulinum toxin A comparison

The ERG accepts that the lack of stratified data on change in monthly MHDs for botulinum toxin A by responder status, means that some assumptions must be made but finds the logic of the company's approach difficult to comprehend. The company's approach appears to be centred on the assumption that the relative difference in MHDs for the whole population is indicative of the relative difference in monthly MHDs for responders. This assumption, however, cannot hold when the change in MHDs for non-responders and the response rate are assumed to be the same across both treatment groups, and necessarily implies that the model will make predictions that do not align with the results of the ITC. See Appendix 1 for a simple mathematical proof of this assertion. Indeed, where the response rate is < 100% this approach will imply that the model will predict a difference in MHDs that is lower than that estimated by the ITC. Even if we accept this assumption on the grounds that this is an approximation, it is unclear why the company took an approach in which the values used for galcanezumab contradict those used in the BSC – relative effects could have been applied to the values used in the BSC comparison. This means that the model makes predictions that contradict the

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

supporting trial evidence and importantly means that an incremental analysis in which the cost-effectiveness of galcanezumab, BSC and botulinum toxin A is assessed cannot be conducted.

Validity of ITC

As noted in Section 3.3, there are several concerns regarding the comparability of the trials included in the ITC and concerns as to whether the included trials are sufficiently homogeneous to satisfy the consistency assumption. Specifically, differences were noted in the definition of migraine headache; the statistical methods for calculating treatment effects; the assessment periods and the placebo used.

The impact of the differences between included studies is unknown, but it means that the results of the ITC are subject to uncertainty beyond that captured in the confidence intervals and by extension in the probabilistic economic analysis. Further, because the magnitude and direction of any bias resulting from these differences is unknown, it is unclear whether the estimated benefits of galcanezumab are either in whole or in part, a reflection of these potential biases. As such, the results of the economic analysis for the comparison between galcanezumab and botulinum toxin A should be interpreted with caution.

1.1.1.4 Discontinuation rate

The per cycle discontinuation probabilities applied differed in the assessment and post assessment periods. The values used in the assessment period were common across subpopulations with values for BSC and galcanezumab drawn from the CONQUER trial. The corresponding values for botulinum toxin A were drawn from the PREEMPT trials. In the post assessment period, the per cycle discontinuation probability for galcanezumab was drawn from the open label CGAJ study. This study assessed the safety and tolerability of galcanezumab over a period of 12 months. The modelled rate of discontinuation was based only on those patients classified as discontinuing due to AEs; patients discontinuing for other reasons were therefore excluded from this calculation. The modelled per cycle discontinuation probability for botulinum toxin A was based on data from the COMPEL study.[36] This study was a prospective open label trial which followed up patients receiving botulinum toxin A for a period of 108 weeks. Table 22 summarises the per cycle discontinuation probabilities applied in the model.

Table 22 Probability of discontinuation (adapted from Table 58 & Table 59 CS pg. 124 & 125)

	Probability of discontinuation	Reference
Assessment period		
Galcanezumab	[redacted]	CONQUER CSR[37]
Botox*	[redacted]	Diener et al. 2014[38]
BSC	[redacted]	CONQUER CSR[37]
Post assessment period		

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Galcanezumab	[redacted]	Study CGAJ[39]
Botulinum toxin A*	[redacted]	COMPEL trial[36]
BSC	[redacted]	Study CGAJ[39]

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

ERG comment

The ERG considers the sources used by the company to model to be generally reasonable, but has some concerns about the validity of using these values in a comparative context and the plausibility of the rates of discontinuation implied. Specifically, the ERG notes that these studies are in quite different populations. The COMPEL study is only in chronic migraine patients while the CGAJ study is combination of both episodic and chronic patients. As such the COMPEL study considers a population with much greater frequency of migraine headache (11.4 vs 22 MHD per month). The predicted rates of discontinuation are also very different with the rate applied to galcanezumab being four times that applied to the botulinum toxin A arm of the model. This difference in the discontinuation rate seems very large and does not fully align with the data from these studies which actually suggests that a smaller proportion of galcanezumab patients experienced serious AE than on botulinum toxin A patients (4.8% vs 10.5%). This higher rate of discontinuation also stands in contrast with the rates of discontinuation observed in the trial evidence which suggest that the short-term rate of discontinuation is actually higher for botulinum toxin A.

This model difference in the discontinuation rate is important in the context of the company's base-case and acts to favour of galcanezumab. This is due to the fact that patients discontinuing galcanezumab are assumed to benefit from a further reduction in MHDs over and above those enjoyed by responders to treatment. Increasing the discontinuation rate for galcanezumab therefore leads to the ICER decreasing. However, under more plausible assumptions, where discontinuers do not receive a premium, this differential rate of discontinuation acts in the favour of botulinum toxin A.

Given the lack of comparative evidence on the rate of discontinuation and the potential for this parameter to distort the results of the economic analysis, the ERG considers that a more reasonable assumption would be to assume equal rates of discontinuation across both active treatments. Section 6 therefore present scenario analysis considering alternative assumptions regarding the rate of discontinuation in the post assessment period.

1.1.1.5 Change in monthly migraine headache days for "discontinuers"

Patients classified as discontinuers comprise of two subgroups – those who discontinue prior to assessment of response and those who discontinue in the post assessment period. In both groups, patients are assumed to wane back to baseline monthly MHDs. The position from which they wane

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

from however, differs. Patients discontinuing in the assessment period are assumed to be non-responders and therefore wane back from the mean monthly MHDs for this group. Patients discontinuing in the post assessment period wane back from the corresponding mean monthly MHDs for responders.

The period over which patients wane back to baseline MHDs is assumed to be common across both these subgroups of discontinuers, but differed according to the population modelled and treatment under consideration. For galcanezumab patients, the waning period was estimated by extrapolating data from the pivotal trials, several of which included a washout period in which patients were observed following discontinuation of treatment. For the EM and HFEM populations, the EVOLVE-2 trial was used to model the waning period. In the chronic population, the REGAIN trial was used to model the waning period. A linear extrapolation was assumed in both populations. The waning period for BSC and botulinum toxin A were based on assumptions. The waning periods for each treatment and population are summarised in in Table 23.

Table 23 Modelled discontinuation parameters

Analysis	Galcanezumab	Comparator	Source
Episodic (vs. BSC)			
Waning period (months)	[redacted]	[redacted]	EVOLVE-2, 'all-comers' population
Chronic (vs. BSC)			
Waning period (months)	[redacted]	[redacted]	REGAIN, 'all-comers' population
Chronic (vs. botulinum toxin type A)			
Waning period (months)	[redacted]	[redacted]	REGAIN, 'all-comers' population
High Frequency Episodic Migraine (vs. BSC)			
Waning period (months)	[redacted]	[redacted]	EVOLVE-2, 'all-comers' population

BSC, best supportive care.

ERG Comment

The ERG is satisfied with the company's underlying assumption that patients discontinuing treatment wane back to baseline monthly MHDs but has several substantial concerns regarding the period over which they are assumed to wane.

The concerns centre around the quality of the data used to generate the predicted waning periods and concerns regarding the clinical and face validity of the estimates produced.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

With regard to the quality of the data used, the ERG notes that the estimated waning periods are based on very short term follow up data of just 4 months. This limited follow up is of concern in the context of the length of the projected waning periods which range from [redacted] months. The ratio of extrapolated to observed data is therefore very high. The extrapolation of this limited data also relies on the assumption that waning is linear; an assumption that does not appear to be supported by the REGAIN wash out data (Section 3.2.1). Further, it is not clear that the washout data are generalisable to a population discontinuing due to adverse events rather than as part of a protocol driven washout period.

The waning periods applied in the model for the chronic population are very long, and imply a waning period that is significantly longer (24x) than that assumed for botulinum toxin A. The ERG considers this unreasonable without some evidence to justify a different waning period across these two active therapies. The ERG also considers the difference in waning period between chronic and episodic migraine patients difficult to justify clinically with chronic migraine patients assumed to wane back over a period that is 4 times longer than episodic patients ([redacted] months). Further, the ERG fails to comprehend why different waning periods are used for galcanezumab depending on the treatment it is being compared to. This is inconsistent and serves to undermine the potential for an incremental cost-effectiveness analysis. Because of the way it is implemented, this assumption also means that patients discontinuing treatment experience an initial decline in MHDs i.e. discontinuing leads to an improvement in symptoms.

Given these concerns regarding the predicted waning period, the ERG presents several scenarios in Section 6, in which alternative assumptions are made regarding the duration of the waning period.

4.2.7 **Health related quality of life**

To model the impact of migraine on HRQoL, utility values were assigned to each of the 30 health states. Utility values were derived by mapping MSQ v2.1 values collected in the CONQUER trial (whole population) to EQ-5D-3L using a published mapping algorithm.[23] The same utility set was used for patients with episodic and chronic migraine. This broad approach is consistent with that adopted in the previous appraisals of erenumab and fremanezumab.[15, 16]

The company noted in their submission that EQ-5D data were collected as part of the CONQUER trial. The company, however, considered the mapped MSQ v2.1 values a preferable source of HRQoL data. This was justified on the basis that the EQ-5D data collected, required patients to evaluate their HRQoL on the day of the clinical visit. The company outlined that this may lead to elicited values underestimating the impact of migraine on HRQoL, due to more severe patients not attending clinical visits. Consistent with this argument, a comparison of mapped and directly generated utility values

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

shows that mapped values predict a substantially larger impact of migraine frequency on HRQoL, see CS Figure 18.

To evaluate the most appropriate approach to modelling utilities, the company consider several alternative assumptions. The assumptions considered were:

- Whether separate utility sets should be used for episodic and chronic migraine patients;
- The functional form of the relationship between utility values and migraine frequency;
- Whether a treatment effect should be included to reflect differences in HRQoL over and above those reflected in migraine frequency.

