Lead team presentation ID1188 erenumab for preventing migraine (STA)

1st Appraisal Committee meeting

Committee D

Lead team: Andrew Hitchings, Malcolm Oswald, Rob Hodgson

ERG: Kleijnen Systematic Reviews

NICE technical team: Anna Brett; Victoria Kelly

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[redacted]

Key issues: clinical effectiveness

- Are the trials generalisable to a UK population with migraine for whom ≥3 prior treatments have failed?
- Is the full spectrum of migraine (in people with ≥4 MMD) adequately covered by the evidence base?
- Is it helpful and meaningful to consider people with chronic, episodic and high frequency episodic migraine, as distinct populations?
- Do the primary outcomes fully capture the clinical benefit valued by patients?
- Are best supportive care and botulinum toxin the only relevant comparators?
- Is there sufficient clinical evidence to support long-term effectiveness of erenumab and durability of response?
- Do the trials adequately capture safety data?

[redacted]

MMD, Monthly migraine days

Key issues: cost effectiveness

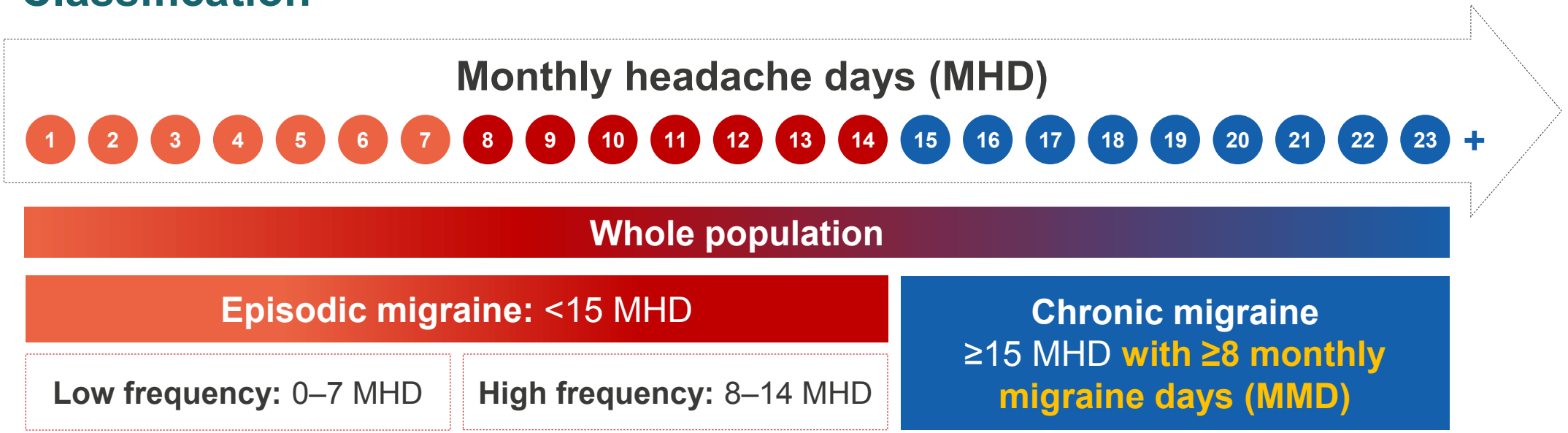
- Is it appropriate to consider a ‘blended dose’ (combining 70 mg and 140 mg dose)?
- Should the 2 doses be considered together in an incremental analysis, or separately, in pairwise analyses?
- Should response to treatment be defined as ≥30% or ≥50% reduction in MMDs?
- Are people whose disease is responding likely to have treatment indefinitely?
- What is the appropriate time horizon: 5 years? 10 years? 15 years? Lifetime?
- Is treatment effect likely to be constant or wane over time (over 5 years? 10 years?)
- When treatment is stopped how is the disease likely to continue to respond (at 12 weeks, in the maintenance phase)? Is this likely to differ according to the reason treatment was stopped (i.e adverse events, non-response)?
- What is the most appropriate source of health utilities; MSQ scores from full trial or subgroup population, or EQ-5D? Are the utility values plausible?
- Are all relevant costs included?

[redacted]MMD, Monthly migraine days; MSQ, Migraine-specific quality of life questionnaire

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



Erenumab (Aimovig, Novartis)

Marketing authorisation (received July 2018)	For the prophylaxis of migraine in adults who have ≥4 migraine days per month when initiating treatment
Mechanism of action	Monoclonal antibody targeting the calcitonin gene-related peptide (CGRP) receptor. CGRP 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	Regular evaluation recommended. Consider stopping treatment if no response after 3 months
List price	£386.50 per dose (70 mg or 140 mg) Patient access scheme agreed (simple discount). Interim complex PAS agreed to ensure 140 mg dose (2 x 70 mg pens) is same price as 70 mg before 140 mg pen available
Average cost of treatment (list price)	Non-responders: £1,159.50 Responders: £35,171.50 (based on modelled 7 year median duration)

Patient perspectives

- The Migraine Trust's response based on several large surveys of patients (n=116-1838 patients)
- Migraine leads to social isolation, depression, loneliness, poor quality of life; prevents normal activities & family life → hard to manage → it is fluctuating, disabling and unpredictable
- "Chronic migraine infiltrates all parts of my life. On the odd day when I'm not in pain, I worry about being in pain. Will it be worse the next time? Will I have to stay home from work (again)?"
- Current preventative treatment options limited because:
  - can be ineffective (re-purposed drugs for treating other conditions used off-label)
  - debilitating side effects (drowsiness, mood disturbance, cognitive dysfunction, weight gain)
  - contraindicated for people with multiple conditions and pregnant women
- Botulinum toxin type A ('Botox') is resource intensive and only available in some hospitals
- Regular use of acute pain-relief risks medication-overuse headaches
- Unmet need for effective preventive treatments, particularly for chronic migraine ("15+ days per month, three consecutive months")
- Erenumab is first treatment developed specifically for migraine; can reduce frequency and severity of attacks and has a rapid onset
- Potential disadvantages: pain at injection site, allergic reaction, needle phobia

Migraine Trust; Organisation for the Understanding of Cluster Headache; patient experts

