Slides for public observers: No confidential information

Chair's presentation

Erenumab for preventing migraine (ID1188)

2nd Appraisal Committee meeting - 16 April 2019

Committee D

Chair: Gary McVeigh

Lead team: Andrew Hitchings, Malcolm Oswald, Rob Hodgson

ERG: Kleijnen Systematic Reviews

NICE technical team: Omar Moreea, Thomas Paling, Victoria Kelly

Company: Novartis

[redacted]

Key issues (1)

High Frequency Episodic Migraine (HFEM)

- Is HFEM a clinically distinct subgroup?
- Is it defined as 8-14 MMD or 10-14 MHD?
- Do the STRIVE and LIBERTY trials adequately capture the effectiveness of erenumab in HFEM defined by the company as 10-14 MHDs?

Comparators

- Is a 4th oral prophylactic used in NHS practice?
- Should a 4th oral preventative treatment be included as a comparator?
- What are the appropriate comparators for chronic migraine and HFEM?
- What is the most appropriate relative treatment effect to use in the analysis of Botox vs erenumab:
  - OR from ITC
  - Midpoint OR
  - OR of 1
  - Is the Botox mode of administration utility decrement (-0.059) scenario applied by the company reasonable?

[redacted]

Key issues (2)

Treatment effect

- What is the most appropriate treatment waning scenario:
  - 5 years
  - 10 years
  - 10 years treatment wane after 5 years (company's new scenario)
  - No treatment waning (company preferred)

Stopping rules

- Is it reasonable to apply a negative stopping rule at 3 months if there is no response to treatment (non-responders defined as those experiencing a <30% reduction in MMDs in the chronic group and <50% reduction in MMDs for the HFEM group)?
- Is the positive treatment discontinuation scenario where treatment is stopped in 20% of patients (who continue to benefit from erenumab at 64.5 weeks) reasonable?

Costs

- Have all the costs of erenumab been captured in the company's modelling?

Equalities considerations

- Are there any additional equalities considerations to address?

[redacted]

