Chair's presentation

Erenumab for preventing migraine [ID1188]

4th Appraisal Committee Meeting – 4th November 2020

Committee D

Chair: Gary McVeigh

Lead team: Andrew Hitchings, Malcolm Oswald, Rob Hodgson

ERG: Kleijnen Systematic Reviews

NICE technical team: Amy Crossley, Caron Jones, Jasdeep Hayre

Company: Novartis

ID1188 - Timeline

1st Committee meeting – December 2018

Appraisal Consultation Document (ACD) produced. Due to high volume of response comments, NICE rescheduled 2nd committee meeting to consider comments

2nd Committee meeting – April 2019

Following discussion with the company, NICE agreed that the company could provide a new value proposition, further evidence and analyses for consideration. Final Appraisal Document (FAD) was suspended as basis for decision making likely to change

3rd Committee meeting – August 2019

NICE issues FAD - joint appeal from the Association of British Neurologists and the British Association for the Study of Headaches (BASH) received

Appeal hearing – December 2019

Appeal panel upheld one appeal point: "*The Committee unreasonably failed to consider the cost-effectiveness of erenumab versus best supportive care in those who had failed to benefit from the comparator drug in patients with chronic migraine".* Panel concluded that the Committee should address this. NICE requested information on erenumab in people for whom botulinum toxin had failed, or in people who are contraindicated to botulinum toxin

4th Committee meeting – November 2020

Consideration of post appeal evidence, evidence on differential utilities, addressing consistency scenario analysis points

Previous FAD

Erenumab is **not recommended**, within its marketing authorisation, for preventing migraine in adults who have at least 4 migraine days per month

Committee's preferred assumptions
Based on evidence available, the Committee considered that while people stay on treatment, it is reasonable to assume that the treatment effect does not wane over time
On balance, it was concluded that the utility values used in the model* may be reasonable but were uncertain
Only the 140 mg dose should be considered in the cost-effectiveness model. The company's updated model using a lifetime time horizon was appropriate. All relevant costs for implementing erenumab in practice are captured in the model
Adverse events in erenumab trials were generally not severe and were comparable with placebo. Erenumab generally well tolerated in the studied populations

*common to all treatments

Key issues

Upheld appeal point - population included in new chronic migraine sub-group analysis

- Is the new clinical analysis from the company robust for:
  - People with chronic migraine (CM), for whom at least 4 prior treatments, including botulinum toxin, had failed (CM ≥4 TF, including botulinum toxin subgroup)?
  - People with chronic migraine (CM) for whom at least 3 prior treatments had failed, who had not previously received botulinum toxin (CM ≥3 TF, no prior botulinum toxin subgroup – used as a proxy for those contraindicated to botulinum toxin)?
- How robust is the new evidence on the longer term clinical effectiveness of erenumab?

Evidence supporting use of differential utilities between erenumab 140 mg and comparators

- How robust is the evidence on differing utilities between 140 mg and comparators, and should they be applied in the decision making?
- If differential utilities can be used, should this just apply in the post-appeal chronic migraine sub-groups, or in episodic migraine population and originally sought positioning in chronic migraine after the failure of 3 prior prophylactic treatments?