Clinician perspectives

- Aim of treatment to reduce frequency, duration and severity of migraine, improve quality of life and reduce need for acute medications to treat attacks
- Limited effective preventive treatments; current options include beta-blockers, tricyclic antidepressants, anti-convulsants, which have a range of often debilitating side effects
- Significant treatment response would be reduction in headache severity, duration and/or frequency by at least 50% in episodic and 30% in high frequency episodic and chronic migraine, and significant reported change in patient quality of life measures
- Unmet need for effective, well-tolerated preventive treatment, particularly for chronic migraine refractory to first line treatments
- “Lack of appropriate resources to manage headache despite high cost to society”
- Erenumab is first migraine-specific preventive treatment targeted at underlying biology
- Clinically meaningful benefits and improved quality of life anticipated, especially in high frequency episodic and chronic migraine, and where current treatments are not tolerated
- Fewer side effects than current oral treatments; potential for reduced follow-up & monitoring
- Self-injectable treatment empowers patients and improves compliance

Association of British Neurologists; British Association for the Study of Headache; Primary Care Neurology Society; clinical experts

Clinician perspectives (implementation)

- Variation in headache care; specialist services for chronic refractory migraine limited; many patients not getting appropriate treatment
- Erenumab likely to be used for refractory chronic migraine
  - Starting and stopping criteria will be needed to appropriately target use
  - Greater investment in specialist headache services may be needed
  - High anticipated demand if recommended
- Concern it will not be widely available given variable access to specialist clinics
- Current lack of capacity in neurology, but erenumab may lessen need for hospital visits compared with Botox
- Likely to be initiated in specialist secondary care clinics given novel nature of drug
- Could potentially be monitored in primary care with shared protocol

Association of British Neurologists; British Association for the Study of Headache; Primary Care Neurology Society; National Hospital for Neurology and Neurosurgery; clinical experts

Decision problem: NICE scope

Population	People with migraine
Intervention	Erenumab
Comparators	Established clinical management for migraine prophylaxis without erenumab, including Botulinum toxin type A for chronic migraine that has not responded to at least 3 prior pharmacological prophylaxis therapies
Outcomes	• Frequency of headache days per month • Frequency of migraine days per month • 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
Subgroups	• People with chronic or episodic migraine • Number of previous prophylactic treatments • Frequency of episodic migraine

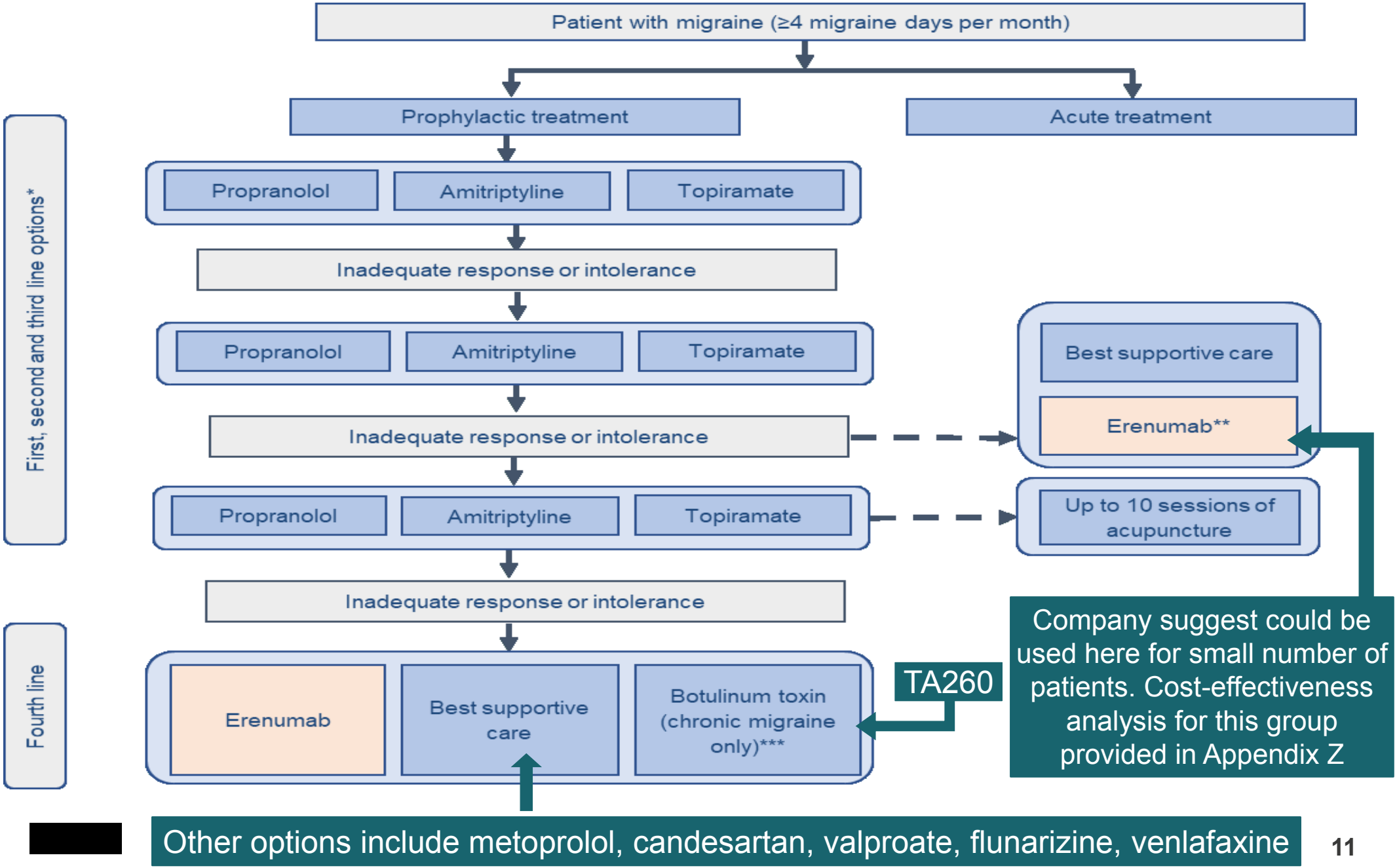
[redacted]