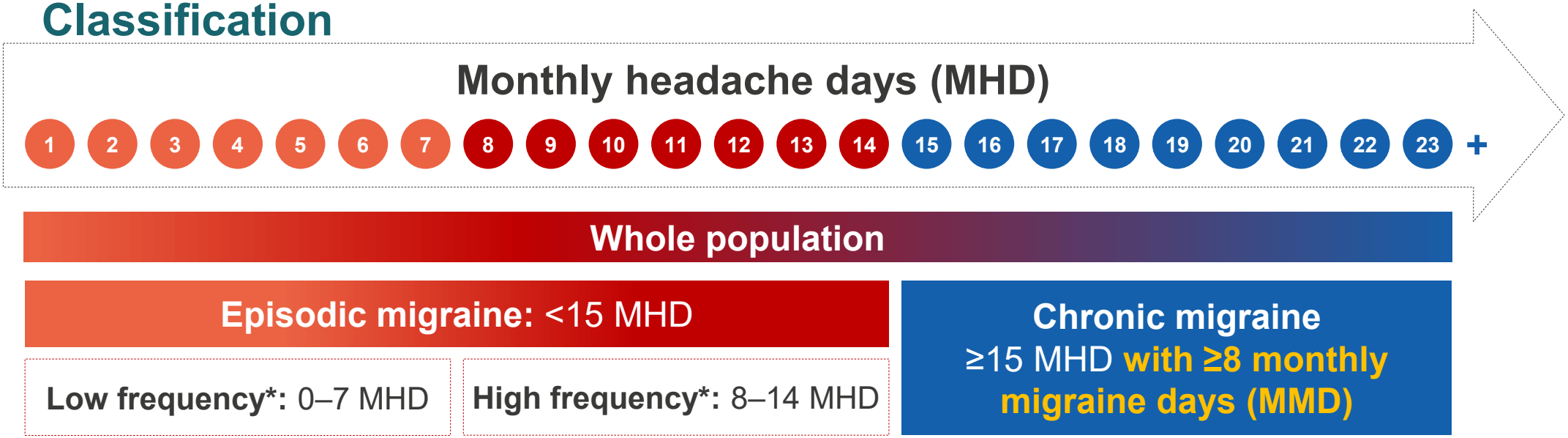
ACD preliminary recommendation

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

Migraine

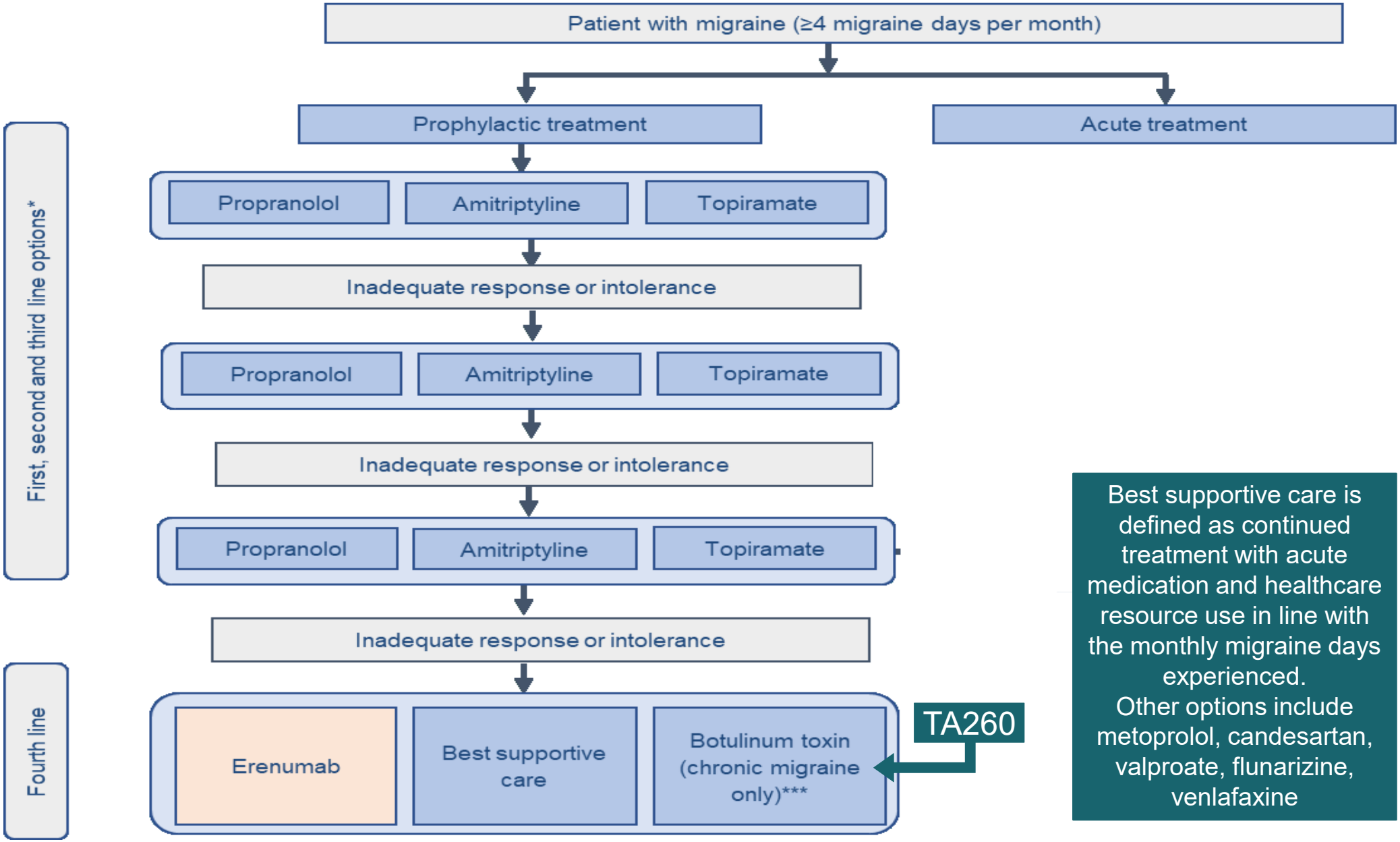
- Headache disorder with recurring attacks usually lasting 4–72 hours
- Often accompanied by nausea, vomiting, sensitivity to light/sound
- Factors triggering attacks can include stress, change in sleep pattern, overtiredness, menstruation, caffeine/alcohol consumption
- Prevalence 5-25% in women; 2-10%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

Classification



*Consultation comments received about the definition of these subgroups (see later)

Migraine treatment pathway



Best supportive care is defined as continued treatment with acute medication and healthcare resource use in line with the monthly migraine days experienced.
Other options include metoprolol, candesartan, valproate, flunarizine, venlafaxine

[redacted]

Source: Company submission: section B.1.2.2 (pages 20-22); Company clarification response question A.14 (page 19)

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 the 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) 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)

[redacted]

Recap: clinical evidence

	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
Migraine type	Chronic	Episodic	Episodic	Episodic
Prior treatments**	≤3 categories	≤2 categories	≤2 categories	2-4 treatments
Dose	70 mg; 140 mg	70 mg; 140 mg	70 mg	140 mg
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; MMD, Monthly migraine days
**Prior treatments refer to either categories of medication or individual medications

Indirect treatment comparison [ITC]: chronic migraine: No direct head-to-head evidence for erenumab vs. Botox in chronic migraine