Regarding whether separate utility data sets should be used for episodic and chronic migraine patients, a comparison of HRQoL values for the two found that the predicted values were generally consistent across the two groups, with only limited evidence of divergence in patients experiencing > 14 monthly MHDs. On this basis, the company concluded that it was reasonable to use a common utility set across both groups.

With regards to the appropriate functional form, the company found that linear and quadratic models both fitted the data well, with the quadratic relationship observed to have a moderately better fit based on AIC and BIC criteria. The company, however, selected the linear model on the grounds that this is a more parsimonious model. The ERG notes also that this is consistent with the previous appraisals of erenumab and fremanezumab.

In exploring the possibility of a treatment related difference in utility values, the company noted that the utility values for galcanezumab were higher across all mean MHD values compared with placebo. Further, regression analysis demonstrated a strong, statistically significant, benefit of galcanezumab relative to placebo. To align with previous committee preferences for a common utility set across treatment arms, the company, however, chose to ignore this evidence and opted not to use treatment specific utility values in the base-case analysis. Scenario analysis presented by the company exploring the use of treatment specific utilities showed it had a modest impact on ICER values.

Table 24 illustrates the utility values applied in the economic model for each MHD health state. In line with the assumptions outlined above, the utility values used in the model were common to both the EM and CM populations, as well as to all treatments and comparators modelled. Based on the modelled utilities, the utility for patients ranges from [redacted] for patients experiencing 30 migraine days a month to [redacted] in patients experiencing no migraine days per month.

Table 24: Utility values for each MHD health state (from Table 61, CS)

MHD	On treatment (pooled)

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

0	[redacted]
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]
10	[redacted]
11	[redacted]
12	[redacted]
13	[redacted]
14	[redacted]
15	[redacted]
16	[redacted]
17	[redacted]
18	[redacted]
19	[redacted]
20	[redacted]
21	[redacted]
22	[redacted]
23	[redacted]
24	[redacted]
25	[redacted]
26	[redacted]
27	[redacted]
28	[redacted]
29	[redacted]
30	[redacted]

Abbreviations: MHD, migraine headache day.

ERG comment

Appropriateness of the CONQUER trial as source of utility values

The ERG notes two related issues regarding the source of the MSQ data used to generate the utility values used in the model. Firstly, that the utility values were based on the whole population of the CONQUER trial and not just on the relevant subgroup of patients who have failed ≥ 3 previous

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

preventative therapies. Secondly, that the utility values are based on data from the CONQUER trial alone, even though relevant HRQoL data were collected in both EVOLVE trials, as well as in the REGAIN trial.

In response to queries raised by the ERG at the PFC stage, the company justified the decision to use the CONQUER trial alone by noting that the EVOLVE and REGAIN trials included treatment naïve patients. As such the company considered that the CONQUER trial, which restricted recruitment to patients who had failed 2 to 4 preventive medication categories (not treatments), was most representative of the modelled population. The ERG agrees with the company's logic, but notes that the whole CONQUER trial population represents a broader population of patients than would be eligible for treatment with galcanezumab. As such, the predicted utility gains may not reflect those realised in the more restrictive population of patients who have failed ≥ 3 previous preventative therapies. Further, the ERG notes that because of the availability of relevant HRQoL from the EVOLVE and REGAIN trials in patients who have failed ≥ 3 previous preventative therapies, there is no need to utilise this broader population to generate utility values. The ERG also notes that scenario analysis presented by the company using the relevant subpopulation of patients who have failed ≥ 3 previous preventative therapies from all four trials results in a substantial increase in the ICER.

Appropriateness of treatment related utilities

Despite the company's conservative assumption to use a single set of utility values for both galcanezumab and BSC patients, compelling clinical evidence was presented to support the use of differential utilities. While no clinical explanation for these differences is presented by the company, the ERG considers that there is scope for such differential utilities between treatments as a result of uncaptured benefits. Specifically, the ERG notes that the company model does not capture either severity of migraine or frequency of headache. Both of these factors have the potential to drive HRQoL over and above a reduction in MHD and may explain the observed differences between treatment arms. Further, the ERG highlights supporting clinical evidence provided in Section 3.4 of the CS which reports a reduction in HDs that exceeds the reduction in MHDs. With regard to the previous appraisals, the ERG notes the lack of compelling empirical or clinical evidence presented to justify the use of differential utility values.

External validity of predicted utilities

In the general population of individuals aged 46 (the average age of the modelled cohort) mean utility is estimated to be 0.847 based on values reported in Ara and Brazer (2011).[40] This is notably higher than the utility value computed for patients experience zero MHD's which range from [redacted] to [redacted] depending on the source population. This apparent inconsistency, however, may be explained by limitations in the model structure which makes no account of severity, and by extension, headache frequency. Clinical advice received by the ERG suggested it is common that migraine patients will

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

continue to experience frequent headaches even when migraine days are significantly reduced. Further, our clinical experts commented that it is common for migraine patients to have co-morbidities which may also act to impact upon quality-of-life, further depressing reported utility values.

Generalisability of utility values over the time horizon

A limitation of the approach to modelling HRQoL is the assumption that utility values remain constant throughout the time horizon of the model and therefore make no account of the fact that quality of life may evolve over time. The impact of this omission may be considerable given the long-time horizon of 25 years, as there is significant scope for natural history to impact on the underlying severity of headache and migraine, as well as for the effects of aging to impact upon quality-of-life. The impact of natural history on quality-of-life is unknown, but it is reasonable to expect that the severity of headache and migraine declines in line with frequency and therefore that the disutility associated with migraine days will diminish over time. The impacts of aging may also act to assuage the benefits of reducing migraine days due to the accumulation of co-morbidities and increased frailty associated with aging. In this regard the ERG notes it is common when considering long-time horizons for utilities to be adjusted to account for the impact of aging and that this practice has been accepted on multiple occasions in previous technology appraisals considering extended time horizons.

4.2.8 **Resources and costs**

The company's model included galcanezumab acquisition costs, administration costs along with health state costs that were associated with the management of acute migraine.

Galcanezumab acquisition costs were sourced from MIMS and estimated per cycle based on a dose of 120 mg every 30 days. In line with the SmPC, the model allows for a loading dose of 240 mg in the first cycle. Administration costs for galcanezumab were included in the first cycle and account for the training of patients to self-administer. No further administration costs were included thereafter – implying all patients can successfully self-administer galcanezumab.

The botulinum toxin type A treatment cost comprised an acquisition cost and a regular administration cost based on an 84 day (12-week dosing) schedule. Drug acquisition costs for botulinum toxin type A were based on the British National Formulary (BNF) and estimated per cycle as per galcanezumab. A confidential CMU discount is available for botulinum toxin A. All analyses presented by the company is exclusive of this discount. Administration costs were based on NHS tariffs, follow-up attendance for single professional (code 400).[41]

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Additional costs associated with acute medication received were assumed to vary in line with MHD and were included as part of health state costs. Table 25 summarises the drug and acquisition costs applied in the model per cycle.

Table 25: Unit costs of the elements of prophylactic treatment

	Pack cost	Cost per 30 day cycle	Initial administration costs	Administration costs – ongoing per cycle	Total cost per cycle
Galcanezumab 120mg	List price: £386.50 PAS Price: [redacted]	List price: £386.50 PAS Price: [redacted]	£39.68	£0.00	[redacted] in the first cycle [redacted] thereafter.
Botulinum toxin type A 200 mg	£276.40	£98.74	£0.00	£41.43	£140.17

PAS, patient access scheme.

ERG comment

The ERG notes the omission of any administration costs for galcanezumab beyond the first cycle and the implicit assumption that all patients will be able self-administer. Consultation with clinical advisors to the ERG suggests that this is not a reasonable assumption and that it is likely that a proportion of patients will not be able to self-administer. This may be for a range of reasons. For example, people with physical or mental disabilities, the elderly or those who have a phobia of needles may not be able to self-administer. The ERG further notes that in the appraisal of fremanezumab the committee concluded it was unlikely that everyone having fremanezumab would be capable of self-administering treatment for the reasons outlined above.[16] In that appraisal it was agreed that applying an administration costs for 10% of people was reasonable, though this proportion was subject to uncertainty and had little effect on the model results. For parity with the previous appraisal of fremanezumab, the ERG implements a scenario in Section 6 applying an administration cost for 10% of galcanezumab patients.

The SmPC states that in patients receiving galcanezumab the need to continue to treatment should be evaluated regularly.[28] The company's economic model, however, does not include any monitoring costs to account for the routine review that patients would undergo. The ERG considers this a potential omission from the model, as advice received from clinical advisors to the ERG suggests that patients would normally be reviewed every 6 to 12 months to evaluate the need to continue therapy. The ERG, however, also highlights that the economic model does not permit "positive" discontinuation (i.e. discontinuation in successfully treated patients). This may mitigate the need to

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

include such costs, as to include them would be inconsistent with the underlying assumption of continuous treatment. See Section 4.2.4 for a full discussion of positive discontinuation.

1.1.1.6 Disease management

Other included healthcare resources identified by the company as supportive of the condition were: GP visits, emergency department visits, hospitalisations, nurse practitioner consultations and neurologist consultations. Unit costs were obtained from the most recent NHS reference cost schedule [42] and the Personal Social Services Research Unit (PSSRU) handbook.[43] The rates of consumption of these resources were sourced from Munakata et al,[44] a US specific survey of migraine patients. In line with values reported in Munakata et al[44] resource use varied with monthly migraine frequency, with a greater frequency of migraines associated with greater healthcare costs. Unit costs associated with the management of migraine are reported in Table 64 of the CS and model cycle consumption rates are presented in Table 65 of the CS, along with the total per cycle cost of disease management by MHD health state.