Company decision problem & ERG critique

Population	Adults with migraine with ≥4 migraine days per month **for whom ≥3 prior prophylactic treatments have failed** • optimised use appropriate to NHS context where low cost oral prophylactics available 1st line • targeted for patients with unmet need and lack of treatment options **ERG comment**: does not fully reflect scope or marketing authorisation, but likely to reflect expected use in NHS
Intervention	Erenumab 70 mg/140 mg (140 mg considered may be appropriate for patients with ≥3 prior failed treatments)
Comparators	• Best supportive care • Botox (for chronic migraine population only) **ERG comment**: appropriate for subgroup
Outcomes	As per NICE scope. Outcomes used in model: • change from baseline in mean monthly migraine days (MMDs) • proportion of patients with ≥50% reduction in mean MMDs from baseline **ERG comment**: Patients may consider reductions <50% clinically meaningful Unclear whether treatment would be stopped if <50% reduction in practice
Subgroups	As per NICE scope

[redacted]

Migraine treatment pathway



Key trials

	Study 295 n=667	STRIVE n=955	ARISE n=577	LIBERTY n=246
Design	Multicentre, randomised, double-blind, placebo-controlled			
	Phase II	Phase III	Phase III	Phase IIIb
Population	Adults (18-65 years) without significant co-morbidity			
Migraine type	Chronic	Episodic	Episodic	Episodic
Prior treatments	≤3	≤2	≤2	2-4
Concurrent treatment	None	One allowed under late protocol amendment (but few patients)		None
Dose	70 mg; 140 mg	70 mg; 140 mg	70 mg	140 mg
Duration of blinded phase	3 months	6 months	3 months	3 months
Primary outcome	Change in MMD from baseline to last month	Change in MMD from baseline to last 3 months	Change in MMD from baseline to last month	≥50% reduction in MMD from baseline to last month

Placebo considered to represent best supportive care, defined by continued treatment with acute medication. Patients in placebo arms of trials had acute treatments aligned with UK clinical guideline recommendations. MMD, Monthly migraine days.

Results (≥3 prior subgroup): MMD reduction

	Placebo	Erenumab 70 mg	Erenumab 140 mg
Study 295 (chronic)	n=XX	n=XX	n=XX
Mean change from baseline Difference (95% CI)	XXX	XXX -2.5 (-4.3, -0.8) p=0.005	XXX –4.1 (–5.8, –2.3) p<0.001
STRIVE (episodic)	n=XX	n=XX	n=XX
Mean change from baseline Difference (95% CI)	XXX	XXX XXXXXXXXXXXXXXXX	XXX XXXXXXXXXXXXXXXX
ARISE (episodic)	n=XX	n=XX	N/A
Mean change from baseline Difference (95% CI)	XXX	XXX XXXXXXXXXXXXXXXX	N/A
LIBERTY (episodic)	n=XX	N/A	n=XX
Mean change from baseline Difference (95% CI)	XXX	N/A	XXX XXXXXXXXXXXXXXXX

[redacted]

MMD, Monthly migraine days; CI, Confidence interval

Results (≥3 prior subgroup): 50% responder

	Placebo	Erenumab 70 mg	Erenumab 140 mg
Study 295 (chronic)	n=[redacted]	n=[redacted]	n=[redacted]
Proportion of patients % (n) Odds ratio vs. placebo (95% CI)	15.3% (15)	34.8% (23) 3.0 (1.4, 6.3) p=0.004	38.5% (25) 3.5 (1.6, 7.4) p=0.001)
STRIVE (episodic)	n=[redacted]	n=[redacted]	n=[redacted]
Proportion of patients % (n) Odds ratio vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]
ARISE (episodic)	n=[redacted]	n=[redacted]	N/A
Proportion of patients % (n) Odds ratio vs. placebo (95% CI)	[redacted]	[redacted]	
LIBERTY (episodic)	n=[redacted]	N/A	n=[redacted]
Proportion of patients % (n) Odds ratio vs. placebo (95% CI)	[redacted]		[redacted]

[redacted]

MMD, Monthly migraine days; CI, Confidence interval

ITC with Botox in chronic migraine

No direct head-to-head evidence for erenumab vs. Botox in chronic migraine → ITC

Study 295
- Outcomes reported at 12 weeks
- % responder rate for monthly **migraine** days

PREEMPT 1&2
- Outcomes reported at 24 weeks
- For ≥3 prior treatments subgroup only % responder rate for monthly **headache** days reported

Results for ≥3 prior treatments subgroup (used in economic model)

Proportion of patients with ≥50% reduction in monthly migraine days at 12 weeks with erenumab vs. proportion of patients with ≥50% reduction in monthly headache days at 24 weeks with Botox

Erenumab 70 mg (n=XX)	Botox (n=189)	Erenumab 140 mg (n=XX)	Botox (n=189)
Odds ratio (95% CI): XXXXXXXXXX		Odds ratio (95% CI): XXXXXXXXXX	

Supporting data also showed point estimates that favoured erenumab compared with Botox in the full trial populations. None of the results were statistically significant

[redacted]

ITC, Indirect treatment comparison

Indirect treatment comparison: limitations

- Company: ‘best available analysis’ of erenumab vs Botox in people with ≥3 prior failed treatments, but notes limitations
- Patients in Study 295 and PREEMPT not stratified by prior treatments so randomisation broken – patient characteristics may be imbalanced between arms
- Baseline characteristics not available for the PREEMPT subgroup so could not be compared to Study 295 subgroup (although baseline characteristics for full trial populations were similar)
- Outcomes reported at different time points (company considers likely to represent conservative estimate for erenumab vs. Botox because results were better for Botox vs. placebo after 24 weeks than 12 weeks in full population)
- Comparing full trial populations overcomes some uncertainties but not relevant to decision problem

[redacted]

Quality of life (MSQ v2.1 results)

- Migraine-Specific Quality of Life Questionnaire; self-administered
- 3 sub-domain scores measuring the extent to which migraine limits daily activities and affects related emotions: Role-function restrictive; role-function preventative; emotional-function
- Chronic migraine (full trial population)
  - Study 295: scores improved from baseline in erenumab patients (both doses) across all 3 domains compared with placebo
- Episodic migraine (full trial populations)
  - STRIVE: erenumab patients had greater improvement in scores across all 3 domains compared with placebo at nearly all assessment timepoints. Earlier improvement and sustained higher scores shown in 140 mg dose compared with 70 mg dose.
  - ARISE: erenumab patients had greater improvement in scores across all 3 domains at week 12 compared with placebo.
  - LIBERTY: MSQ not collected. Minimal differences observed in EQ-5D-5L but EQ-5D-5L not considered to adequately reflect health-related quality of life in migraine.
- MSQ results mapped to EQ-5D and used in economic model