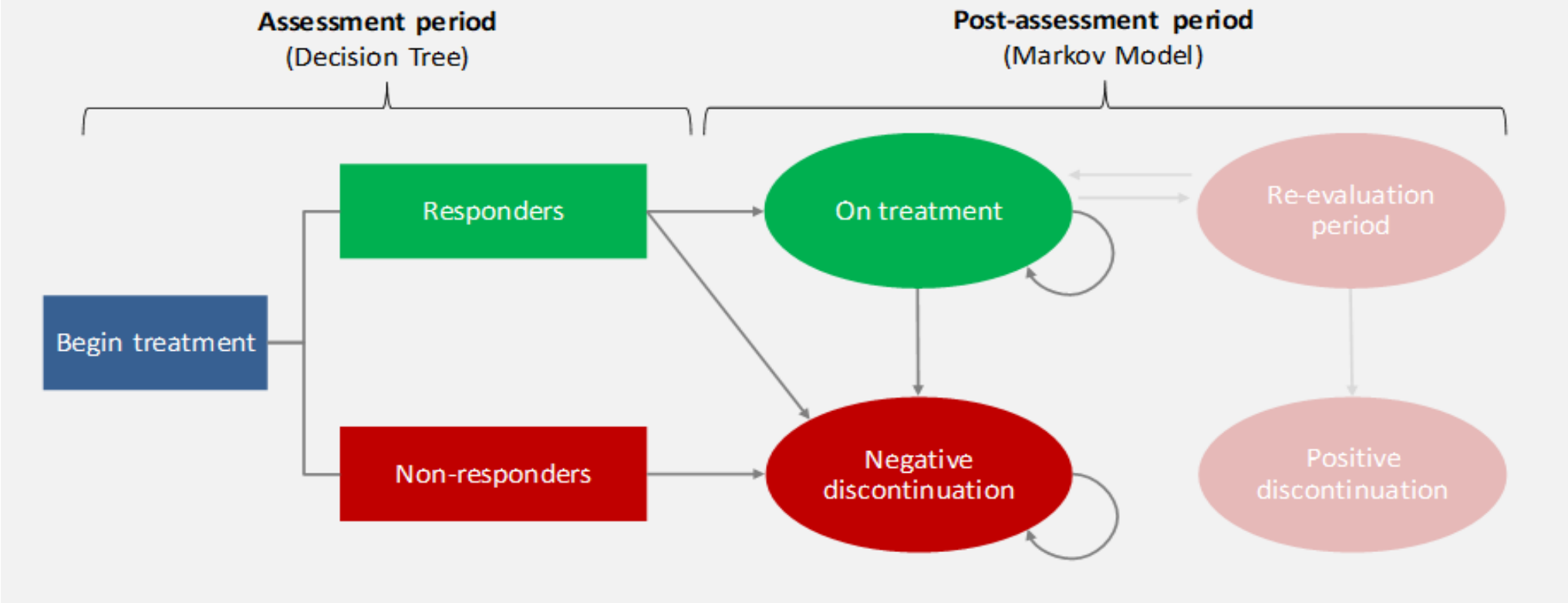
Study 295: Erenumab ↔ Placebo ↔ PREEMPT 1&2: Botox

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

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

Recap: economic evidence (1)

Model structure



Recap: economic evidence (2)

Evidence sources:

- Episodic migraine: pooled results from STRIVE, ARISE and LIBERTY
- Chronic migraine: study 295 for the comparison with placebo, and indirect treatment comparison for the comparison with Botox type A

Economic model

Model structure	Decision tree (assessment period) • 12 weeks (24 weeks for botulinum toxin type A) Markov (post-assessment period) • 3 states: on treatment, off treatment and death
Population	Adults with ≥3 prior failed treatments
Intervention	• Erenumab 70 mg and 140 mg 'blended dose' (50%; 50%) • Erenumab 140 mg
Comparators	• Episodic migraine: Best supportive care (BSC) • Chronic migraine: Botox and BSC
Outcomes	Reduction in MMDs and proportion of patients with at least 50% reduction
Utility values	Migraine-Specific Quality of Life Questionnaire (MSQ) mapped to EQ-5D-3L
Time horizon	10 years
Treatment effect	Assumed to remain constant while people were on treatment

Recap: results

	Chronic migraine	Episodic migraine
	Clinical effectiveness	
Monthly Migraine Days (MMDs)	• Erenumab 140 mg reduced the MMDs by 4.1 days more on average than placebo • Erenumab 70 mg reduced the MMDs by 2.5 days more on average than placebo	• Erenumab 140 mg more effective than placebo in reducing MMDs
50% reduction in Monthly Migraine Days (MMDs)	• 38.5% erenumab 140 mg • 34.8% erenumab 70 mg • 15.3% for placebo • ITC with Botox showed odds ratios that favour erenumab for both doses but the results were not statistically significant	• [redacted] for erenumab 140 mg vs placebo in STRIVE and LIBERTY
	Cost effectiveness	
Company base-case	• 140 mg vs. Botox £17,832 (pairwise)	• Blended dose vs. BSC £35,787 (pairwise)
ERG base-case, constant effect*	• 140 mg £15,641 (incremental)	• 140 mg Dominated (incremental)
ERG base-case, 5 year waning*	• 140 mg £36,659 (incremental)	• 140 mg £310,725 (incremental)
ERG base-case, 10 year waning*	• 140 mg £26,351 (incremental)	• 140 mg £97,527 (incremental)

[redacted]

* In the chronic group the analysis included Botox, BSC and the 70 mg dose.
In the episodic group the analysis included BSC and the 70 mg dose.

Recap: ACD considerations (1)

Issue	Committee's considerations
Relevant comparators (ACD 3.4)	Company's trial evidence does not include all the relevant comparators. Botox or a 4th oral preventative treatment would be the relevant comparators in chronic migraine. A 4th oral preventative treatment or BSC would be the relevant comparators for episodic migraine.
Trial populations do not reflect relevant subgroup (ACD 3.5)	People excluded from the trials were likely to represent the people most in need of treatment and were therefore the most clinically important subgroup → trials excluded people with no therapeutic response (defined as no reduction in headache frequency, duration or severity after at least 6 weeks' treatment) to a number of previous treatments (>4 in LIBERTY) or treatment categories (>3 in study 295, >2 in STRIVE and ARISE).
Chronic migraine (ACD 3.6)	Erenumab 140 mg is more effective than the 70 mg dose compared with BSC. Considered a 30% reduction in MMDs is a clinically meaningful response.
Episodic migraine (ACD 3.7)	The 140 mg dosage may work better than BSC but the 70 mg dosage does not.