Treatment effect versus botulinum toxin

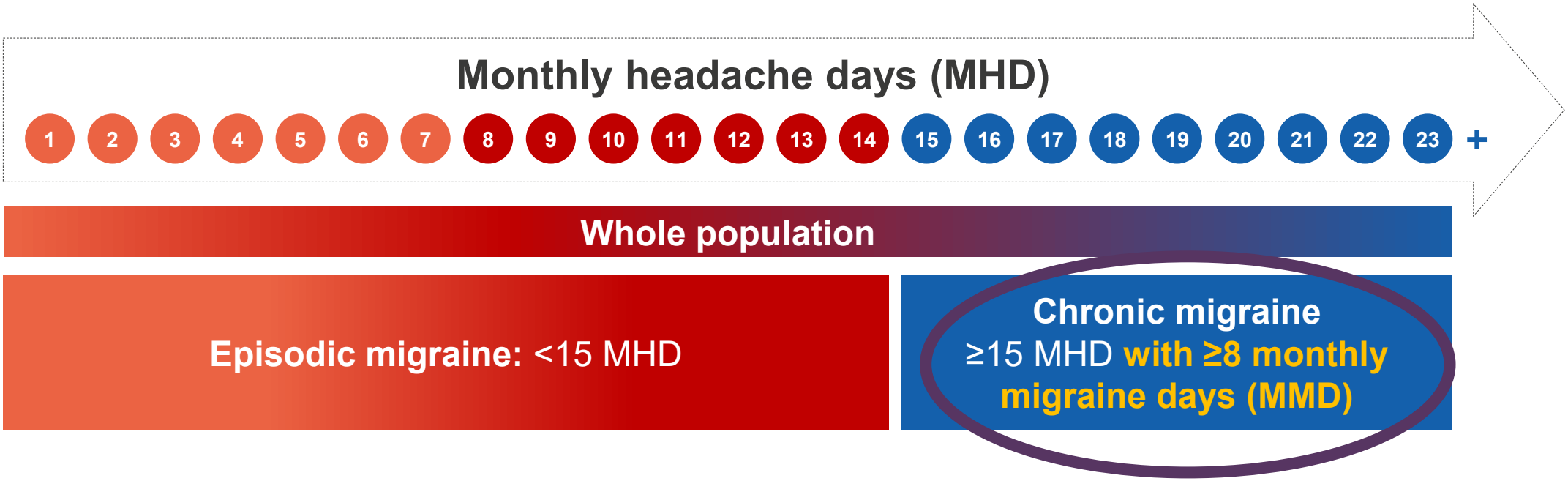
- Is the company's interpretation on different assumptions in ID1188, ID1372 and TA631 correct given the differing evidence provided?
- Should the company's scenario analysis on treatment effect versus botulinum toxin be used in decision making for this topic?

TF: prior prophylactic treatment failure

Migraine

- Headache disorder with recurring attacks usually lasting 4–72 hours
- Often accompanied by nausea, vomiting, sensitivity to light/sound
- Factors triggering attacks can include stress, change in sleep pattern, overtiredness, menstruation, caffeine/alcohol consumption
- Prevalence 5-25% in women, 2-10% in men

Classification



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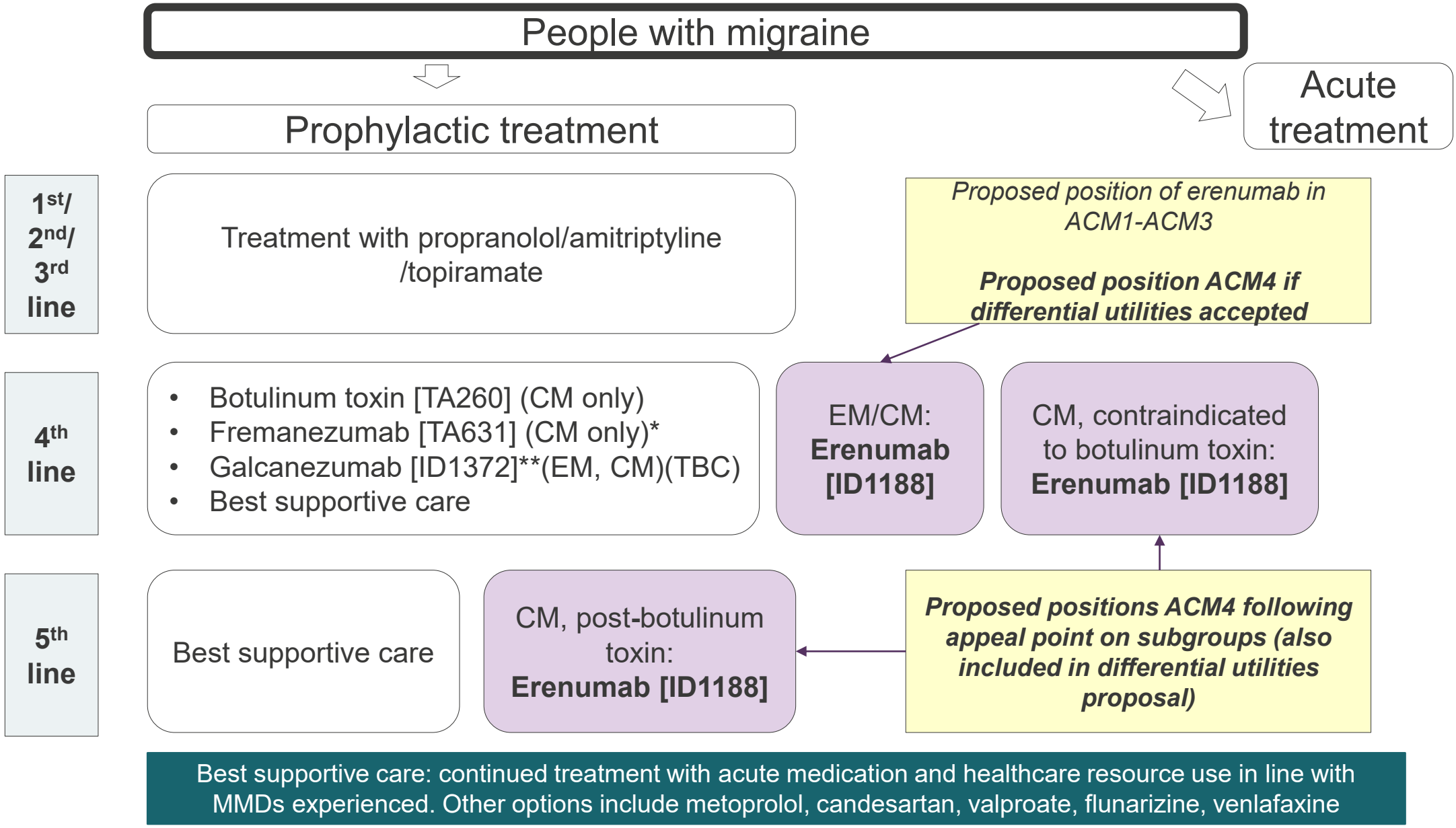
Migraine treatment pathway and erenumab