Adverse events (full trial populations)

Trial	Treatment-emergent adverse events	Placebo	Erenumab 70 mg	Erenumab 140 mg
Study 295	Adverse events	39.0%	43.7%	46.8%
	Serious adverse events	2.5%	3.2%	1.1%
	Events leading to discontinuation	0.7%	0.0%	1.1%
STRIVE	Adverse events	63.0%	57.3%	55.5%
	Serious adverse events	2.2%	2.5%	1.9%
	Events leading to discontinuation	2.5%	2.2%	2.2%
ARISE	Adverse events	54.7%	48.1%	N/A
	Serious adverse events	1.7%	1.1%	N/A
	Events leading to discontinuation	0.3%	1.8%	N/A
LIBERTY	Adverse events	54.0%	N/A	54.7%
	Serious adverse events	0.8%	N/A	1.7%
	Events leading to discontinuation	0.8%	N/A	0.0%

ERG critique: clinical effectiveness

- Placebo considered representative of best supportive care
- Males, non-white populations and older people under-represented in the trials
- Exclusion criteria for previous failed treatments: >3 (Study 295) and >2 (STRIVE and ARISE); how does this impact on how the subgroup of interest is defined? No response or intolerability to prior treatments? Failure of individual treatments or treatment classes?
- No evidence for people with ≥15 headache days per month of which 4 – 7 are migraines (not covered by either chronic or episodic definition)
- 3/4 studies had double-blind phases of just 12 weeks which may be inadequate given primary outcome is mean monthly migraine days
- Subgroup relatively small (~20% of studied population) and is post-hoc analysis
- Better outcomes for erenumab (both doses) compared with placebo
- No statistically significant results for 70 mg in episodic migraine (≥3 prior failed treatments subgroup)
- Lack of long-term data (beyond 24 weeks) on comparative effectiveness
- No concerns about methods or results for indirect treatment comparison, but no evidence that difference in outcome timepoints would be likely to favour Botox

Key issues: clinical effectiveness

- Are the trials generalisable to a UK population with migraine for whom ≥3 prior treatments have failed?
- Is the full spectrum of migraine (in people with ≥4 MMD) adequately covered by the evidence base?
- Is it helpful and meaningful to consider people with chronic, episodic and high frequency episodic migraine, as distinct populations?
- Do the primary outcomes fully capture the clinical benefit valued by patients?
- Are best supportive care and botulinum toxin the only relevant comparators?
- Is there sufficient clinical evidence to support long-term effectiveness of erenumab and durability of response?
- Do the trials adequately capture safety data?

[redacted]