[redacted]

Recap: ACD considerations (2)

Issue	Committee's considerations
Long-term effectiveness (ACD 3.8)	Long-term effectiveness of erenumab is uncertain in the episodic migraine and chronic migraine compared with BSC.
ITC for erenumab vs Botox (ACD 3.9)	Committee considered that the company's methods for the ITC were appropriate, but noted that different outcomes were reported in each of the trials: proportion of people with at least 50% reduction in monthly migraine days for erenumab and monthly headache days for Botox. OR favoured erenumab but was not statistically significant. Committee requested a scenario where erenumab and Botox have similar effectiveness.
Time horizon (ACD 3.11)	The company considered a 10-year time horizon in their economic model. A lifetime time horizon should be used to fully capture the costs and benefits for people on treatment.
Treatment effect waning (ACD 3.12)	The treatment effect was unlikely to be maintained indefinitely. In absence of evidence committee wanted a 5 and 10 year treatment waning effect explored.

[redacted]

Recap: ACD considerations (3)

Issue	Committee's considerations
Positive discontinuation (ACD 3.13)	The company included a positive discontinuation scenario where 20% of responders to treatment would stop treatment at an assessment period. Committee: this scenario was not appropriate because there is no evidence that treatment benefit continues once treatment had stopped.
Utility values (ACD 3.14)	Concerns about the reliability of the utility values used in the company model. There is uncertainty in the data as it is derived from a broader population and mapped from MSQ* to EQ-5D-3L.
Service costs (ACD 3.15)	Concerns that for erenumab additional resources would likely be needed, and that the cost of setting up these additional services should be accounted for in the model. Agreed that the company's use of the oral triptan price for triptan injections was inappropriate.
Erenumab doses (ACD 3.16)	The 70 mg and 140 mg doses of erenumab should be considered separately for the chronic and episodic migraine populations.
Acceptable ICER (ACD 3.17)	Given the uncertainty in the clinical evidence and utility values, an acceptable probabilistic ICER would be around £20,000 per QALY gained. Most plausible ICER for chronic migraine >£20,000 and most plausible for episodic migraine >£70,000.

*Migraine-Specific Quality of Life Questionnaire

[redacted]

ACD consultation responses

- Web comments (including professionals, patients, carers and public) (n=280)
- Patient group comments from:
  - The Migraine Trust
- Clinical expert & Professional group comments from:
  - Association of British Neurologists Advisory Group on headache and pain (ABNAG)
  - British Association for the Study of Headache (BASH)
- Commentator comments from:
  - Allergan
- Consultee comments, Novartis:
  - ACD response
  - Revised PAS
  - Revised base case
- 'No comments' responses from:
  - Organisation for the Understanding of Cluster Headache (OUCH)

[redacted]

Web comments

Professionals, patients, carers & public comments: summary of responses

- The consultation received 280 individual comments from professionals, patients, carers and the public
- We have reviewed all the comments and summarised the general themes
- The majority of comments do not agree with the ACD decision
- Comments are generally requesting that erenumab is recommended

[redacted]

Web comments

Professionals, patients, carers and public comments (1)

Impact of migraine	Current treatments
• Everyday life negatively affected • Restricts daily activities • Can be housebound during migraine episode • Rely on others for help / loss of independence • Also impacts on family / friends • Depression, anxiety, social isolation • Feel like life is not worth living / no quality of life • Leads to frequent health service visits • Prevent attendance at work • Costs to employer – Fear for job security • Lack of understanding of the condition • Affects all age groups • Affects more women than men	• Existing treatments are not effective • Some work but only for short term • Tried many different treatments • Medication overuse can be an issue • Side effects can be very bad • Botox requires many injections and travel to clinics • Treatments often use specialist services • Dihydroergotamine (DHE) is also an option • Not all treatments work for everyone • There is an unmet need for a well tolerated drug

Web comments

Professionals, patients, carers and public comments (2)

Erenumab – effects	Erenumab – costs
• Erenumab is an improvement on current treatments • It has been shown to work for many people (in the US and trials in the UK) • Helped when no other treatments worked • It has few side effects • It is specifically designed to treat migraine • Can self administer the drug • Noticeable beneficial effect in days • Seen as a last resort • Gives hope when other treatments have failed • Chance of leading a normal life • Can return to work / social life / family life • May not be effective for everyone	• Too expensive for private treatment • Could reduce sickness absence / disability payments / loss of productivity • Analyses should take into account the increase in working days and impact on economy • Can offer it to selected patients only • Trials could be extended to offer to more people • Other costs of current treatments need to be taken into account • Botox is not the relevant comparator • A 4th oral drug is not standard practice • Could make more availability in Botox clinics for other conditions • Can't place a price on regaining your life

[redacted]