NICE *Fremanezumab [TA631] published June 2020. **Galcanezumab, final guidance still to be published
ACM: Appraisal Committee Meeting; EM: episodic migraine; CM: chronic migraine

Erenumab (Aimovig, Novartis)

Marketing authorisation (received July 2018)	For the prophylaxis of migraine in adults who have ≥4 migraine days per month
Mechanism of action	Monoclonal antibody targeting calcitonin gene-related peptide (CGRP) receptor. It is involved in the migraine pathway (pain transmission/vasodilation)
Administration	Subcutaneous injection
Dose	70 mg or 140 mg every 4 weeks (recommended dose 70 mg but some patients may benefit from 140 mg)
Discontinuation	Consider stopping treatment if no response after 3 months. Regular evaluation recommended thereafter
List price	£386.50 per dose (70 mg or 140 mg) Patient access scheme agreed (simple discount) [redacted]
Average cost of treatment (list price)	Non-responders: £1,159.50 Responders: £35,171.50 (based on modelled 7 year median duration)

Clinical evidence

Clinical evidence for upheld appeal point comes from a post-hoc subgroup from **Study 295**

Study 295	
Design	Multicentre, randomised, Phase II, double-blind, placebo-controlled
Migraine type	Chronic
Dose	70 mg, 140 mg
Primary outcome	Change in monthly migraine days (MMD) from baseline to last month
Placebo comparator	Best supportive care
Prior treatments	≤3 categories of medication or individual medications
Key exclusion criteria	no therapeutic response to >3 previous treatment categories

Upheld appeal point

Erenumab versus best supportive care in those who had failed to benefit from the comparator drug in patients with chronic migraine

Company presented new evidence for erenumab in two populations from Study 295

- People with chronic migraine, for whom at least 4 prior treatments, including botulinum toxin, had failed (**CM ≥4 TF**, **including botulinum toxin** subgroup)

- People with chronic migraine for whom ≥3 prior prophylactic treatments had failed, and had not previously received botulinum toxin (**CM ≥3 TF, no prior botulinum toxin** subgroup – used as a proxy for those contraindicated to botulinum toxin)

ERG comments on population included in analyses

- Study 295 excluded those for whom more than 3 treatment categories had failed, meaning patients with the most refractory disease were not included

- Small sample size of the subgroups - these small subgroups may not be able to be analysed in a meaningful way