MMD, Monthly migraine days

Cost-effectiveness

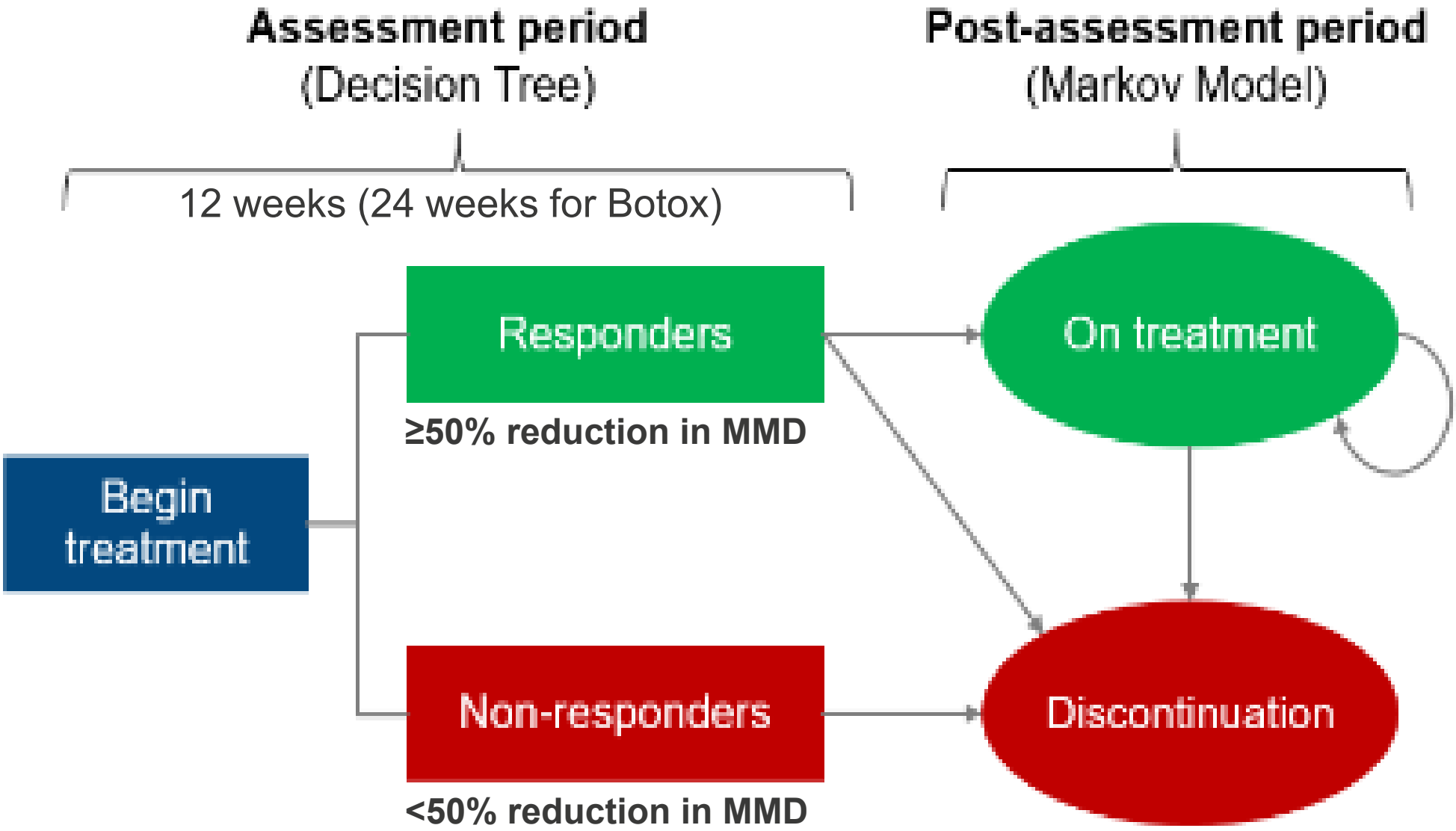
Economic model

NICE Reference case	Company's model		
Type	• Decision tree (assessment period) • Markov (post-assessment period)		
Population	Adults with ≥3 prior failed treatments • Whole population (66% chronic; 34% episodic) • Chronic migraine population • Episodic migraine population • High frequency episodic migraine population (sub group)		
Intervention	• Erenumab 70 mg and 140 mg 'blended dose' (50%; 50%) • Erenumab 140 mg		
Comparators	• Episodic migraine: Best supportive care • Chronic migraine: Botox and best supportive care		
Time horizon	10 years	**Cycle length**	12 weeks
Measure of health effects	QALYs	**Discounting of utilities and costs**	3.5%
Perspective	NHS/PSS		

[redacted]

QALYs, Quality-adjusted life years; PSS, Personal Social Services

Economic model structure



MMD, Monthly migraine days

ERG critique: model structure

- Ratio of chronic/episodic in whole migraine population reasonable but more informative to consider chronic and episodic populations separately because:
  - in line with trials
  - does not assume all people with ≥4 migraine days are covered
- Use of blended dose illogical; the 2 erenumab doses should be presented separately because:
  - no patient will receive a blended dose
  - decision needed about which single treatment to provide
- 10 year time horizon does not represent lifetime
- Natural progression of disease not captured which adds uncertainty
- Response defined as ≥50% reduction in monthly migraine days because company stated this is the trial outcome, most patients consider it important and the whole migraine population is being considered in their base case, however:
  - in TA260 (Botox) committee concluded ≥30% reduction most clinically relevant
  - most modelled population have chronic migraine so ≥30% a relevant scenario

[redacted]

Clinical parameters: methods

- **Response to treatment was modelled using MMD frequency distributions assigned to each health state → informs health utilities, resource use and cost**
- Baseline MMD distributions taken from patient level trial data (Study 295 and ITC for chronic migraine; pooled results from STRIVE, ARISE and LIBERTY for episodic) and weighted (66% chronic; 34% episodic) and a 'normal' distribution fitted - chosen because most closely matched trial data
- MMD frequency distributions at 12 weeks were similarly taken from trial data, with an appropriate normal distribution fitted to the data to model the predicted proportion of patients associated with each MMD frequency
- Patient-level data were not available to fit equivalent distributions for Botox so erenumab distributions applied
- Probability of response (≥50% reduction) then applied to the MMD frequency distributions

	Erenumab 70 mg	Erenumab 140 mg	BSC	Botox
Chronic	XXXX	XXXX	XXXX	XXXX
Episodic	XXXX	XXXX	XXXX	XXXX

[redacted]

MMD, Monthly migraine days

Clinical parameters: MMD distributions

Baseline distributions from trial data (pooled for erenumab and placebo)

Whole migraine population

Chronic migraine

Episodic migraine

Distributions at 12 weeks predicted by model (by treatment; responders & non-responders)

Clinical parameters: long-term efficacy

- **Treatment effect assumed to be maintained over time**
- Improved monthly migraine days at 12 weeks maintained until end of time horizon while still on treatment
- Company justifies this assumption based on ongoing open label extension study of phase II trial in episodic migraine and of Study 295 in chronic migraine
- Literature review of long-term progression of patients having prophylactic treatments identified 10 studies of either erenumab, Botox, beta-blockers or topiramate which showed efficacy maintained for a year or more and associated with sustained improvements in quality of life

Episodic (ongoing phase II trial)	Week 64
383 patients having erenumab 70 mg for median duration of ~20 months	
Mean MMD change from baseline	-5.0 (SD 4.2)
≥50% responder rate	65%
Associated with sustained quality of life benefit	

Chronic (Study 295)	Week 24	Week 52
549 patients having erenumab 70 mg, 140 mg or 70 mg followed by 140 mg		
Mean MMD change from baseline	-8.36 (-8.92, -7.80)	-9.29 (-9.96, -8.62)

MMD, Monthly migraine days

Clinical parameters: stopping treatment

Stopping because of adverse events in 12 week assessment period (24 weeks for Botox)

- Patients revert to baseline MMDs
- Rate derived from trials for erenumab and Diener et al. (2014) for Botox

Stopping because of non-response

- Patients maintain MMDs at 12 weeks for remaining time horizon
- This was justified with reference to regression to the mean and assumes that the observed partial response observed in non-responders reflects the regression of the average MMD frequency across patients to the true mean baseline.

Stopping because of other reasons (in post-assessment period)

- Patients revert to baseline MMDs
- Constant per cycle risk of 2.38% applied (based on long-term discontinuation observed for patients having erenumab 70 mg in ongoing open label extension of phase II study)

Positive discontinuation scenario to reflect that treatment may not continue indefinitely

- Responders re-evaluated after 64.5 weeks (enter 12 week assessment period)
- 20% assumed to stop treatment and maintain improvement in MMDs (treatment benefit maintained for remaining time horizon)
- [redacted] Remaining patients resume treatment and re-enter re-evaluation period every 76.5 weeks

ERG critique: clinical parameters

Long-term efficacy

- Supporting data from open label extension studies (a phase II trial in episodic migraine and Study 295 in chronic), suggests reasonable to assume treatment effect maintained but no data on maintenance of comparative effectiveness
- Without evidence of long-term effectiveness beyond the open label extension studies it is uncertain whether the treatment effect wanes over time
- Company provided scenario during clarification whereby costs and utilities for erenumab and Botox were linearly reduced over the 10 year time horizon for those patients still on treatment, until they became those associated with BSC non-responders; ERG adopts this scenario and also models effect waning over 5 years