Consultation comments

Patient groups: The Migraine trust

The impact of erenumab

- People able to resume living and working normally
  - Reduced number of sick days
  - Substantial societal cost of missed work could be avoided
- More convenient self administration → Botox requires injections in 31-39 sites
- Erenumab is well tolerated

Equalities

- 3 times more women than men experience migraine → recommendations discriminate against women
- Chronic migraine can be sometimes be considered a disability → denying people the chance to contribute more to society is unfair

[redacted]

Consultation comments

Clinical expert and professional groups (1)

There is an unmet need for a convenient and tolerable treatment

- Erenumab is well tolerated
- Unlike Botox, people on erenumab can self administer
- Botox requires attendance at outpatient clinics and patients receive 31 injections
- Tolerability is a major problem amongst people with migraine

Comparators

- Best supportive care is the relevant comparator for episodic and chronic migraine
- A 4th oral treatment is not a relevant comparator as this is not standard clinical practice

Duration of treatment and waning effect

- Duration uncertain. Standard care with preventative treatments is that if migraine is well controlled for 6-12 months then treatment is re-evaluated and often withdrawn usually without immediate return to former state.
- If a patient requires longer term use we would certainly advocate re-evaluation of need for treatment at least every 18 months

[redacted]

Consultation comments

Clinical expert and professional groups (2)

Clinical evidence

- There are no published phase III trials in chronic migraine (Study 295 is a phase II trial)
- Chronic depression and anxiety is high in chronic migraine, however the trials excluded people with comorbid psychiatric disease
- No long-term studies supporting continued benefit after stopping of successful treatment
- Responder rates of ≥50% reduction in monthly migraine days are a truer reflection of the efficacy of treatments in everyday clinical practice
- The therapeutic gain versus placebo is significantly greater for erenumab compared to Botox:
  - The ≥50% responder rate for erenumab in chronic migraine is 38.5% (140 mg) compared to 15.3% for placebo
  - The ≥50% responder rate for Botox is 48% compared to 36% for placebo

[redacted]

Consultation comments

Commentator comments: Allergan (Botox manufacturer)

- General agreement with the committee's conclusions:
  - Uncertainty in the long-term effectiveness of erenumab
  - Lack of robust evidence that erenumab is more clinically effective than Botox
  - Erenumab is unlikely to be cost-effective compared to Botox for chronic migraine
- The Institute for Clinical and Economic Research in the US also found erenumab is unlikely to be cost-effective compared with Botox
- The economic evidence provided by the company underestimates the uncertainty regarding the cost-effectiveness of erenumab compared to Botox

[redacted]

Consultation comments

Commentator comments: Allergan (Botox manufacturer)

Evidence for Botox

- There is substantial long term effectiveness evidence on Botox (based on over 5,600 patients)
- Results show the long-term effectiveness and safety of Botox in chronic migraine:
  - show improvements in quality of life and work productivity
  - improved symptoms of depression and anxiety in chronic migraine patients

Economic model for erenumab

- The scenario analyses incorporate utility decrements for Botox but the PREEMPT trials indicate that Botox patients had generally higher utility scores than placebo patients
- Botox is associated with a range of benefits beyond the reduction in headache days
- The cost-effectiveness analyses of erenumab do not incorporate the long-term effectiveness evidence of Botox published since the NICE Botox guideline (2012)
- Allergan believes that the economic evidence underestimates the degree of uncertainty regarding the cost-effectiveness of erenumab vs Botox, and that the range ICERs for erenumab is likely to be substantially higher than the estimates in the ACD

[redacted]

ACD consultation comments (Novartis)

Summary of company's comments & updated evidence

- "Disappointed by the draft recommendation". Company response as follow:
- **Intervention**: consider only the 140 mg erenumab dose (not 70 mg)
- **Population**: focus on the following populations
  - Chronic migraine
  - High-frequency episodic migraine (10–14 MHDs) (but not episodic migraine)
- **Comparators:** Disagree with committee about consideration of a 4th oral comparator
  - Chronic migraine: Botulinum toxin (no longer considering BSC)
  - High-frequency episodic migraine (10–14 MHDs): BSC
- **Model:** Revised commercial arrangement; use lifetime horizon in the model, using a 30% reduction in MMD as response threshold
  - Disagree with committee on
    - The benefit of erenumab vs Botox
    - Erenumab's long-term treatment effect / waning
    - Additional services costs

[redacted]

Clinical expert questionnaire

- Following the consultation on the ACD and the company's submission of new evidence NICE sought the views of clinical experts on the issues raised. The questions related to:
  - Definition of HFEM
  - Appropriate comparators
  - Comparison with Botox
  - Erenumab discontinuation rules
  - Erenumab treatment waning
  - Erenumab service costs
- 3 of 8 experts responded
- Views of experts presented in slides 25-39

[redacted]

ACD consultation comments (Novartis)

Population: high frequency episodic migraine (HFEM) (1)

Committee considerations (ACD section 3.1)

- Episodic migraine is defined as <15 headache days a month
- HFEM = people with 10-14 headache days a month
- Chronic migraine is a debilitating condition and HFEM (10-14 headache days a month) has a similar burden on quality of life

Company response (ACD response point 2)