In addition to the healthcare resources described, the economic analysis also captures acute medication use, which similarly varied by monthly MHD. Acute medication costs included those associated with triptans, acetaminophen (paracetamol and containing products) and NSAIDs. Resource costs per MHD were estimated based on resource data collected as part of the CONQUER trial, full details of which are reported in Appendix V of the CS.

Unit costs used in the economic model are presented in Table 64 of the CS and model cycle consumption rates are presented in Table 65, along with the total per cycle cost of disease management by MHD health state.

ERG comment

The costs attributable to each of the 30 health states have an important role in the economic analysis, with an associated impact on cost-effectiveness. For example, in the EM sub-population the costs associated with the management and acute care of migraine account for 54% of total costs in the galcanezumab arm and 100% in the BSC. Within the company's economic analysis, about three quarters of the health state costs are associated with the supportive management of migraine, with the remainder attributed to acute medications used. Increasing the costs associated with either the management or acute treatment of migraine will tend to favour more effective therapies as it increases the costs associated with managing migraine.

In considering the values used by the company to populate these costs the ERG is relatively satisfied with the company's approach to the modelling of acute treatment costs, which are drawn principally from the available trial evidence, an approach consistent with the previous appraisals of erenumab and

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

fremanezumab. The ERG, however, has some concerns about the company's approach to modelling the healthcare and management costs associated with migraine and in particular those used to estimate the consumption rates of healthcare resources.

In the erenumab and fremanezumab appraisals the use of healthcare resources was based on the National Health and Wellness Survey (NHWS) 2016.[45] This study aimed to characterise the incremental migraine burden from the European patients' perspective according to frequency of migraine. The study included patients from five European countries (France, Germany, Italy, Spain and the UK). The NHWS study collected cross section data from respondents based on headache days with healthcare consumption evaluated based on four categories of headache days per month < 4, 4 to 7, 8-14, > 14. In this appraisal the company did not use the NHWS study, but instead opted to use a US survey Munakata et al,[44] which presented data on average healthcare resource in migraine population along with the average migraine days per month. Unlike the NHWS study, the Munakata et al[44] study did not explore the impact of migraine or headache days on healthcare consumption. To model the relationship between the MHDs and healthcare consumption the company therefore assumed a simple linear relationship between MHD and resource use by dividing average resource use by the average number of migraine days to generate figures per MHD.

In considering the appropriateness of these two approaches the ERG notes the company's comment in their submission that the resource rates are similar to those used in previous appraisals and that the method employed allows for a more complete relationship between MHD and resource consumption. The ERG, however, contests this statement and notes that resource consumption rates tend to be higher using the company's approach than using the data available from the NHWS. See Table 26 for a side by side comparison. Furthermore, the ERG considers that there are several factors that favour the use of the NHWS. Firstly, the NHWS study is more likely to be representative of resource consumption in the NHS given the population recruited is based on European patients, including UK patients. Secondly, the NHWS includes information on how resource use relates to frequency of headache. This avoids the need to make strong assumptions about the relationship between migraine frequency and healthcare utilisation. The ERG notes that the assumption of a linear relationship between MHD and healthcare utilisation is entirely arbitrary and is not supported by the available data from the NHWS. Thirdly, the ERG considers that there is a case for using the NHWS on the grounds that this is consistent with the previous appraisals and allows for a greater degree of parity in the evaluation of the cost-effectiveness of the alternative CGRPs. In this regard it is important to note that use of the Munakata et al[44] study offers an advantage to galcanezumab as predicted care costs are greater using the Munakata et al[44] study compared with the NHWS.[45]

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Table 26 Side by side comparison of health state consumption rates (derived from CS Table 65)

MHD	Hospitalisations		A&E Visits		GP Visits		Nurse Practitioner Visits		Neurologist Visits	
	Munakata	NHWS	Munakata	NHWS	Munakata	NHWS	Munakata	NHWS	Munakata	NHWS
0	0	0.023	0	0.030	0	0.202	0	0.063	0	0.003
1	0.0039	0.042	0.0088	0.067	0.0379	0.288	0.0379	0.102	0.0116	0.015
2	0.0078	0.042	0.0176	0.067	0.0758	0.288	0.0758	0.102	0.0232	0.015
3	0.0117	0.042	0.0264	0.067	0.1137	0.288	0.1137	0.102	0.0348	0.015
4	0.0156	0.040	0.0352	0.058	0.1516	0.413	0.1516	0.175	0.0464	0.013
5	0.0195	0.040	0.0440	0.058	0.1895	0.413	0.1895	0.175	0.0580	0.013
6	0.0234	0.040	0.0528	0.058	0.2274	0.413	0.2274	0.175	0.0696	0.013
7	0.0273	0.040	0.0616	0.058	0.2653	0.413	0.2653	0.175	0.0812	0.013
8	0.0312	0.040	0.0704	0.092	0.3032	0.553	0.3032	0.048	0.0928	0.038
9	0.0351	0.052	0.0792	0.092	0.3411	0.553	0.3411	0.048	0.1044	0.038
10	0.0390	0.052	0.0880	0.092	0.3790	0.553	0.3790	0.048	0.1160	0.038
11	0.0429	0.052	0.0968	0.092	0.4169	0.553	0.4169	0.048	0.1276	0.038
12	0.0468	0.052	0.1056	0.092	0.4548	0.553	0.4548	0.048	0.1392	0.038
13	0.0507	0.052	0.1144	0.092	0.4927	0.553	0.4927	0.048	0.1508	0.038
14	0.0546	0.052	0.1232	0.092	0.5306	0.553	0.5306	0.048	0.1624	0.038
15	0.0585	0.052	0.132	0.117	0.5685	0.585	0.5685	0.127	0.1740	0.073
16	0.0624	0.052	0.1408	0.117	0.6064	0.585	0.6064	0.127	0.1856	0.073
17	0.0663	0.052	0.1496	0.117	0.6443	0.585	0.6443	0.127	0.1972	0.073
18	0.0702	0.052	0.1584	0.117	0.6822	0.585	0.6822	0.127	0.2088	0.073
19	0.0741	0.052	0.1672	0.117	0.7201	0.585	0.7201	0.127	0.2204	0.073
20	0.0780	0.052	0.1760	0.117	0.7580	0.585	0.7580	0.127	0.2320	0.073
21	0.0819	0.052	0.1848	0.117	0.7959	0.585	0.7959	0.127	0.2436	0.073
22	0.0858	0.052	0.1936	0.117	0.8338	0.585	0.8338	0.127	0.2552	0.073
23	0.0897	0.052	0.2024	0.117	0.8717	0.585	0.8717	0.127	0.2668	0.073
24	0.0936	0.052	0.2112	0.117	0.9096	0.585	0.9096	0.127	0.2784	0.073
25	0.0975	0.052	0.2200	0.117	0.9475	0.585	0.9475	0.127	0.2900	0.073
26	0.1014	0.052	0.2288	0.117	0.9854	0.585	0.9854	0.127	0.3016	0.073

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

27	0.1053	0.052	0.2376	0.117	1.0233	0.585	1.0233	0.127	0.3132	0.073
28	0.1092	0.052	0.2464	0.117	1.0612	0.585	1.0612	0.127	0.3248	0.073
29	0.1131	NA	0.2552	NA	1.0991	NA	1.0991	NA	0.3364	NA
30	0.1170	NA	0.2640	NA	1.1370	NA	1.1370	NA	0.3480	NA

NHWS, National Health and Wellness Survey

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

Galcanezumab has a confidential PAS, comprising a simple discounted price of [redacted] per 120mg dose. This is a discount of approximately [redacted] on the list price.

The cost effectiveness results outlined in this section are provided from a corrected and updated company analysis following the ERG's clarification questions and subsequent model corrections. The results presented below include the simple PAS discount for galcanezumab. Note that the company do not present a combined analysis for all migraine patients in which the outcomes of EM and CM are combined.

5.1.1 **Base case results**

Table 27 presents the base-case deterministic analysis of galcanezumab for the EM population. It shows that galcanezumab was associated with increased costs (cost difference of [redacted]) and was more effective (gain of [redacted] QALYs), compared with BSC. The company's base-case ICER was £29,230 per QALY.

Table 27 Updated company base case results: Episodic migraine, vs BSC (Table 53, PFC response)

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]		
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,230

For the CM population comparisons were presented with both BSC and botulinum toxin A. Incremental results cannot be generated using the company's base-case model because of the alternative modelling approaches used in these two comparisons. As noted in Section 4.2.2 and Section 1.1.1.3 this is a fundamental weakness in the company's approach to modelling the comparison between galcanezumab and botulinum toxin A. As a consequence of this limitation results of the company's economic analysis for the CM population are presented separately for each comparator, see Table 28 and Table 29.

In the comparison with BSC, galcanezumab was associated with increased costs (cost difference of [redacted]) and was more effective (gain of [redacted] QALYs), compared with BSC. The company's base-case ICER was £8,080 per QALY.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

In the comparison with botulinum toxin A, galcanezumab was associated with increased costs (cost difference of [redacted]) and was more effective (gain of [redacted] QALYs), compared with botulinum toxin. The company's base-case ICER was £2,560 per QALY.

Table 28 Updated company base case results: Chronic migraine, vs BSC (Table 54, PFC response)

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]		
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,080

Table 29 Updated company base case results: Chronic migraine, vs botulinum toxin (Table 55, PFC response)

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]		
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,560

5.1.2 Probabilistic sensitivity analysis

The ERG performed a probabilistic sensitivity analysis (PSA), on behalf of the company using the updated model running 5,000 iterations of the economic model.