Stopping treatment

- Patients maintaining MMDs at 12 weeks when stopping because of non-response (compared with patients reverting to baseline MMDs after stopping for other reasons)
  - Company's rationale inconsistent with modelling; non-responders have XXXX (i.e XXXX) MMD frequency than baseline in chronic migraine, and frequencies are XXXX in episodic
  - ERG therefore assumed all those stopping treatment after assessment would revert to a 12 week non-responder MMD frequency
- ERG adopts positive discontinuation scenario but notes there is no evidence that positive discontinuers do not incur cost and maintain benefit of treatment

Health state utility values: methods

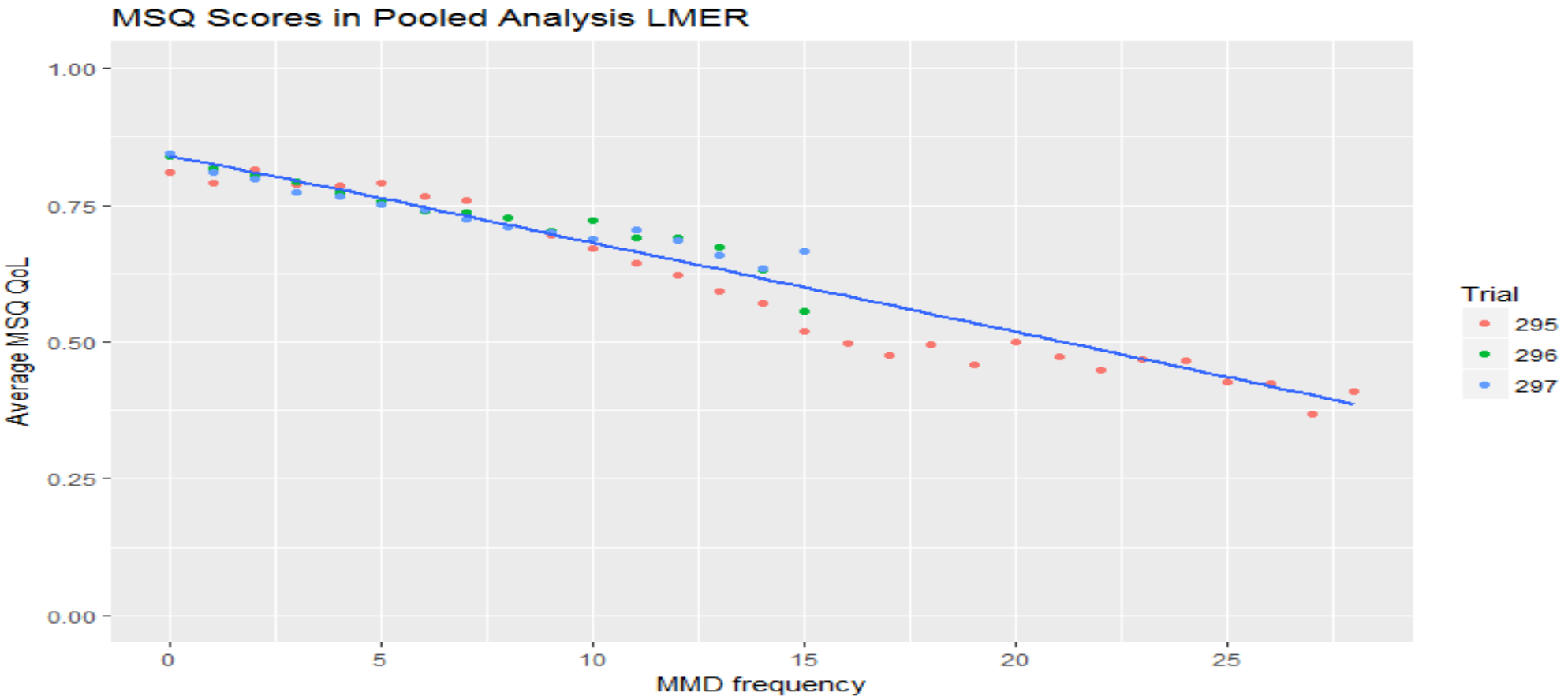
- **Utilities were determined based on distribution of MMD, with utility values generated by regressing quality of life on MMD**
- Utility values generated based on MSQ v2.1 results mapped to EQ-5D-3L to generate utility values for each MMD frequency using Gillard et al. (2012) algorithm
- MSQ data from ITT populations of Study 295, STRIVE and ARISE
- EQ-5D-5L collected in LIBERTY but not considered sensitive to changes in quality of life with migraine because data not collected during migraine (questions ask about current health status and data is collected on appointment days which patients would likely postpone if they were experiencing migraine at that time)
- MSQ questionnaire has 4 week recall period so considered more appropriate
- Separate algorithms used for mapping to chronic/episodic migraine; applied at individual patient level based on number of migraine/headache days at baseline
- No treatment effect assumed
- No adverse event disutility applied (mostly non-severe; comparable across arms)
- Botox values the same as erenumab (same MMD distribution assumed)

MSQ, Migraine-specific quality of life questionnaire; ITT, Intention-to-treat; MMD, Monthly migraine days

[redacted]

Health utility values for each MMD frequency

	Co-efficients
MMD frequency	0.0163 (0.0024)
Constant	0.1614 (0.0157)



MSQ, Migraine-specific quality of life questionnaire; MMD, Monthly migraine days

Health state utilities: values used in model

	Baseline and discontinuation (adverse event or long-term)	Responder at 12 weeks	Non-responder discontinuation	On treatment post-assessment
Whole population				
Erenumab 70 mg	0.577	0.743	0.601	0.741
Erenumab 140 mg	0.577	0.762	0.603	0.761
Placebo	0.577	0.746	0.592	0.741
Chronic migraine				
Erenumab 70 mg	0.466	0.735	0.491	0.735
Erenumab 140 mg	0.466	0.752	0.512	0.752
Placebo	0.466	0.731	0.495	0.731
Episodic migraine				
Erenumab 70 mg	0.688	0.769	0.695	0.760
Erenumab 140 mg	0.688	0.784	0.686	0.779
Placebo	0.688	0.770	0.685	0.756

Resource use and costs

Treatment costs	Erenumab	Botox
Dose	70 mg or 140 mg	155-195 units
Acquisition	£386.50 (PAS available)	£276.40 per 200 IU vial (No PAS)
Administration	£40.04 Self-administration training – 1 hour Band 5 hospital nurse Applied as one-off cost	£116 Trained specialist for each administration – 1 follow-up appointment Applied every cycle
No vial sharing assumed No best supportive care costs because acute medicines given alongside erenumab and Botox		