- Questioned whether patients discontinuing botulinum toxin treatment for *'other reasons'* should be included in the definition of treatment failure ([redacted] in the placebo group and [redacted] in the erenumab group)

Further ERG comments

- Questioned validity of non-receipt of botulinum toxin treatment, for patients with chronic migraine and ≥3 prophylactic treatment failures, as a proxy for botulinum toxin being contraindicated (other reasons for not receiving botulinum toxin)

- Agreement with company's statement that overall baseline characteristics comparable between ITT population and **CM ≥3 TF, no prior botulinum toxin subgroup.** However, lack of evidence about effectiveness of erenumab in males and in non-white populations, identified in the ERG report, is exacerbated in this very small subgroup

- Appears that [redacted] of patients included in the CM ≥4 TF, including prior botulinum toxin subgroup did not meet the definition of having failed botulinum toxin treatment, i.e. these patients had discontinued botulinum toxin for reasons other than treatment failure

Chronic

Clinical effectiveness results

Sub-group: CM with ≥4 TF including botulinum toxin

Outcome	Result
Monthly Migraine Days (MMDs)	Erenumab 140 mg reduced the MMDs by [redacted] days more on average than placebo [redacted] compared to [redacted] p value = [redacted]
30% reduction in MMDs*	• [redacted] erenumab 140 mg • [redacted] for placebo

Sub-group: CM with ≥3 TF, no prior botulinum toxin (used as a proxy for those contraindicated to botulinum toxin)

Outcome	Result
MMDs	Erenumab 140 mg reduced the MMDs by [redacted] days more on average than placebo [redacted] compared to [redacted] p value = [redacted]
30% reduction in MMDs*	• [redacted] erenumab 140 mg • [redacted] for placebo

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*considered clinically meaningful and used to define non responders in the model

Additional real-world evidence

In addition to the post-hoc subgroups data from study 295, the company and the British Association for the Study of Headache (BASH) submitted evidence from other studies

Outcome	Erenumab 140 mg outcome
Change from baseline in MMDs at Week 12	
Study 295, week 12	[redacted]
Published Real World Study (RWS)[11]	-6.1
Proportion of patients with ≥30% reduction in MMDs from baseline at approximately Week 12	**N(%)**
Study 295[a] - week 12	[redacted]
Published real world study[b] - 3 months	19 (51.4)
Guy's & St Thomas's, London[c] - 3 months	(50)
Manchester[c] - 10 weeks; 18 weeks	21 (47.7); 24 (54.5)
King's College London[c] - 3 months	16/43 (37.2)

Source: [a]published real world study[11]: note that dose of erenumab was 70 mg; [b]Tables 1 and 3, post-appeal CS[2]; [c]BASH[3]: note that reported outcome for Manchester is ≥30% reduction in severe headache days.
CI: confidence interval; CMH: Cochran-Mantel-Haenszel; LSM: least squares mean; MMD: monthly migraine day; RWS: real world study; SE: standard error.

From table 3.5, ERG post appeal addendum, page 19

ERG critique – real world evidence

- ERG acknowledges the ‘real-world’ evidence, provides some additional support for the efficacy of erenumab treatment in patients with chronic migraine who have failed at least three prophylactic treatments and have also failed botulinum toxin treatment

- The ‘real-world’ evidence from UK centres participating in the free-of-charge scheme, provided by BASH, includes some indication of longer-term efficacy (18 weeks to 6 months).

- Although the response from the Manchester centre lists ‘waning of efficacy’ among reasons for discontinuation, this is not demonstrated in the apparent increase in the number of responders between 10 weeks and 18 weeks reported by this centre

- As in original submission, no data on the long-term (>12 weeks) effectiveness of erenumab compared to placebo in either CM ≥4 TF, including botulinum toxin subgroup or the CM ≥3 TF, no prior botulinum toxin subgroup

Company model

- State transition model with three health states: on treatment, discontinuation and death. Model cycle length 12 weeks

- People discontinue erenumab if no clinically meaningful response (<30% reduction in MMD). Reflected by modelling discontinuation of non-responders at the assessment timepoint (12 weeks) and 2.38% all-cause discontinuation rate every 12 weeks