In the episodic population the mean probabilistic ICER of galcanezumab compared with BSC was £29,034 per QALY. The cost-effectiveness plane showing the results of the PSA can be seen in **Error! Reference source not found.**. As can be seen from **Error! Reference source not found.**, the cost-effectiveness of galcanezumab is subject to considerable uncertainty and there is a substantial risk that the ICER in this population is greater than the typical thresholds of £20 to £30k per QALY gained.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

[redacted]

The mean probabilistic ICER of galcanezumab compared with BSC in the chronic population was £7,987 per QALY. The cost-effectiveness plane showing the results of the PSA can be seen in **Error! Reference source not found.**. As with the Episodic population the mean cost-effectiveness of galcanezumab is subject to considerable uncertainty, however, unlike the EM population this uncertainty is contained well within typical willingness to pay thresholds and as such the probability of the ICER being greater that of £20 to £30k per QALY gained is very low.

[redacted]

The probabilistic ICER in the comparison with botulinum toxin was £1,531 per QALY. Similar to the comparison with BSC the cost-effectiveness plane shows a very low probability that the ICER exceeds the typical thresholds of £20 to £30k per QALY gained, see **Error! Reference source not found.**.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

[redacted]

5.1.3 Subgroup analysis of high frequency episodic migraine (HFEM)

This analysis used efficacy data from the CONQUER clinical trial in patients with 8-14 monthly headache days. This patient group was assumed to have the baseline characteristics of the overall EM population. Responders had baseline mean MHDs of [redacted] compared to [redacted] for non-responders. The galcanezumab treatment effect compared to BSC was [redacted] MHDs in responders and [redacted] MHDs in non-responders. At least a 50% reduction in MHDs was seen in [redacted] of galcanezumab patients and [redacted] of BSC patients.

Table 30 presents the result of the subgroup analysis. The results of this analysis show that incremental costs and QALYs are consistent with the main analyses of EM and CM, with the ICER for galcanezumab versus BSC lying marginally below that in the whole EM population.

Table 30 Updated company base case results: High frequency episodic migraine, vs BSC

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]		
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,346

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

5.2 Company's sensitivity analyses

The company presented a series of deterministic sensitivity analyses (DSA) in the form of univariate sensitivity analyses to assess the impact of varying key model input parameters upon the ICER. The DSA inputs can be seen in the company's economic model. A series of tornado diagrams summarising the most influential parameters for each population EM and CM are presented in **Error! Reference source not found.**, **Error! Reference source not found.** and **Error! Reference source not found.**. The results indicate that varying the rate of response for either galcanezumab, botulinum toxin A, or BSC has a significant impact on the estimated ICER. The reduction in monthly migraine days experienced by responders to treatment was also found to be significant driver of cost-effectiveness

[redacted]

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

[redacted]

[redacted]

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

5.3 Additional scenario analysis requested by the ERG and PFC

Several additional scenarios were requested by the ERG and were provided by the company at the clarification questions stage. The scenarios related to the utility values used in the model, the source of treatment effectiveness data used in the model, the methods used in the galcanezumab vs botulinum toxin A comparison, assumptions made regarding the duration of the placebo response, and assumptions made regarding waning following discontinuation of botulinum toxin A. A brief exposition of the issues and results from these analyses is presented below.

HRQoL scenarios

The ERG noted that the company generated the utility values used in the economic analysis from the whole population of the CONQUER trial (i.e. not just patients who failed ≥ 3 preventive treatments). The company therefore supplied an additional analysis where utility values used in the economic model are generated for the subpopulation who failed ≥ 3 prior preventative treatments. The results of this analysis are presented in Table 31.

Table 31 Utility values from CONQUER in the failed ≥ 3 prior preventative treatment subpopulation

Population	Points for Clarification response Table	Incremental Costs	Incremental QALYs	ICER (£/QALY)
EM (vs BSC)	Table 23	[redacted]	[redacted]	£26,847
CM (vs BSC)	Table 24	[redacted]	[redacted]	£7,421
CM (vs Botox)	Table 25	[redacted]	[redacted]	£2,352

In addition to the above, the ERG also highlighted to the company that MSQ data from which utilities were mapped was also available in the REGAIN and EVOLVE studies. As part of the response the company provided an additional scenario analysis in which all four trials were used as a source of utility values. In line with the modelled population, utility values were only drawn from the population of patients who had failed ≥ 3 preventive treatments. Results of this additional analysis are presented in Table 32.

Table 32 Scenario analysis using CONQUER pooled with REGAIN and EVOLVE failed ≥3 prior preventative treatment subpopulation

Population	Points for Clarification response Table	Incremental Costs	Incremental QALYs	ICER (£/QALY)
EM (vs BSC)	Table 32	[redacted]	[redacted]	£37,149
CM (vs BSC)	Table 33	[redacted]	[redacted]	£10,269
CM (vs Botox)	Table 34	[redacted]	[redacted]	£3,254

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Source of treatment effectiveness data

At the PFC stage, the ERG noted that the company uses different studies to populate treatment effect parameters within the model, with some based on CONQUER alone, while others combine data from CONQUER and REGAIN. In the company's response they therefore decide to present a series of scenario analyses in which all results were based on the CONQUER trial alone, see Table 33. Unfortunately, no results were presented where all inputs were based on both the CONQUER and REGAIN studies.

Table 33 Scenario analysis using CONQUER inputs only

Population	Points for Clarification response Table	Incremental Costs	Incremental QALYs	ICER (£/QALY)
EM (vs BSC)	Table 42	[redacted]	[redacted]	£29,412
CM (vs BSC)	Table 43	[redacted]	[redacted]	£8,080
CM (vs Botox), fixed effects ITC	Table 44	[redacted]	[redacted]	£2,965
CM (vs Botox), Random effects ITC	Table 45	[redacted]	[redacted]	£2,828

Methods used in the comparison between galcanezumab and botulinum toxin A

At the PFC stage the ERG requested that the company present a scenario analysis using the same modelling approach adopted for the comparison of galcanezumab with BSC (so as to allow for a full incremental analysis). In response, the company provided an analysis in which the mean change from baseline in monthly MHDs for responders was approximated by making assumptions about the mean change from baseline in monthly MHDs for non-responders (assumed equal to BSC). Scenario analyses using this approach are presented in Table 34.

Table 34 Scenario analysis, approximated responder and non-responder MHDs for botulinum toxin A

Population	Clarification response Table	Incremental Costs	Incremental QALYs	ICER (£/QALY)
CM (vs Botox)	Table 47	[redacted]	[redacted]	Galcanezumab Dominates

Post placebo response duration

At the PFC stage the ERG noted that in the company's base-case it is assumed that patients who respond to BSC wane back to baseline after a period of 12 months. As no data are available to support this assumption, the company were requested to justify this assumption and why they did not consider that the placebo effect would impact on both galcanezumab and BSC arms equally. In the company's response, they presented two scenarios considering alternative assumptions regarding the duration of the placebo effect. In the first they assumed that placebo responders maintained their response for the

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

life-time of the model. In the second, it was assumed that the placebo effect waned after a period of 60 months. The results of this analysis are presented in Table 35.

Table 35 Scenario analysis, dissipation of the placebo effect

Population	Points for Clarification response Table	Incremental Costs	Incremental QALYs	ICER (£/QALY)
EM (vs BSC) no dissipation of placebo effect	Table 48	[redacted]	[redacted]	£50,282
CM (vs BSC) no dissipation of placebo effect	Table 49	[redacted]	[redacted]	£18,578
EM (vs BSC) dissipation of placebo effect over 60 months	Table 50	[redacted]	[redacted]	£36,918
CM (vs BSC) dissipation of placebo effect over 60 months	Table 51	[redacted]	[redacted]	£10,239

Waning of treatment effect following discontinuation

As part the clarification process the ERG highlighted that there is a significant difference in the assumed waning period for patients receiving galcanezumab and botulinum toxin A ([redacted] vs 3 months) and that there was no evidence presented by the company to justify this difference. As part of their response, the company provided an additional scenario analysis in which the waning period for both galcanezumab and botulinum toxin A was assumed to be [redacted] cycles based on data from the REGAIN trial. The result of this analysis is presented in Table 36.

Table 36 Scenario analysis where patients who discontinue galcanezumab and botulinum toxin A return to baseline MHDs over 72 cycles

Population	Points for Clarification response Table	Incremental Costs	Incremental QALYs	ICER (£/QALY)
CM (vs Botox)	Table 53	[redacted]	[redacted]	£10,903

5.4 Model validation and face validity check

Validation undertaken by the company

The company stated that the internal validity of the model processes was assessed by an independent third party who undertook a technical validation of the model. This included an assessment of the scope of the model, its ease of use, model inputs, accuracy, sensitivity analyses, VBA coding, and results. The company stated that the model was deemed suitable with only minor discrepancies identified, which were subsequently rectified. The predictions of the economic analysis were compared with the results of the trial to assess their face validity.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Validation undertaken by the ERG

As part of the ERG assessment of the economic analysis the ERG checked the internal validity of the model and considered the face validity of the model's predictions. This included a series of model calculation checks, including pressure tests and formula auditing. The ERG felt that the executable model was in general well presented, but contained a degree of redundancy, in that it contained calculations that did not contribute to model function. Several minor model errors were identified as part of the ERG's validation checks. These errors concerned the timing of when post-response discontinuation was applied; the duration over which waning occurred post discontinuation and the functionality of the probabilistic analysis. A number of inconsistencies were also identified in the values to model the rate of discontinuation. These errors were corrected by the ERG, and a revised model supplied to the company with altered cells highlighted to aid verification. These corrections did not impact substantively on the model's predictions. Revised results are presented in Section 6.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory analyses undertaken by the ERG

The ERG conducted the following exploratory analyses for patients with episodic migraine and chronic migraine.