- **Resource use frequency and associated cost estimated for each MMD frequency; management costs for each health state a weighted average of costs per MMD frequency based on that population's MMD frequency distribution**
- Frequency of healthcare professional resource use sourced from National Health and Wellness Survey 2017: patients' perspective on burden according to frequency of headache (assumed to approximate migraine)
- Frequency of medication usage sourced from Study 295, STRIVE, ARISE and LIBERTY; linear regression used to predict number of migraine days with/without medication
- No adverse event costs applied (mostly non-severe; comparable across arms)

ERG critique: utilities and costs

Utilities

- EQ-5D in line with NICE reference case and collected in LIBERTY; reason for not using EQ-5D-5L data is plausible but it does have a large impact on cost effectiveness analysis
- Values informed by data from full trial populations not the subgroup – inconsistent with effectiveness data
  - Values informed by data from the subgroup produce a greater increase in disutility associated with each MMD frequency (0.019 compared with 0.0163 in full population)
- Disutility from adverse events not included because not considered severe, however:
  - when having continuous treatment, grade 1/2 adverse events may affect quality of life
  - adverse events may be XXXXX in subgroup but small sample size so this is uncertain

Costs

- Informed by data from people with migraine not just those with ≥3 prior failed treatments – inconsistent with effectiveness data and no evidence that prior treatments don't affect costs
- Questionable whether data on monthly headache days can approximate monthly migraine days given that these are different outcomes
- Disease management medicine costs: sumatriptan injection costs assumed same as oral
- Unclear if acute medicine brands selected are representative of UK clinical practice

Comparison of base case assumptions

	Company's base case	ERG's base case
Analysis	Pairwise	1) Incremental 2) Pairwise
Population	1) Whole population 2) Chronic migraine 3) Episodic migraine	1) Chronic migraine 2) Episodic migraine
Dose	1) Blended dose 2) 140 mg dose	1) 70 mg dose 2) 140 mg dose
Time horizon	10 years	Lifetime
Treatment effect	Maintained over time	1) Maintained over time 2) Wanes over 5 years
Stopping treatment	Revert to baseline monthly migraine days except non-responders who maintain any benefit seen at 12 weeks	Revert to non-responder monthly migraine days at 12 weeks
Utilities	MSQ results from full trial populations	MSQ results from full trial populations
Costs	Triptan injection price reflects the price of oral triptan	Triptan injection price reflects the price of triptan injections

[redacted]

Company base case: Whole population

Treatment	Total		Incremental		ICER per QALY (with PAS)
	Costs	QALYs	Costs	QALYs	
Blended dose					
BSC	[redacted]	[redacted]			
Erenumab	[redacted]	[redacted]	[redacted]	[redacted]	**£22,446**
				Probabilistic	**£22,309**
140 mg dose					
BSC	[redacted]	[redacted]			
Erenumab	[redacted]	[redacted]	[redacted]	[redacted]	**£19,827**
				Probabilistic	**£19,472**

Probability of cost-effectiveness	Blended dose	140 mg dose
At £20,000 per QALY gained threshold	35%	50%
At £30,000 per QALY gained threshold	70%	81%

[redacted] BSC, Best supportive care; QALY, Quality-adjusted life year; ICER, Incremental cost-effectiveness ratio

Company chronic migraine results

Pairwise analyses	ICER per QALY (with PAS)
Blended dose vs. Botox	£18,893
140 mg dose vs. Botox	£17,832
Blended dose vs. BSC	£17,212
140 mg dose vs. BSC	£13,340

Incremental analyses			
Treatment	**Total costs**	**Total QALYs**	**ICER per QALY (with PAS)**
Blended dose			
BSC	XXXXXX	XXXX	
Botox	XXXXXX	XXXX	£15,953
Erenumab	XXXXXX	XXXX	£18,824
140 mg dose			
BSC	XXXXXX	XXXX	
Botox	XXXXXX	XXXX	£10,601
Erenumab	XXXXXX	XXXX	£17,795

[redacted] BSC, Best supportive care; QALY, Quality-adjusted life year; ICER, Incremental cost-effectiveness ratio

Company episodic migraine results

Treatment	Total		Incremental		ICER per QALY (with PAS)
	Costs	QALYs	Costs	QALYs	
Blended dose					
BSC	[redacted]	[redacted]			
Erenumab	[redacted]	[redacted]	[redacted]	[redacted]	**£35,787**
140 mg dose					
BSC	[redacted]	[redacted]			
Erenumab	[redacted]	[redacted]	[redacted]	[redacted]	**£40,662**

[redacted] BSC, Best supportive care; QALY, Quality-adjusted life year; ICER, Incremental cost-effectiveness ratio

ERG base case: Chronic migraine

ERG changes (including fixing errors)	Incremental		Pairwise vs BSC	
	70 mg	140 mg	70 mg	140 mg
Company's base case	Dominated	£17,832	£24,668	£13,340
1) Lifetime time horizon	Dominated	£27,038	£36,554	£11,855
2) Triptan injection costs	Dominated	£16,593	£23,633	£11,996
3) Non-responder MMD after stopping treatment	Dominated	£16,186	£23,556	£12,039
ERG base case incremental analysis – assuming constant treatment effect				
BSC	XXXXX	XXXXX		
Botox	XXXXX	XXXXX	XXXXX	XXXXX	**£3,813**
Erenumab 140 mg	XXXXX	XXXXX	XXXXX	XXXXX	**£15,641**
Erenumab 70 mg	XXXXX	XXXXX	XXXXX	XXXXX	**Strictly dominated**
ERG base case incremental analysis – assuming treatment effect waning over 5 years				
BSC	XXXXX	XXXXX	XXXXX	XXXXX	
Botox	XXXXX	XXXXX	XXXXX	XXXXX	**£26,526**
Erenumab 70 mg	XXXXX	XXXXX	XXXXX	XXXXX	**Strictly dominated**
Erenumab 140 mg	XXXXX	XXXXX	XXXXX	XXXXX	**£36,659**