- Company's model structure is the same as that used in ACM3, with new data from each of the two post-hoc subgroups

The company conducted scenario analyses for both subgroups in which patients who discontinue treatment were assumed to rebound to baseline MMDs, rather than maintain the non-responder MMD improvement achieved at week 12 (as in the base-case)

ERG critique of company's updated cost effectiveness analyses (chronic migraine subgroups)

- ERG confirmed it could reproduce the company's cost-effectiveness estimates and that the ERG and company's base case results are aligned
- Despite this, ERG states that there remains uncertainty (that is not quantified in the health economic analyses) regarding the evidence used (from Study 295) and therefore, the interpretation of these results
- Questionable whether extrapolating benefits for non-responders (i.e. in MMD frequency distribution) is plausible (for CM ≥4 TF, including botulinum toxin subgroup the non-responder mean MMD are [redacted] and [redacted] for erenumab and best supportive care [BSC]). Mitigated in the company's scenario analysis assuming rebound to baseline MMDs after discontinuation and to some extent mitigated in treatment waning scenario given decreased MMD frequency distributions benefits over time

Chronic

Cost-effectiveness results – upheld appeal point

Deterministic ICER results for both post-hoc subgroups from study 295

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CM ≥4 TF, including botulinum toxin subgroup					
Company base-case					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario assuming rebound to baseline MMDs after discontinuation					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM ≥3 TF, no prior botulinum toxin subgroup					
Company base-case					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario assuming rebound to baseline MMDs after discontinuation					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC: best supportive care; CM: chronic migraine; ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year. MMD: monthly migraine days

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Cost-effectiveness results (probabilistic) – upheld appeal point

Technologies	Total costs (£)	QALYs	Inc costs (£)	Inc QALYs	ICER(£/QALY)
CM ≥4 TF, including botulinum toxin subgroup					
Company base-case					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario assuming rebound to baseline MMDs after discontinuation					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM ≥3 TF, no prior botulinum toxin subgroup					
Company base-case					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario assuming rebound to baseline MMDs after discontinuation					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key issue – upheld appeal point

Population included in new company chronic migraine sub-group analysis

- Is the new clinical analysis from the company robust for:
  - People with chronic migraine, for whom at least 4 prior treatments, including botulinum toxin, had failed (CM ≥4 TF, including botulinum toxin subgroup)?

  - People with chronic migraine for whom at least 3 prior treatments had failed, who had not previously received botulinum toxin (CM ≥3 TF, no prior botulinum toxin subgroup – used as a proxy for those contraindicated to botulinum toxin)?

- How robust is the new evidence on the longer term clinical effectiveness of erenumab?

Differential utilities - background

- In the FAD for galcanezumab for preventing migraine (ID1372, final guidance not yet published), the company for that topic provided high-quality, compelling evidence of a treatment-related difference in utility values
- Showed that utilities for galcanezumab were higher across all mean migraine headache day values compared with placebo (also a large, statistically significant difference between treatments in regression analysis)
- Committee were able to accept that galcanezumab reduced levels of impairment and burden between migraine attacks, which was supported by clinical expert opinion, and considered that there was evidence for use of differential utilities

- Company given opportunity to present any evidence it may have for use of differential utilities between erenumab and comparators, followed approach taken in ID1372
- New multilevel regression models based on data from Study 295 (CM) and STRIVE (EM). Separate regression models used to generate utility values - baseline MSQ data included in one regression model with MMD frequency as only covariate; post-baseline MSQ data included in second regression model with MMD frequency and treatment as covariates.
- In addition to utility models incorporating data from full trial populations, analyses for differential utilities were also conducted using only data from patients with ≥3 previous treatment failures (but power to detect statistical significance limited by reduced sample size)

MSQ: Migraine Specific Quality of Life Questionnaire

Differential utilities – company's evidence

Off-treatment (baseline) multilevel regression models including MMD frequency as covariate – **Full study population**

	Full population – CM+EM (Combined Study 295, STRIVE; Normal)		Full population – CM (Study 295; Normal)		Full population – EM (STRIVE; Normal)	
No. of observations	[redacted]		[redacted]		[redacted]	
	Estimate	p-value	Estimate	p-value	Estimate	p-value
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMD frequency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