1) Including galcanezumab administration cost for 10% of patients

As discussed in Section 4.2.8, the ERG considers the company's omission of administration costs beyond the first model cycle to be unrealistic. It is likely that a proportion of the population would not be capable of self-administering galcanezumab. For parity with the appraisal of fremanezumab, the ERG assumes an administration cost for 10% of the population. This has been costed as a 30-minute appointment with a Band 5 hospital-based nurse at an hourly rate of £38.00.[43]

2) Alternative resource consumption rates

In Section 1.1.1.6, the ERG discussed concerns regarding the resource use consumption values used to calculate disease management costs. The ERG used alternative values generated by the NHWS[45] and presented in Table 26. The ERG considered these values more appropriate than those presented in the US study Munakata et al[44] (see Section 1.1.1.6). Furthermore, using NHWS resource use results is consistent with the previous appraisals of erenumab and fremanezumab.

3) Alternative source used to generate HRQoL

In Section 4.2.7, the ERG discussed concerns regarding the source of the MSQ data used to generate the utility values used in the model. The original utility values were based on the whole of the CONQUER trial, not only on those patients who have failed ≥ 3 previous preventative therapies. In addition, the modelled values excluded MSQ data captured in relevant populations in the EVOLVE and REGAIN trials. In response to clarification questions the company presented a scenario analysis restricting the CONQUER study to the relevant population and a further scenario in which utility values are based on data from CONQUER, EVOLVE and REGAIN (in the DTT-3 population).

4) Differential utilities to include treatment effect

As described in Section 4.2.7, the ERG considered the company's assumption of using the same utility values for both galcanezumab and comparator to be too conservative given compelling evidence presented to support differential utilities. The ERG therefore presents a scenario in which the model allows a treatment effect on HRQoL. This was done using functionality already contained within the company model.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

5) Age-related disutility

The ERG considers the assumption that HRQoL remains constant over time for a given number of MHDs to be strong, given the 25-year time horizon of the economic model. To account for age-related disutility, the ERG considers a scenario analysis in which the utilities used in the model are weighted according to literature derived age-decrements for the UK general population.[40] These utilities are presented in Table 37.

Table 37 General population age decrements

Age (5-year intervals)	Baseline Utility	Weight
45-50	0.8639	1.000
50-55	0.8344	0.966
55-60	0.8222	0.952
60-65	0.8072	0.934
65-70	0.8041	0.931
70-75	0.779	0.902
75-80	0.7533	0.872
80-85	0.6985	0.809
85<	0.6497	0.752

6) Consistent waning period between episodic and chronic migraine populations

As described in Section 1.1.1.3, the ERG considers the waning periods used for patients discontinuing galcanezumab to be inconsistent and unrealistic. The company's base case model assumes waning periods of [redacted] months, [redacted] months for episodic, chronic (vs. BSC) and chronic (vs. Botulinum toxin type A), respectively (see Table 23).

To explore the impact of the length of the modelled waning period on the company's base case ICER, the ERG considers a waning period of [redacted] months for patients discontinuing galcanezumab in all three cases. In these scenarios, the company's assumptions of a 1-month waning period for BSC and 3 months for botulinum toxin type A are retained.

7) Consistent waning period between galcanezumab and botulinum toxin A

In Section 1.1.1.5, the ERG highlighted that the waning periods applied to galcanezumab and botulinum toxin A are very different. There is, however, no evidence to justify this difference. As part the clarification response, the company presented the cost-effectiveness results of assuming a [redacted] month waning period for both galcanezumab and botulinum toxin A. Given the ERG's concerns

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

regarding a waning period of [redacted] months, the ERG also presents a further scenario in which the waning period for both galcanezumab and botulinum toxin A is assumed to be [redacted] months.

8) Removal of treatment waning

To explore the impact of the modelled waning period on the base case ICERs in all populations, an illustrative and exploratory scenario is presented to illustrate the removal or treatment waning. This assumption is consistent with the previous appraisals of erenumab[46] and fremanezumab.[22] This analysis is achieved by setting the waning period to 1 month for patients discontinuing due to AEs (discontinuers) and patients discontinuing due to lack of response (non-responders). This is applied to all treatments.

9) Dissipation of placebo effect

In Section 1.1.1.3, the ERG described the inconsistency in the company's approach to modelling the dissipation of the placebo (BSC) effect. The company base case assumes a unilateral application of the placebo dissipation by applying it only to placebo responders and not to galcanezumab responders. This is despite the fact that effects of galcanezumab as observed in the supporting trial evidence likely also include a placebo effect.

As detailed in Section 5.3, in response to clarification questions, the company presented two analyses. One in which the dissipation of the placebo effect was removed, and one in which the placebo effect dissipates after 60 months. The scenario analysis presented below utilises the company scenario in which placebo dissipation was removed. This scenario is selected over the 60-month placebo dissipation scenario due to the previously highlighted issue of unilateral application of this dissipation effect in the latter scenario. The ERG notes, however that the preference would have been to match both galcanezumab and placebo i.e. for the placebo effect to dissipate in both arms. This is due to the strength of the assumption required to remove placebo dissipation in the placebo arm i.e. placebo effect is assumed to be experienced for 25 years.

10) Patients discontinuing treatment assumed to wane back from responder MHDs

As described in Section 1.1.1.5, the ERG considers the modelled change from baseline in MHDs for galcanezumab patients (vs. botulinum toxin type A) to lack face validity. One consequence of this approach is that the model predicts patients who discontinue galcanezumab will initially receive a further reduction in MHDs before waning back to baseline. The ERG therefore presents a scenario in which this further reduction in MHDs on discontinuation is removed so that patients wane back from the MHD applied to responders. Note that, due to the way in which the model is structured, the

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

removal of this effect also leads to a reduction in the waning period from approximately [redacted] months to [redacted] months.

11) Exploration of alternative methods of incorporating indirect evidence on the effectiveness of galcanezumab compared with botulinum toxin A

As is described throughout Section 4.2.6, the ERG has concerns regarding the company's approach to generate the modelled treatment effects for galcanezumab and botulinum toxin. In particular, it is noted that the use of a different model structure for this comparison means that a full incremental analysis cannot be implemented.

The ERG therefore considers several alternative treatment effect scenarios using the response-based model structure used in the comparison between galcanezumab and BSC. In all these scenarios the ERG assumes that the effectiveness parameters for galcanezumab are the same as those used in the company's base analysis for the BSC comparison. This ensures an incremental analysis can be conducted. The parameters changed across the individual scenarios are therefore those used in the botulinum toxin A arm of the model and focus on the effectiveness parameters: response rate and change in MHDs for responders. Change in MHDs for non-responders is assumed common across galcanezumab and botulinum toxin A in all scenarios. In total, four scenarios are implemented as follows:

- ERG Scenario 11a: Assume equal effectiveness across all parameters for galcanezumab and botulinum toxin A
- ERG Scenario 11b: Response rate differs between galcanezumab and botulinum toxin A – relative effect based on ITC of responders (50%; whole population: 'all-comers').
- ERG Scenario 11c: Change from baseline in MHD for responders allowed to differ between galcanezumab and botulinum toxin A – value estimated using the ITC of change from baseline in MHD (DTT-3 population)
- ERG Scenario 11d: Scenario 11b and Scenario 11c combined

The modelled parameters for each of these scenarios can be seen in Table 38. Where the response rate is allowed to differ between galcanezumab and botulinum toxin, the odds ratio from the ITC of response (50%, whole population) is applied to the response rate for galcanezumab (30%). Where the change in MHDs for responders can differ, the treatment effect is drawn from the ITC of change in MHD (DTT-3 population) and applied using the formula presented in Appendix T of the CS. This allows an estimate of the change in MHD for responders in the botulinum toxin A arm to be calculated. Note that in all these scenarios the rate of discontinuation in the post-assessment period is

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

assumed to be common to both active treatments, where this is not done, this analysis will produce non-sensical results.

Table 38 Alternative treatment effectiveness parameters (response-based model structure)

Scenario	CFB MHD botulinum toxin A responders	CFB MHD botulinum toxin A non-responders	Response rate botulinum toxin A	CFB MHD GMB responders	CFB MHD GMB non-responders	Response rate GMB
11a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11c	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11d	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CFB, change from baseline; GMB, galcanezumab; MHD, migraine headache days

In considering the most appropriate set of assumptions to model the treatment effect, the ERG considers that a valid argument can be made for all four of these scenarios, as each has its own advantages and disadvantages. For the purpose of producing the ERG base case, the ERG prefers Scenario 11d, as this best aligns with the previous committee decision in fremanezumab to accept the results of the ITC as valid (despite the noted issues). Exploratory analyses are, however, also run on the ERG base-case considering the alternative treatment effect scenarios.

12) Incorporation of natural history

A significant limitation of the company's model is the exclusion of the natural history of migraine due to a lack of data on the long-term effects of migraine. The ERG considers this an important omission likely to impact considerably on the cost-effectiveness of any active treatment. The ERG therefore implements an exploratory scenario in which migraine symptoms improve in all patients over time. This scenario assumes all patients gradually revert to complete remission (0 MHDs) by the end of the modelled time horizon (25 years). This analyses therefore assumes by 70 years old, patients no longer suffer from migraine. This a strong assumption, and is implemented only to illustrate the potential effects of natural history rather than to represent a definitive analysis suitable for decision making.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

A summary of the ERG exploratory analyses for patients with episodic migraine are presented in

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Table 39. For chronic migraine patients, a summary of the pairwise analyses are presented in Table 40 and a summary of the fully incremental analyses are presented in Table 41. ERG base case results for chronic migraine patients are presented in Table 42 (for full results of the incremental analyses see Appendix 3). These results are presented inclusive of the PAS available for galcanezumab, but exclude the CMU discount for botulinum toxin A. Results including the CMU discount are presented in a confidential Appendix.