ERG base case: Episodic migraine

ERG changes (including fixing errors)	Incremental		Pairwise vs. BSC	
	70 mg	140 mg	70 mg	140 mg
Company's base case	£29,200	£73,282	£29,200	£40,662
1) Lifetime time horizon	£13,782	Dominated	£13,782	£36,510
2) Triptan injection costs	£27,613	£72,785	£27,613	£39,312
3) Non-responder MMD distribution after stopping treatment	£28,106	£90,985	£28,106	£41,690
ERG base case (constant treatment effect)	**£10,207**	**Dominated**	**£10,207**	**£35,482**
ERG base case (effect waning over 5 years)	**£94,984**	**£310,725**	**£94,984**	**£143,414**

Note: ERG note cost-effectiveness of 70 mg dose compared with 140 mg dose is inconsistent with clinical evidence. Effectiveness of 70 mg in patients for whom ≥3 prior treatments have failed not supported by evidence (no statistically significant results). Favourable cost-effectiveness driven by MMD frequency distribution for non-responders (lower than for 140 mg and BSC). Questionable whether there would be an advantage for 70 mg vs. 140 mg for non-responders.

ERG scenario analyses: chronic; episodic

	Incremental		Pairwise vs. BSC	
Chronic migraine	**70 mg**	**140 mg**	**70 mg**	**140 mg**
ERG base case (constant treatment effect)	Dominated	£15,641	£25,818	£7,064
1) Response definition ≥30% reduction	Dominated	↑ £18,862	↑ £60,941	↑ £18,862
2) Positive discontinuation	Dominated	↓ £1,549	Dominated	↓ £1,549
3) Botox response benefits after 12 weeks	Dominated	↓ £15,083	↔ £25,818	↔ £7,064
4) Treatment effect waning over 10 years	Dominated	↑ £26,351	↑ £58,135	↑ £19,787
5) Utilities from ≥3 prior subgroup	Dominated	↑ £17,000	↑ £28,061	↓ £7,678
6) Utilities from EQ-5D	Dominated	↑ £43,847	↑ £72,375	↑ £19,803
Episodic migraine				
ERG base case (constant treatment effect)	£10,207	Dominated	£10,207	£35,482
1) Response definition ≥30% reduction	↑ £90,984	Dominated	↑ £90,984	Dominated
2) Positive discontinuation	↓ £3,670	↓ £17,773	↓ £3,670	↓ £6,755
3) Treatment effect waning over 10 years	↑ £74,349	↑ £97,527	↑ £74,349	↑ £84,245
4) Utilities from ≥3 prior subgroup	↓ £7,528	Dominated	↓ £7,528	↓ £26,170
5) Utilities from EQ-5D	↑ £19,418	Dominated	↑ £19,418	↑ £67,498

High Frequency Episodic Migraine (HFEM)

- HFEM a recognised subgroup of episodic migraine patients who are considered to have a clinical burden similar to patients with chronic migraine, who have high unmet need because cannot access treatments recommended for chronic migraine (Botox)
- Company defines HFEM as 8-14 MHDs but analysis uses clinical data for 8-14 MMDs
- ERG questions using MMDs to approximate MHDs when these are separate outcomes

Company's subgroup analysis	
Whole population (chronic and HFEM)	
Blended dose: £22,260	140 mg: £19,239
Episodic migraine (restricted to people with HFEM)	
Blended dose: £37,607	140 mg: £37,749
ERG's subgroup analysis	
Assuming constant treatment effect	
70 mg Incremental: £10,782 70 mg Pairwise: £10,782	140 mg Incremental: Dominated 140 mg Pairwise: £29,259
Assuming effect waning over 5 years	
70 mg Incremental: £113,147 70 mg Pairwise: £113,147	140 mg Incremental: £125,865 140 mg Pairwise: £119,351
Alternative HFEM definition of 10-14 MHDs (Assuming constant treatment effect)	
70 mg Incremental: £13,556 70 mg Pairwise: £13,556	140 mg Incremental: Dominated 140 mg Pairwise: £40,972

[redacted]

MHD, Monthly headache days; MMD, Monthly migraine days

Innovation and equality issues

Innovation

- Erenumab is a ‘step-change’ in the management of migraine
- A first-in-class therapy
- Well tolerated, with few discontinuations because of adverse events
- Rapid onset of action
- Response maintained in longer-term
- Potential wider societal value of migraine prophylaxis
- More convenient and less resource-intensive alternative to Botox

Equality issues

- Migraine can be classed as a disability under the Equality Act 2010
- Migraine most common in people of working age and affects more women than men, therefore women further disadvantaged in the workplace by migraine
- Unequal access to specialist headache clinics and barriers to recommended treatments
- New treatment option may expose inequality of access to specialist services
- No issues raised by the company

[redacted]

Key issues: cost effectiveness

- Is it appropriate to consider a ‘blended dose’ (combining 70 mg and 140 mg dose)?
- Should the 2 doses be considered together in an incremental analysis, or separately, in pairwise analyses?
- Should response to treatment be defined as ≥30% or ≥50% reduction in MMDs?
- Are people whose disease is responding likely to have treatment indefinitely?
- What is the appropriate time horizon: 5 years? 10 years? 15 years? Lifetime?
- Is treatment effect likely to be constant or wane over time (over 5 years? 10 years?)
- When treatment is stopped how is the disease likely to continue to respond (at 12 weeks, in the maintenance phase)? Is this likely to differ according to the reason treatment was stopped (i.e adverse events, non-response)?
- What is the most appropriate source of health utilities; MSQ scores from full trial or subgroup population, or EQ-5D? Are the utility values plausible?
- Are all relevant costs included?

[redacted]MMD, Monthly migraine days; MSQ, Migraine-specific quality of life questionnaire

Key issues: clinical effectiveness

- Are the trials generalisable to a UK population with migraine for whom ≥3 prior treatments have failed?
- Is the full spectrum of migraine (in people with ≥4 MMD) adequately covered by the evidence base?
- Is it helpful and meaningful to consider people with chronic, episodic and high frequency episodic migraine, as distinct populations?
- Do the primary outcomes fully capture the clinical benefit valued by patients?
- Are best supportive care and botulinum toxin the only relevant comparators?
- Is there sufficient clinical evidence to support long-term effectiveness of erenumab and durability of response?
- Do the trials adequately capture safety data?

[redacted]

MMD, Monthly migraine days