On-treatment (post-baseline) multilevel regression models including MMD frequency and treatment effect as covariates – **Full study population**

	Full population – CM+EM (Combined Study 295, STRIVE; Normal)		Full population – CM (Study 295; Normal)		Full population – EM (STRIVE; Normal)	
No. of observations	[redacted]		[redacted]		[redacted]	
	Estimate	p-value	Estimate	p-value	Estimate	p-value
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMD frequency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Differential utilities – company's evidence

Off-treatment (baseline) multilevel regression models including MMD frequency as covariate – **Population with ≥3 prior prophylactic treatment failures**

	≥3 prior prophylactic treatment failures population – CM+EM (Combined Study 295, STRIVE; Normal)		≥3 prior prophylactic treatment failures population – CM (Study 295; Normal)		≥3 prior prophylactic treatment failures population – EM (STRIVE; Normal)	
No. of observations	[redacted]		[redacted]		[redacted]	
	Estimate	p-value	Estimate	p-value	Estimate	p-value
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMD frequency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

On-treatment (post-baseline) multilevel regression models including MMD frequency and treatment effect as covariates – **Population with ≥3 prior prophylactic treatment failures**

	≥3 prior prophylactic treatment failures population – CM+EM (Combined Study 295, STRIVE; Normal)		≥3 prior prophylactic treatment failures population – CM (Study 295; Normal)		≥3 prior prophylactic treatment failures population – EM (STRIVE; Normal)	
No. of observations	[redacted]		[redacted]		[redacted]	
	Estimate	p-value	Estimate	p-value	Estimate	p-value
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMD frequency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Differential utilities – company's evidence

- Treatment effect of erenumab 140 mg, independent of the reduction in MMDs, is statistically significant in all utility regression models including data from the full trial populations. The regression models only utilising data from patients with ≥3 prior treatment failures showed a numerical benefit of erenumab 140 mg versus placebo beyond the reduction of MMDs
- Company carried out face validity checks, found that predictions of the erenumab utility models might 'have higher face validity than utility values in other migraine NICE appraisals'
- Longitudinal utilities assessment (Di Tanna et al, 2019) found mapped utility values higher for erenumab-treated patients than for patients with same number of MMDs receiving placebo, "indicating that treating migraine may have benefit beyond simply reducing the number of migraines a patient experiences and may translate into improvements in HRQoL"
- Post ACM3 FAD: "Committee recognised that erenumab 140 mg also improved other outcomes compared with placebo, including the severity of migraine pain and the number of headache days each month"
- MMDs not only meaningful measure. Company carried out correlation analyses between MMDs, monthly headache days and five patient-reported outcome instruments collected in erenumab trials, found MMDs alone do not capture the impact of migraine on both ictal (during migraine) and interictal (between migraines) periods so economic model may be underestimating erenumab's cost-effectiveness compared to BSC

Episodic
Chronic
Chronic
Chronic

Cost-effectiveness results – differential utilities (deterministic)

Episodic migraine ≥3 prior treatment failures: Base case results with **differential utilities**

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case: Utility model CM+ EM – ≥3 treatment failure population					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Chronic migraine ≥3 prior treatment failures: Base case results with **differential utilities**

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case: Utility model CM+ EM – ≥3 treatment failure population					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Chronic migraine ≥4 prior treatment failures, post-botulinum toxin: Base case results with **differential utilities**

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case: Utility model CM+ EM – ≥3 treatment failure population					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Chronic migraine ≥3 prior treatment failures, contraindication to botulinum toxin: Base case results with **differential utilities**

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case: Utility model CM+ EM – ≥3 treatment failure population					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cost effectiveness results - differential utilities

- Results are considered commercial in confidence due to the patient access scheme, so cannot be shown here

- **Company** view:
  - After incorporating differential utilities for erenumab and BSC, cost-effectiveness results for **episodic** migraine are within range that is commonly accepted as cost-effective
  - As incorporation of differential utilities does not impact comparison versus botulinum toxin (except for utilities applied in off-treatment states), they are less relevant for fully incremental cost-effectiveness analyses in **chronic migraine population after ≥3 TF**
  - Results versus BSC in the **chronic migraine subgroups** (≥4 TF, and ≥3 TF with contraindication to botulinum toxin) demonstrate improved value with inclusion of differential utilities
  - Scenario analyses with alternative differential utility models demonstrate that conclusions are robust to changes in applied differential utilities models

- **ERG** view:
  - ERG base case did not include differential utilities, as they believed the company's original regression model for this issue was flawed. Company then changed it to better match regression carried out in galcanezumab topic. ERG preferred the updated regression analysis and said it seemed reasonable.