All results are presented deterministically. The ERG's preference would have been to present results probabilistically, however due to time constraints the ERG was unable to implement this in the ERG base case.

6.2.1 Interpreting the results for episodic migraine

The deterministic ICER for episodic migraine is £34,370 in the ERG base case (

Table 39). Three ERG analyses resulted in a considerable increase in the company base case ICER: using the NHWS resource use increased the ICER by £6,820; using the combined data from CONQUER, REGAIN, EVOLVE-1 and EVOLVE-2 to generate utilities increased the ICER by £7,919; and the removal of the dissipation of placebo effect increased the ICER by £7,689. The incorporation of differential utilities to reflect a treatment effect resulted in a decrease the ICER by £15,998. The incorporation of natural history as an exploratory analysis increased the ICER to over £30,000 per QALY.

6.2.2 Interpreting the results for chronic migraine

The assumption around which treatment effectiveness values to use is a driver of cost-effectiveness. Assuming equal effectiveness of galcanezumab and botulinum toxin A (Scenario 11a) results in an ICER of £64,281 and assuming equal response rates and differential CFB in MHDs (Scenario 11c) results in an ICER of £8,454. The ERG's preferred assumption of differential response rates and CFB in MHD produces an ICER of £11,734.

The deterministic ICER for chronic migraine is £22,830 in the ERG preferred base case which uses treatment effectiveness Scenario 11d (Table 42). Three alternative ERG base cases are presented which use the alternative treatment effectiveness estimates from the ITC of galcanezumab compared to botulinum toxin A. The alternative ICERs are: £190,641 (ERG base case including Scenario 11a); £45,840 (ERG base case including Scenario 11b); and £24,539 (ERG base case including Scenario 11c).

Scenario 11 and the ERG base cases include a key assumption: equal long-term discontinuation rates between galcanezumab and botulinum toxin A. This is despite the CS presenting differential long-

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

term discontinuation rates for galcanezumab ([redacted]) and botulinum toxin A ([redacted]). The ERG assumes the long-term discontinuation rate is [redacted] for both treatments, due to issues around the validity of using these results due to the sources used to generate them (see Section 1.1.1.4 for more details) and the considerable influence these differential rates have on the cost-effectiveness results. Analyses undertaken by the ERG show that maintaining the differential discontinuation rates, results in galcanezumab being dominated by botulinum toxin A in numerous scenarios.

The incorporation of natural history as an exploratory analysis increased the ERG preferred base case ICER by almost £35,000.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Table 39 Exploratory ERG analyses (episodic migraine)

Analysis	Discounted costs		Discounted QALYs		ICER	Change from company base case ICER
	Galcanezumab	BSC	Galcanezumab	BSC		
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	**£29,230**	-
ERG correction of model errors	[redacted]	[redacted]	[redacted]	[redacted]	£29,313	£83
1) Galcanezumab administration cost for 10% of patients	[redacted]	[redacted]	[redacted]	[redacted]	£29,563	£334
2) Alternative resource consumption rates	[redacted]	[redacted]	[redacted]	[redacted]	£36,049	£6,820
3) Alternative source used to generate HRQoL	[redacted]	[redacted]	[redacted]	[redacted]	£37,149	£7,919
4) Differential utilities for galcanezumab and comparator	[redacted]	[redacted]	[redacted]	[redacted]	£13,232	-£15,998
5) Age-related disutility	[redacted]	[redacted]	[redacted]	[redacted]	£30,247	£1,017
8) Removal of treatment waning	[redacted]	[redacted]	[redacted]	[redacted]	£36,918	£7,689
9) Dissipation of placebo effect	[redacted]	[redacted]	[redacted]	[redacted]	£36,918	£7,689
ERG base case (1, 2, 3, 4, 5, 9)	[redacted]	[redacted]	[redacted]	[redacted]	**£34,370**	**£5,140**
Base case + Incorporation of natural history (12)	[redacted]	[redacted]	[redacted]	[redacted]	£37,633	£8,403

BSC, best supportive care; ERG, evidence review group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness analysis; QALY, quality-adjusted life year
Note: All results correspond to deterministic analyses, scenario 12: natural history is for illustrative purposes only.

Table 40 Exploratory ERG analyses - Chronic migraine pairwise analyses (separate models for comparison to BSC and botulinum toxin)

Analysis	Comparator	Discounted Costs	Discounted QALYs	Pairwise

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

		Galcanezumab	Comparator	Galcanezumab	Comparator	ICER	Change from company base case
Company base case	**BSC**	[redacted]	[redacted]	[redacted]	[redacted]	**£8,080**	-
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	**£2,560**	-
ERG correction of model errors	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£8,053	-£27
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£4,203	£1,643
1) Galcanezumab administration cost for 10% of patients	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£8,243	£163
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£3,255	£694
2) Alternative resource consumption rates	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£14,892	£6,813
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£9,534	£6,974
3) Alternative source used to generate HRQoL	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£10,269	£2,189
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£3,254	£694
4) Differential utilities for galcanezumab and comparator	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£4,456	-£3,624
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	n/a
5) Age-related disutility	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£8,347	£268
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£2,622	£61
6) Consistent waning period between episodic and chronic migraine populations	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£9,602	£1,522
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£25,168	£22,608
7) Consistent waning period between galcanezumab and botulinum toxin A	BSC	n/a	n/a	n/a	n/a	n/a	n/a
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£5,464	£2,904
8) Removal of treatment waning	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£10,068	£1,988
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£42,566	£40,006
9) Dissipation of placebo effect	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£22,344	£14,264
	Botulinum toxin A	n/a	n/a	n/a	n/a	n/a	n/a
	BSC	n/a	n/a	n/a	n/a	n/a	n/a

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

10a) Patients discontinuing treatment assumed to wane back from responder MHDs	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£26,645	£24,085
10b) Equivalent long-term discontinuation rate for galcanezumab and botulinum toxin (0.44%)	BSC	n/a	n/a	n/a	n/a	n/a	n/a
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£11,742	£9,181

BSC, best supportive care; ERG, evidence review group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness analysis; MHDs, migraine headache days; QALY, quality-adjusted life year

Note: All results correspond to deterministic analyses

Table 41 Exploratory ERG analysis - Scenario 11 (chronic migraine)

Analysis	Discounted Costs			Discounted QALYs			Incremental ICER (Galcanezumab)
	BSC	Botulinum toxin A	Galcanezumab	BSC	Botulinum toxin A	Galcanezumab	
11a) Equal effectiveness (ITC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£64,281
11b) Response rate differs (ITC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,167
11c) CFB in MHD differs (ITC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,454
11d) 11b and 11c combined	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,734

BSC, best supportive care; ERG, evidence review group; ICER, incremental cost-effectiveness analysis; ITC, indirect treatment comparison; MHDs, migraine headache days; QALY, quality-adjusted life year

Note: All results correspond to deterministic analyses

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Table 42 ERG base case and exploratory analysis (chronic migraine)

Analysis	Discounted Costs			Discounted QALYs			Incremental ICER (Galcanezumab)
	BSC	Botulinum toxin A	Galcanezumab	BSC	Botulinum toxin A	Galcanezumab	
ERG base case 4 (1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11d)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£22,830**
ERG exploratory analysis							
ERG base case 1 (1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11a)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£190,641
ERG base case 2 (1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11b)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,840
ERG base case 3 (1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11c)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,539
ERG preferred base case + Incorporation of natural history (12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,721

BSC, best supportive care; ERG, evidence review group; ICER, incremental cost-effectiveness analysis; ITC, indirect treatment comparison; MHDs, migraine headache days; QALY, quality-adjusted life year

Note: All results correspond to deterministic analyses, scenario 12: natural history is for illustrative purposes only.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

6.3 Conclusions of the cost effectiveness section

The company performed a targeted literature review to identify cost-effectiveness evaluations of preventative treatments for people with migraine. No prior economic evaluations of galcanezumab were identified in the review, but several relevant studies were identified for other preventative treatments including other CGRPs. The identified studies included economic evaluations carried out as part of the NICE appraisal of erenumab and fremanezumab, as well as the Institute for Clinical and Economic Review report which considered the cost effectiveness of erenumab and fremanezumab.

The company developed a *de novo* economic analysis to appraise the cost and benefits of galcanezumab treatment in patients with episodic and chronic migraine. These groups were evaluated separately. For both episodic and chronic migraine populations, galcanezumab was compared to BSC; an additional analysis comparing galcanezumab to botulinum toxin A was conducted for chronic migraine patients.

The model structure developed was similar to that used in previous NICE appraisals of CGRPs and is driven by frequency of migraine modelled in terms of average monthly MHDs. For comparisons with BSC, the mean reduction in monthly MHD change is linked to response, with treatment effectiveness data sourced from four pivotal trials EVOVLE-1 and -2, REGAIN and CONQUER. For comparisons with botulinum toxin A, data from an ITC of change from baseline in MHDs was used to populate the model. The model structure used in the botulinum toxin A comparison was different to that used in the BSC comparison due to lack of data on change in MHDs for botulinum toxin A by response status. Consequently, a full incremental analysis of galcanezumab, BSC and botulinum toxin A cannot be conducted using the company's model.

ICERs for galcanezumab as compared to BSC in the company's base case were £29,230 for EM and £8,080 for CM. In CM, the ICER for galcanezumab as compared to botulinum toxin was £2,560. Presented PSAs suggested a high likelihood of acceptability at thresholds of £20,000 and £30,000 in the chronic migraine population.