- The company's new evidence includes only people with chronic migraine and HFEM (defined as 10-14 headache days a month)
- RECAP: Results from STRIVE (n=17 erenumab 140mg) show change from baseline MMD of [redacted] vs placebo
- LIBERTY (n=76 erenumab 140mg) demonstrated a change from baseline MMD of [redacted] vs placebo

[redacted]

ACD consultation comments (Novartis)

Population: high frequency episodic migraine (HFEM) (2)

ERG comments

- The company's evidence for HFEM is based on 8-14 monthly migraine days (MMD) not 10-14 monthly headache days (MHD). Therefore the trials do not provide adequate effectiveness for erenumab in a HFEM population defined as 10-14 MHD

Clinical expert comments

- HFEM and chronic migraine are considered as part of the same spectrum
- There is no evidence or formal criteria to determine the cut-off points of HFEM
- Data from studies that use 8-14 MMD can adequately be used to inform the effectiveness of erenumab in HFEM
- Experiencing 10-14 MHD has a similar burden on quality of life as chronic migraine

- ❑ Is HFEM a clinically distinct subgroup?
- ❑ Is it defined as 8-14 MMD or 10-14 MHD?
- ❑ Do the STRIVE and LIBERTY trials adequately capture the effectiveness of erenumab in HFEM defined by the company as 10-14 MHDs?

[redacted]

ACD consultation comments (Novartis)

Appropriate comparators (1)

Committee consideration (ACD section 3.4)

- A 4th oral preventative treatment would also be a relevant comparator for erenumab

Company response (ACD response point 5)

A 4th oral treatment is not a relevant comparator

- Use of a 4th oral prophylactic does not accurately reflect the treatment pathway for migraine treatment in the UK
- "Standard management" was accepted as the only comparator in the appraisal of Botox (TA260)
  - The choice of comparator in TA260 was informed by a NICE clinical guideline (CG150) which has not been updated since TA260 guidance was published
  - Considering a 4th oral treatment as a relevant comparator implies a change in the treatment pathway
- Clinical expert feedback from 2017 stated that clinical practice has been largely unchanged for several years
- No treatments are licensed as a 4th oral comparator → no supporting evidence
- Company consider the following as the relevant comparators:
  - Chronic migraine: Botox
  - HFEM: BSC

[redacted]

ACD consultation comments (Novartis)

Appropriate comparators (2)

Clinical expert comments

- The treatment regimen would be similar for chronic migraine and HFEM
- Initial prophylactic treatment follows NICE guidelines:
  - Topiramate
  - Propranolol
  - Amitriptyline
- Then they would try either:
  - Candesartan
  - Valproate
  - Flunarizine
  - Possibly pizotifen
- 1 expert noted that "I typically have a selection of 4 drugs (amitriptyline, propranolol, topiramate and candersartan) … after 3 drugs I have one further drug that I will use then I have to try drugs with little evidence of efficacy"
- Botox [TA260] would only be used for chronic migraine if 3 oral agents failed
- If there is no response to Botox, then occipital nerve stimulation (IPG452)

- ❑ Is a 4th oral prophylactic used in NHS practice?
- ❑ Should a 4th oral preventative treatment be included as a comparator?
- ❑ What are the appropriate comparators for chronic migraine and HFEM?

[redacted]

ACD consultation comments (Novartis)

Comparison with Botox for chronic migraine (1)

Recap from ACM 1:

- No direct head-to-head evidence for erenumab vs Botox in chronic migraine
- Indirect Treatment Comparison (ITC) of Study 295 (erenumab for chronic migraine) and PREEMPT 1 & 2 trials (botox for chronic migrane)
- 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
- The ITC odds ratio favoured erenumab but the result was not statistically significant:
  - Erenumab 140 mg [redacted] vs Botox (n=189)
  - Odds ratio (95% CI): [redacted]

Committee consideration (ACD section 3.9):

- The committee considered that the company's methods for the indirect treatment comparison were appropriate but noted the issues with comparing MHDs to MMDs and the baseline characteristics of people in the PREEMPT trials were not available to the company and so it was uncertain whether the populations were similar
- A scenario where erenumab and Botox are considered to have similar effectiveness was requested

[redacted]

ACD consultation comments (Novartis)

Comparison with Botox for chronic migraine (2)

Company response (ACD response point 4)

Assuming equal efficacy is unrealistic and highly conservative

- Although not statistically significant, erenumab has a numerical benefit versus Botox, suggesting a clinical benefit
- Claxton et al: "decisions should be based only on the mean net benefits irrespective of whether differences are statistically significant"
- Other appraisals e.g TA533; ocrelizumab for multiple sclerosis have accepted the results of indirect treatment comparisons despite lack of statistical significance
- Company present scenario where the odds ratio (OR) is set to 1 (similar efficacy) and a scenario where it is set to [redacted] (a 'mid-point' between an OR of 1 and the OR of the ITC)

Botox mode of administration utility decrement

- Company provided scenario analysis incorporating a utility decrement associated with the mode of administration (MoA) of Botox (-0.059)
- A vignette-based time trade off utility valuation study was conducted in the UK to derive MoA decrements for migraine prophylaxis treatments relative to erenumab
- *The company have included a scenario analysis*: the utility decrements represent the average decrease in utility associated with adding each treatment mode to an otherwise identical health state, experienced by a patient
- The MoA decrements are applied (additively) to each MMD-specific utility value