Cost effectiveness results - differential utilities

- **ERG** view (continued):
  - Company's further evidence (beyond that from trial) might support statement that MMDs alone do not capture the impact of migraine on both ictal and interictal periods. However, it did not provide compelling evidence of a differential utility of erenumab 140 mg versus BSC independent of MMD frequency
  - Contra intuitive that ICERs of erenumab 140 mg versus the relevant comparator, in general, slightly decreased (when considering the estimated coefficients for the "treatment" covariate of 29th Oct and 16th Oct submitted regression models) - likely due to the assumed utilities after discontinuation (company assumes patients are assigned 'off-treatment' i.e. baseline utilities and not BSC utilities). Might impact the estimated QALYs (particularly driven by difference in discontinuation due to the proportions of non-responders)
  - Additionally, this assumption seems inconsistent with assumptions for MMD frequency after discontinuation - that patients maintain the non-responder MMD improvement (and will not rebound back to baseline MMD). Using the approach described in the table in the next slide (used in company's 16th Oct analyses) but with the newly estimated utility values (from company's 29th Oct analyses) might be a reasonable alternative – this has been explored by ERG

ERG exploratory analyses

Source of differential utility values by intervention and model state in economic model dated 16 October 2020*

Cost-effectiveness model state		Source of utility values by intervention and model state		
		Erenumab 140 mg	BSC	Botulinum toxin
Assessment period (decision tree)	Baseline	BSC	BSC	BSC
	Responders	Erenumab 140 mg	BSC	Erenumab 140 mg
	Non-responders	Erenumab 140 mg	BSC	Erenumab 140 mg
Post-assessment period (Markov model)	On treatment	Erenumab 140 mg	BSC	Erenumab 140 mg
	Negative discontinuation (non-response; AE-related; long-term)	BSC	BSC	BSC

*From table 6, Response to ERG addendum v2 (2/11/2020)

ERG carried out scenario analysis using the company's 16th October 2020 approach while implementing the differential treatment utility ([redacted]) estimated in the 29th October 2020 submitted document by the company. The results indicate that when adopting a differential treatment utility, the exact approach to implement this is unlikely to be a main driver of the cost-effectiveness of erenumab 140 mg.

ERG exploratory analyses

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Episodic migraine ≥3 prior treatment failures					
Company base-case (differential utility; utility model CM+EM – ≥3 treatment failure population) 16 October 2020					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base-case (differential utility; utility model CM+EM – ≥3 treatment failure population) 29 October 2020[a]					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base-case 16 October 2020 + differential utility of 29 October 2020 ([redacted])					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (no differential utility) – consistent with ERG base-case in original ERG report (assuming constant treatment effectiveness)					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Please see 'ERG addendum 2 differential utilities' for results of CM ≥3 TF, CM ≥3 TF with prior botulinum toxin, and CM ≥3 TF contraindicated to botulinum toxin sub-groups.

Key issue – differential utilities

Evidence supporting use of differential utilities between erenumab 140 mg and comparators

- How robust is the evidence on differing utilities between 140 mg and comparators, and should they be applied in the decision making?
- If differential utilities can be used, should this just apply in the post-appeal chronic migraine sub-groups, or in episodic migraine population and originally sought positioning in chronic migraine after the failure of 3 prior prophylactic treatments?