The ERG's critique identified substantive structural uncertainties associated with the company's approach that potentially limit the reliability of company's analysis. Specifically, the ERG noted the focus on migraine frequency to the exclusion of other trial outcomes. This represents a limitation of the present economic analysis as other aspects of migraine including severity and frequency of non-migraine headache may impact on the burden of the condition. The economic analysis also makes strong assumptions about the durability of the treatment effect extrapolating short term effects observed over a period of 3 months to a 25-year time horizon, this together with the omission of the modelling of the effects of natural history means there is substantial uncertainty regarding the long-term benefits of galcanezumab.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

While high quality trial evidence is available to support the comparisons to BSC, the comparison of galcanezumab with botulinum toxin A is considered weak because it is drawn from an ITC which is subject to several uncertainties and concerns regarding its validity. These include concerns regarding the comparability of the respective trial populations, notable differences in the observed placebo response rate, as well as differences in the definition of headache/migraine headache across studies. Given these limitations, the results of the economic analysis for this comparison should be interpreted with caution and are subject to additional uncertainty, not expressed in the probabilistic analysis.

The economic analysis presented by the company also has the significant limitation of only evaluating the cost-effectiveness of specific treatments rather than evaluating alternative treatment sequences. This is an important omission, as the positioning of galcanezumab within the treatment pathway may have important implications for its cost-effectiveness. It is also inconsistent with clinical practice where it is anticipated that galcanezumab would be used as part of a treatment sequence, being positioned either prior to or post botulinum toxin A treatment.

In addition to the largely structural issues described above, the ERG also identified many issues relating to the inputs and assumptions used in the model. These related to:

- The most appropriate sources of effectiveness data;
- The most appropriate way to incorporate the limited data on the relative effectiveness for the galcanezumab versus botulinum toxin comparison;
- Assumptions made regarding the duration of waning effects post discontinuation of treatment;
- The durability of responses to BSC;
- The sources of HRQoL data used in the model;
- The appropriateness of modelling different HRQoL for specific treatments;
- The omission of administration costs for galcanezumab beyond the first cycle of the model;
- Concerns regarding the source of data used to model resource use consumption rates.

To address these concerns the ERG implemented extensive further scenario analyses and proposed an alternative base-case analysis to address several of the key uncertainties identified. The main changes implemented by the ERG included:

- The revision of the model structure used in the botulinum toxin A comparison so that a consistent model structure was used across all comparisons allowing for a full incremental analysis to be implemented;
- Revision of assumptions so that a common value of [redacted] months is used to represent the waning period across all populations and treatments being evaluated;

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

- Revision of the source of utility data to include all trials reporting HRQoL data in the relevant failed > 3 preventative treatments population;
- The incorporation of treatment specific utilities;
- Revision of the resource consumption rates in line with previous appraisals of CGRPs.

All of these scenarios were found to have a substantive impact on the ICER (> £3,000 change in the ICER).

The results of the ERG's revised base-case imply an ICER of £34,370 in the EM population and an ICER of £22,830 of in the CM population. An exploratory analysis incorporating natural history highlights the potential for continuous treatment with galcanezumab to substantially increase the ICER and the importance of adhering to SMPC guidance which outlines the need to regularly evaluate patients to assess the continuing need for treatment.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

7 REFERENCES

1. National Institute for Health and Care Excellence. *Fremanezumab for preventing migraine.* . London: NICE; 2019. Available from: https://www.nice.org.uk/guidance/gid-ta10339/documents/html-content-2

2. National Institute for Health and Care Excellence. *Erenumab for preventing migraine*. London: NICE; 2018.

3. Bolay H, Ozge A, Saginc P, Orekici G, Uluduz D, Yalin O, et al. Gender influences headache characteristics with increasing age in migraine patients. *Cephalalgia* 2015;**35**:792-800. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25424708

4. Houle TT, Turner DP, Smitherman TA, Penzien DB, Lipton RB. Influence of random measurement error on estimated rates of headache chronification and remission. *Headache* 2013;**53**:920-9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23721239

5. Merikangas KR, Cui L, Richardson AK, Isler H, Khoromi S, Nakamura E, et al. Magnitude, impact, and stability of primary headache subtypes: 30 year prospective Swiss cohort study. *BMJ* 2011;**343**:d5076.

6. National Institute For Health And Care Excellence. *Erenumab for preventing migraine*. London: NICE; 2019. Available from: https://www.nice.org.uk/guidance/gid-ta10302/documents/html-content-2

7. Canadian Agency for Drugs and Technologies in Health (CADTH). *onabotulinumtoxinA for injection (Botox). Common Drug Review. Clinical Review Report*: CADTH; 2015.

8. Cole JC, Lin P, Rupnow MF. Minimal important differences in the Migraine-Specific Quality of Life Questionnaire (MSQ) version. *Cephalalgia* 2009;**29**:1180-7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19830883

9. European Medicines Agency. *Emgality. International non-proprietary name: galcanezumab. Procedure no. EMEA/H/C/004648/0000*. EMA; 2018. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/emgality [accessed 17th April 2020].

10. National Institute for Health and Care Excellence. *Botulinum toxin type A for the prevention of headaches in adults with chronic migraine*. London: NICE; 2012. Available from: https://www.nice.org.uk/guidance/ta260

11. Eli Lilly and Company. *A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Chronic Migraine – the REGAIN Study: Final Results from the Double-Blind Treatment Phase and Interim Results from the Open-Label Treatment Phase Galcanezumab (LY2951742) Migraine Prevention*. Washington, USA; 2017.

12. Diener HC, Schorn CF, Bingel U, Dodick DW. The importance of placebo in headache research. *Cephalalgia* 2008;**28**:1003-11. Available from: https://www.ncbi.nlm.nih.gov/pubmed/18727647

13. Diederich NJ, Goetz CG. The placebo treatments in neurosciences New insights from clinical and neuroimaging studies. *Neurology* 2008;**71**:677-84.

14. Salanti G, Marinho V, Higgins JP. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. *J Clin Epidemiol* 2009;**62**:857-64. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19157778

15. National Institute for Health and Care Excellence. *Single Technology Appraisal. Erenumab for preventing migraine*. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10302/documents

16. National Institute for Health and Care Excellence. *Fremanezumab for preventing migraine [ID1368]. Single Technology Appraisal*. London: NICE. Available from: https://www.nice.org.uk/guidance/gid-ta10339/documents/committee-papers

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

17. Lipton RB, Brennan A, Palmer S, Hatswell AJ, Porter JK, Sapra S, et al. Estimating the clinical effectiveness and value-based price range of erenumab for the prevention of migraine in patients with prior treatment failures: a US societal perspective. *J Med Econ* 2018;**21**:666-75. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29571276

18. Sussman M, Benner J, Neumann P, Menzin J. Cost-effectiveness analysis of erenumab for the preventive treatment of episodic and chronic migraine: Results from the US societal and payer perspectives. *Cephalalgia* 2018;**38**:1644-57.

19. Porter JK, Di Tanna GL, Villa G, Brennan A, Palmer S, Lipton RB, et al. Parametric Modelling of Migraine Day Frequency In Migraine Prevention: A Case Study Of Erenumab Clinical Trial Data. *Value Health* 2017;**20**:A733. Available from: https://doi.org/10.1016/j.jval.2017.08.2004

20. Smolen L, Gandhi SK, Klein T, Iyer R, Thompson S, Cohen JM, et al. PND21 10-YEAR COST-EFFECTIVENESS ANALYSES OF FREMANEZUMAB AS PREVENTIVE TREATMENT IN CHRONIC AND EPISODIC MIGRAINE. *Value Health* 2019;**22**:S273. Available from: https://doi.org/10.1016/j.jval.2019.04.1294

21. Institute for Clinical and Economic Review. *Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine: Effectiveness and Value. Final Evidence Report*. ICER; 2018. Available from: https://icer-review.org/wp-content/uploads/2017/11/ICER_Migraine_Final_Evidence_Report_070318.pdf [accessed 20th April 2020].

22. National Institute for Health and Care Excellence. *Fremanezumab for preventing migraine. Final appraisal document [ID1368]*. NICE; 2020. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10339/documents [accessed 17th April 2020].

23. Gillard PJ, Devine B, Varon SF, Liu L, Sullivan SD. Mapping from disease-specific measures to health-state utility values in individuals with migraine. *Value Health* 2012;**15**:485-94. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22583459

24. Hagen K, Kristoffersen E, Winsvold B, Stovner L, Zwart J. Remission of chronic headache: An 11-year follow-up study. Data from the Nord-Trøndelag Health Surveys 1995–1997 and 2006–2008. *Cephalagia* 2018;**38**:2026-34.

25. Bigal M, Lipton R. The prognosis of migraine. *Curr Opin Neurol* 2008;**21**:301-8.

26. Lyngberg A, Rasmussen B, Jørgensen T, Jensen R. Prognosis of migraine and tension-type headache: a population-based follow-up study. *Neurology* 2005;**65**:580-5.

27. Stovner L, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalagia* 2007;**27**:193-210.

28. European Medicines Agency. *EMGALITY (galcanezumab). United Kingdom. Summary of Product Characteristics*. 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/emgality-epar-product-information_en.pdf [accessed 16th March 2020].

29. Bigal M, Liberman J, Lipton R. Age-dependent prevalence and clinical features of migraine. *Neurology* 2006;**67**:246-51.

30. Victor T, Hu X, Campbell J, Buse D, Lipton R. Migraine prevalence by age and sex in the United States: a life-span study. *Cephalalgia* 2010;**30**:1065-72.

31. National Institute for Health and Care Excellence. *Brodalumab for treating moderate to severe plaque psoriasis [TA511]*. NICE; 2018. Available from: https://www.nice.org.uk/guidance/ta511 [accessed 20th April 2020].