[redacted]

ACD consultation comments (Novartis)

Comparison with Botox for chronic migraine (3)

ERG comments

- Difficult to determine the most appropriate odds ratio to use. ERG suggest there is no justification for the use of a 'mid-point' odd ratio
- Weak evidence for utility decrements

Clinical expert comments

- It is plausible to consider erenumab and Botox to have similar effectiveness

However:

- The data suggests that erenumab is slightly better than Botox with an increase in therapeutic gain
- Erenumab has a significantly reduced burden on the patient compared with botox
- Botox requires multiple injections in the head and neck which are performed by a specialist. However, erenumab can be self-administered following initial training
- The provision of erenumab would result in better addressing the needs of migraine sufferers than Botox

- ❑ What is the most appropriate relative treatment effect to use in the analysis of Botox vs erenumab: OR from ITC ([redacted]), Midpoint OR ([redacted]), OR of 1 (similar to Botox), Other OR
- ❑ Is the Botox mode of administration utility decrement (-0.059) scenario applied by the company reasonable?

[redacted]

ACD consultation comments (Novartis)

Long-term effectiveness of erenumab (1)

Committee consideration (ACD section 3.12)

- 5 and 10 year treatment effect waning to be explored; no evidence of a life time treatment effect whilst the patient remains on erenumab

Company response (ACD response point 3)

ACD considerations do not reflect the evidence on the long-term efficacy of erenumab:

- Comparative efficacy of erenumab was observed in the extension studies
- Clinical experts at ACM1 suggested there would be no treatment effect waning over time
  - Additional headache specialist feedback: no evidence to suggest treatment effect waning in people who respond to erenumab
- No evidence of treatment effect waning in Study 295 and STRIVE → effectiveness was maintained to week 52 for chronic migraine and week 64 for episodic migraine
- Erenumab is a calcitonin gene-related peptide (CGRP) receptor antagonist that is not associated with a waning effect
- Inappropriate to base assumptions of long-term effectiveness on rheumatoid arthritis
- Continued treatment benefit has been accepted in other appraisals of non-progressive diseases: (TA339; omalizumab for chronic urticaria, TA278 & TA431; omalizumab and mepolizumab for asthma)

[redacted]

ACD consultation comments (Novartis)

Long-term effectiveness of erenumab (2)

Company response cont.

Expected use of erenumab in UK clinical practice affects waning considerations

- It is expected that patients will not stay on erenumab in the long-term
- Aligns with the marketing authorisation: “consideration should be given to discontinuing treatment in patients who have shown no response after 3 months of treatment”
- Guidelines from the European Headache Foundation state that anti-CGRP monoclonal antibodies be stopped after 6-12 months of treatment
- Company’s updated model includes a negative discontinuation scenario with a 30% response rate (as per TA280; Botox)
- Company’s updated analyses include 2 scenarios applying treatment waning:
  - 10 year treatment waning beginning from week 12
  - 10 year treatment waning beginning from 5 years

ERG comments

- Long-term effectiveness is a key uncertainty
  - No comparative evidence after 12 weeks
  - No clinical effectiveness evidence beyond 64 weeks
  - Longer-term data from the open label studies are presented for the whole study populations (not those with 3 or more prior treatments or those with HFEM)
- Unclear whether there is and to what extent the treatment effect of erenumab wanes

[redacted]

ACD consultation comments (Novartis)

Long-term effectiveness of erenumab (3)

Clinical expert comments

- It is not appropriate to model this far into the future
- Around 10% of patients stop responding to Botox in spite of a very good response at the start. Consider that these patients have developed resistance to treatment and this may even happen with erenumab
- In the absence of evidence it is not clear how one can assume a linear decline in effectiveness if this has not been seen in the 12 month period
- If decline in treatment effect is not observed over 12 months, there is no rational reason to assume this will occur over several years
- Treatment effectiveness would initially be assessed at 3 months then at 6 and 12 months
- A negative stopping rule is applied to those who do not respond at 3 months

- ❑ What is the most appropriate treatment waning scenario:
  - 5 years, 10 years, 10 years treatment wane after 5 years *(company's new scenario), No treatment waning (company preferred)*
- ❑ Is it reasonable to apply a negative stopping rule at 3 months if there is no response to treatment (non-responders defined as those experiencing a <30% reduction in MMDs in the chronic group and <50% reduction in MMDs for the HFEM group)?

[redacted]

ACD consultation comments (Novartis)

Positive discontinuation (1)

Committee consideration (ACD section 3.13)

- The company's positive discontinuation scenario was not appropriate as there is no evidence that benefit continues when people stop treatment

Company response (ACD response point 3)

- Company's positive discontinuation scenario assumes patients who continue to benefit from treatment remain on erenumab for a maximum of 64.5 weeks
- Patients will be re-evaluated over 12 weeks and approx. 20% would stop erenumab ('positive discontinuation')
- 2 scenarios provided:
  - Company assume the benefits last for 12 weeks and then MMD return to those levels seen in the placebo arm of the trial
  - Company assume the MMD are maintained at the treatment response level
- Those patients who do not maintain a treatment response would return to treatment and be reassessed at 76.5 week intervals

ERG comments

- No evidence to underpin the positive discontinuation scenario

[redacted]