Possible inconsistencies

- Company compared this topic [ID1188] with galcanezumab [ID1372] and fremanezumab [TA631] for preventing migraine, and investigated some areas where it believed there were differences in assumptions, via scenario analyses

Company's interpretation:

	Fremanezumab [TA631]	Galcanezumab [ID1372]	Erenumab [ID1188]
1) Administration costs for CGRP inhibitor	Included for 10% of people receiving fremanezumab	Included for 10% of people receiving galcanezumab	Not included (all patients self-administer erenumab after being trained)
2) Age-related disutility	No evidence of inclusion of age-related disutility could be identified	Included age-related decrements	Not included
3) Dissipation of placebo effect in BSC responders	Treatment effect in BSC responders wanes to baseline over 1 year; all patients discontinuing treatment revert to baseline MMDs	Treatment effect in BSC responders wanes to baseline over 1 year; all patients discontinuing treatment revert to baseline MMDs; no evidence that this assumption was removed in final model	Treatment effect in BSC responders is maintained throughout the lifetime time horizon of the model; all patients discontinuing treatment maintain the non-responder MMD improvement
4) Treatment effect versus botulinum toxin	Equivalence assumed between fremanezumab and botulinum toxin	Galcanezumab vs. botulinum toxin treatment effect used in final decision-relevant model	Equivalence assumed between erenumab 140 mg and botulinum toxin

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Company's scenarios:

	Change made in erenumab model for scenarios
1) Administration costs for CGRP inhibitor	Administration costs applied for 10% of patients, costed as 30 min hospital appointment with nurse
2) Age-related disutility	Utility values weighted based on age-decrements for UK general population published in Ara and Brazier (2011)
3) Dissipation of placebo effect in BSC responders	BSC responders revert to baseline MMDs at the end of year 1 (sudden and full loss of placebo effect), and all patients discontinuing treatment are assumed to rebound to baseline MMDs (slightly more conservative than company's understanding of ID1372 and TA631 assumptions)
4) Treatment effect versus botulinum toxin	Indirect treatment comparison carried out for erenumab 140 mg vs botulinum toxin (found some evidence to suggest that erenumab may be more effective), used these clinical-effectiveness estimates in model

Chair, lead team and technical team agreed with changes 1-3

Chronic

Company-run scenario analysis 4: chronic migraine ≥3 prior treatment failures (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case (including differential utilities)					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: Erenumab treatment effect over botulinum toxin (OR=[redacted])					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
Erenumab 140 mg	[redacted]	[redacted]	[redacted] (vs BSC)	[redacted] (vs BSC)	[redacted] (vs BSC)

Company's interpretation of their scenario analysis result - treatment effect versus botulinum toxin

- In population with chronic migraine and ≥3 prior treatment failures, with differential utilities estimates an odds ratio of [redacted] of erenumab 140 mg vs botulinum toxin in the ≥30% MMD reduction outcome would be sufficient to achieve an ICER <£20,000 (£[redacted]); an ICER <£30,000 would result from an odds ratio of [redacted] (ICER £[redacted]). The existence of at least such a minimal treatment effect seems highly plausible, given the consistent, at least numerical benefit of erenumab 140 mg vs botulinum toxin demonstrated in ITCs

Key issues – other company-run scenario analysis

Treatment effect versus botulinum toxin

- Is the company's interpretation on different assumptions in ID1188, ID1372 and TA631 correct given the differing evidence provided?
- Should the company's scenario analysis on treatment effect versus botulinum toxin be used in decision making for this topic?

Key issues - recap

Upheld appeal point - population included in new chronic migraine sub-group analysis

- Is the new clinical analysis from the company robust for:
  - People with chronic migraine (CM), for whom at least 4 prior treatments, including botulinum toxin, had failed (CM ≥4 TF, including botulinum toxin subgroup)?
  - People with chronic migraine (CM) for whom at least 3 prior treatments had failed, who had not previously received botulinum toxin (CM ≥3 TF, no prior botulinum toxin subgroup – used as a proxy for those contraindicated to botulinum toxin)?
- How robust is the new evidence on the longer term clinical effectiveness of erenumab?

Evidence supporting use of differential utilities between erenumab 140 mg and comparators

- How robust is the evidence on differing utilities between 140 mg and comparators, and should they be applied in the decision making?
- If differential utilities can be used, should this just apply in the post-appeal chronic migraine sub-groups, or in episodic migraine population and originally sought positioning in chronic migraine after the failure of 3 prior prophylactic treatments?

Treatment effect versus botulinum toxin

- Is the company's interpretation on different assumptions in ID1188, ID1372 and TA631 correct given the differing evidence provided?
- Should the company's scenario analysis on treatment effect versus botulinum toxin be used in decision making for this topic?