32. National Institute for Health and Care Excellence. *Certolizumab pegol for treating moderate to severe plaque psoriasis [ta574]*. NICE; Available from: https://www.nice.org.uk/guidance/ta574/resources/certolizumab-pegol-for-treating-moderate-to-severe-plaque-psoriasis-pdf-82607142805189 [accessed 20th April 2020].

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

33. National Institute for Health and Care Excellence. *Tildrakizumab for treating moderate to severe plaque psoriasis [TA575]*. NICE; 2019. Available from: https://www.nice.org.uk/guidance/ta575 [accessed 20TH aPRIL 2020].

34. National Institute for Health and Care Excellence. *Single Technology Appraisal. Appeal Hearing. Advice on erenumab for preventing migraine [ID1188]* NICE; 2019. Available from: https://www.nice.org.uk/guidance/gid-ta10302/documents/appeal-decision [accessed 20th April 2020].

35. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;**392**:1789-858.

36. Blumenfeld AM, Stark RJ, Freeman MC, Orejudos A, Manack Adams A. Long-term study of the efficacy and safety of Onabotulinum toxin A for the prevention of chronic migraine: COMPEL study. *J Headache Pain* 2018;**19**:13. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29404713

37. Data on File. *Eli Lilly and Co.: I5Q-MC-CGAW Clinical Study Report*; 2019.

38. Diener H-C, Charles A, Goadsby PJ, Holle D. New therapeutic approaches for the prevention and treatment of migraine. *The Lancet Neurology* 2015;**14**:1010-22.

39. Camporeale A, Kudrow D, Sides R, Wang S, Van Dycke A, Selzler KJ, et al. A phase 3, long-term, open-label safety study of Galcanezumab in patients with migraine. *BMC Neurol* 2018;**18**:188. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30413151

40. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. *Value Health* 2011;**14**:539-45.

41. NHS England, NHS Improvement. *2017/18 and 2018/19 National Tariff Payment System*. London. Available from: https://improvement.nhs.uk/documents/1044/2017-18_and_2018-19_National_Tariff_Payment_System.pdf

42. NHS Improvement. *National schedule of NHS costs -Year 2018-2019*. Available from: https://improvement.nhs.uk/resources/national-cost-collection/ [accessed 20th April 2020].

43. Curtis L, Burns A. *Unit Costs of Health and Social Care 2019*. Canterbury, Kent: Personal Social Services Research Unit, University of Kent 2020. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/

44. Munakata J, Hazard E, Serrano D, Klingman D, Rupnow MF, Tierce J, et al. Economic burden of transformed migraine: results from the American Migraine Prevalence and Prevention (AMPP) Study. *Headache* 2009;**49**:498-508. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19245386

45. Vo P, Fang J, Bilitou A, Laflamme AK, Gupta S. Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. *J Headache Pain* 2018;**19**:82. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30203163

46. National Institute for Health and Care Excellence. *Erenumab for preventing migraine. Final appraisal document*. London: NICE; 2019. Available from: https://www.nice.org.uk/guidance/gid-ta10302/documents/html-content-2

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

APPENDIX 1

Proof that the difference in monthly MHDs for the whole population cannot equal the difference in monthly MHDs for responders unless response is 100% or there is no treatment difference.

Where:

$Rsp_{galc/bot}$ = Response rate for galcanezumab/botulinum toxin A

$R\_MHD_{galc/bot}$= change in monthly MHDs for responders to galcanezumab/botulinum toxin A

$NR\_MHD_{galc/bot}$= change in monthly MHDs for non-responders to galcanezumab/botulinum toxin A

The difference in month MHDs for the whole population can be written as:

$$\left(Rsp_{galc} * R\_MHD_{glac} - \left(1 - Rsp_{galc}\right) * NR\_MHD_{galc}\right) - \left(Rsp_{bot} * R\_MHD_{bot} - (1 - Rsp_{bot}) * NR\_MHD_{bot}\right) \quad (1)$$

And the difference in monthly MHDs for responders can be written as:

$$R\_MHD_{galc} - R\_MHD_{bot} \quad (2)$$

Setting equations (1) and (2) equal to one another as implied by the company's analysis

$$\left(Rsp_{galc} * R_{MHD_{glac}} - \left(1 - Rsp_{galc}\right) * NR_{MHD_{galc}}\right) - \left(Rsp * R_{MHD_{bot}} - (1 - Rsp_{bot}) * NR_{MHD_{bot}}\right) = R\_MHD_{galc} - R\_MHD_{bot} \quad (3)$$

If $Rsp_{galc} = Rsp_{bot}$ and $NR\_MHD_{galc} = NR\_MHD_{bot}$ then equation (3) collapses to

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

$$Rsp * R\_MHD_{galc} - Rsp * R\_MHD_{bot} = R\_MHD_{galc} - R\_MHD_{bot} \quad (4)$$

This can be rearranged to:

$$Rsp * (R\_MHD_{galc} - R\_MHD_{bot}) = R\_MHD_{galc} - R\_MHD_{bot} \quad (5)$$

Equation (5) can only be true when either the response rate equals 100% or the difference in month MHDs for responders is zero. In the latter case this also implies that the difference in monthly MHDs for the whole population is zero i.e. that the treatments are equally effective. Where the response rate is < 100% and the difference in monthly MHDs for responders is non-zero, equation (5) also implies that the difference in the MHDs between treatments will always be smaller than the difference for responders.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

APPENDIX 2

Table 43 Quality assessment of included CEA study using Drummond et al. checklist completed by the ERG

	CEA quality assessment questions	Answer (Yes/No/Unclear)	Notes/Explanation for No or Unclear
1	Was the research question stated?	Yes	-
2	Was the economic importance of the research question stated?	Yes	-
3	Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	-
4	Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	-
5	Were the alternatives being compared clearly described?	Yes	-
6	Was the form of economic evaluation stated?	Yes	-
7	Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	-
8	Was/were the source(s) of effectiveness estimates used stated?	Partly	Effectiveness estimates from the ITC were stated but the details of the analysis used to generate the parameters were not initially available.
9	Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	-
10	Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	Full details to reproduce the ITCs (such as all data sources used; calculations to transform extracted data to useable data; justification for random or fixed effects and R script) were not initially provided.
11	Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	-
12	Were the methods used to value health states and other benefits stated?	Yes	-

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

13	Were the details of the subjects from whom valuations were obtained given?	Partly	The trial sources were provided but no detail was given on whether utilities were restricted to patients who have failed ≥3 prior therapies.
14	Were productivity changes (if included) reported separately?	Yes	-
15	Was the relevance of productivity changes to the study question discussed?	Yes	-
16	Were quantities of resources reported separately from their unit cost?	Yes	-
17	Were the methods for the estimation of quantities and unit costs described?	Yes	-
18	Were currency and price data recorded?	Yes	-
19	Were details of price adjustments for inflation or currency conversion given?	N/A	-
20	Were details of any model used given?	Yes	-
21	Was there a justification for the choice of model used and the key parameters on which it was based?	Partly	The company provided justification for using the model structure selected (e.g. precedent for previous CGRP-i appraisals). However, the company did highlight a previous model in which severity was captured yet severity was not included.
22	Was the time horizon of cost and benefits stated?	Yes	-
23	Was the discount rate stated?	Yes	-
24	Was the choice of rate justified?	Yes	-
25	Was an explanation given if cost or benefits were not discounted?	N/A	-
26	Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	-
27	Was the approach to sensitivity analysis described?	Yes	-

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

28	Was the choice of variables for sensitivity analysis justified?	Yes	-
29	Were the ranges over which the parameters were varied stated?	Yes	-
30	Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Partly	Company did not consider sequential treatment of active interventions i.e. botulinum toxin A following galcanezumab etc. This approach of sequential treatments has been common in appraisals of interventions compared to active comparators in other therapeutic indications.
31	Was an incremental analysis reported?	Partly	Correct pairwise incremental analysis was reported for episodic in which there was only one comparator. However, for the chronic migraine population, pairwise analyses were presented rather than a fully incremental analysis despite there being two comparators.
32	Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	-
33	Was the answer to the study question given?	Yes	-
34	Did conclusions follow from the data reported?	Yes	-
35	Were conclusions accompanied by the appropriate caveats?	No	-
36	Were generalisability issues addressed?	Partly	Incident population (which could be considerably lower than the modelled population) was not addressed.

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

APPENDIX 3

Table 44 ERG Scenario 11a) Equal effectiveness (ITC)

Intervention	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	-	-	-
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	£1,189
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£64,281

Table 45 ERG Scenario 11b) Response rate differs (ITC)

Intervention	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	-	-	-
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	£1,295
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£34,167

Table 46 ERG Scenario 11c) CFB in MHD differs (ITC)

Intervention	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	-	-	-
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	£7,825
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£8,454

Table 47 ERG Scenario 11d) 11b and 11c combined

Intervention	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	-	-	-
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	£5,641
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£11,734

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Table 48 ERG base case 1 (Scenarios 1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11a)

Intervention	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	-	-	-
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	£9,416
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£190,641

Table 49 ERG base case 2 (Scenarios 1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11b)

Intervention	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	-	-	-
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	£10,341
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£45,840

Table 50 ERG base case 3 (Scenarios 1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11c)

Intervention	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	-	-	-
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	£14,592
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£24,539

Table 51 ERG base case 4 (Scenarios 1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11d) – preferred

Intervention	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	-	-	-
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	£14,344
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£22,830

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.

Table 52 ERG preferred base case + 12) Incorporation of natural history

Intervention	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	-	-	-
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	£467
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£57,721

Copyright 2020 Queen's Printer and Controller of HMSO. All rights reserved.