ACD consultation comments (Novartis)

Positive discontinuation (2)

Clinical expert comments

- Clinicians would apply a positive stopping rule if guidelines were clear
- Experience of providing Botox treatment shows that treatment is stopped due to a positive response in 50% of people at 2 years and 75% of people at 5 years (only 25% are still on treatment at year 5)
- Both clinicians and patients would always seek to ensure a therapy was still required
- It is plausible that about 20% of those on erenumab who are experiencing benefit will stop treatment each year
- 50% chance of relapse if erenumab treatment is stopped (experience from Botox)
- Plausible that benefit could be sustained beyond 12 weeks of stopping treatment
- It is likely that some patients will remain on erenumab indefinitely
- Erenumab treatment is likely to be continued even if chronic migraine converts to HFEM following a response to treatment

❑ Is the positive treatment discontinuation scenario where treatment is stopped in 20% of patients (who continue to benefit from erenumab at 64.5 weeks) reasonable?

[redacted]

ACD consultation comments (Novartis)

Additional service costs of erenumab (1)

Committee consideration (ACD section 3.15)

- The cost of setting up additional services for the monitoring requirements of the most refractory cases of migraine should be accounted for in the model

Company response (ACD response point 6)

Including additional service set-up costs is inappropriate

- Erenumab is expected to be initiated by headache specialists and after initiation it can be self-administered
- Not anticipating that the introduction of erenumab will require specialist services
  - Erenumab may have a lower administrative burden compared with Botox
  - Following an initial adjustment it may help alleviate pressure on services
- Patient population (CM and HFEM) with 3 or more prior treatments are likely to be managed in specialists services already
- Reduction of migraine days is likely to reduce the number of patient visits to health services
- Do not consider additional resource costs to be relevant to the appraisal or economic model

[redacted]

ACD consultation comments (Novartis)

Additional service costs of erenumab (2)

Clinical expert comments

Treatment initiation

- Erenumab treatment would be initiated in specialist headache clinics
- Following initiation, the patient can be trained to self-administer at home

Treatment monitoring

- Adverse effects can be monitored by a nurse not necessarily in specialist headache clinics
- If administered at home by the patient, specialist assessment would be required at 3 months then again at 12 months
- There will be a cost to train patients to self-administer, this support should come from the company not the NHS
- Repeat prescriptions could be initiated in tertiary care and after 3 months the GP could prescribe
- Follow-up appointments could be conducted by a specialist nurse

Impact on referrals

- May not be a large impact on referrals to specialist clinics if erenumab became available
- An impact on resources was also considered for Botox when it became available but the increase in referrals never really happened.
- This patient group already are being seen in specialist clinics – and typically need repeated follow-up as their headaches are poorly managed. So its likely burden on specialist clinics (and A/E and general neuro clinics) might reduce

[redacted]

❑ Have all the costs of erenumab been captured in the company's modelling?

ACD consultation comments

Other issues for information

Issue	Comments
Magnitude of benefit for responders	The company's ACD response point 7 notes that the magnitude of benefit for responders was not adequately considered in the ACD. The difference in monthly migraine days between those who respond and those who do not respond to erenumab should be acknowledged →There is a substantial benefit to those who do respond to erenumab: • Chronic migraine responders on 140 mg had [redacted] MMD at 12 weeks compared to [redacted] days for non-responders

Equalities	• Consultation comments noted that:
	  • 3 times more women than men experience migraine → recommendations discriminate against women
	  • Chronic migraine can be sometimes be considered a disability → denying people the chance to contribute more to society is unfair
	• In the ACD section 3.20 these same points were raised however the committee concluded that these were not issues that could be addressed by NICE guidance

[redacted]

❑ Are there any other equalities issues that need to be taken into account?
❑ Has the magnitude of benefit for erenumab been fully addressed in the ACD?

Committee preferences and company's new analysis

Committee preference:	Did company include?
Include a 4th oral comparator (ACD section 3.4)	X
Evidence to reflect subgroup of people with no *therapeutic* response to at least 3 previous prophylactic treatments (ACD section 3.5)	X
Long term comparative effectiveness data vs BSC (ACD section 3.8)	X
Scenario where erenumab and Botox are considered to have similar effectiveness (ACD section 3.9)	✓
An economic model with a lifetime time horizon (ACD section 3.11)	✓
Scenarios with treatment effect waning over 5 and 10 years (ACD section 3.12)	✓*
Scenario without the positive discontinuation rule (ACD section 3.13)	✓
Include all relevant service resource costs for implementing erenumab in practice (ACD section 3.15)	X
The 70 mg and 140 mg doses should be considered separately in both the chronic and episodic populations (ACD section 3.16)	✓

[redacted]

*Partial resolution of issue

ACD consultation comments

Company revised analysis

Variable	Committee Assumptions	Company Revised Base Case Assumptions
Population	• Chronic migraine • Episodic migraine	• Chronic migraine • High-frequency episodic migraine (10–14 MHDs)
Analysis	• Incremental/Pairwise	• Pairwise
Dose	• 70mg / 140mg	• 140mg
Time horizon	• Lifetime	• Lifetime
Comparators	• Chronic migraine: Botox and BSC • High-frequency episodic migraine (10–14 MHDs): BSC	• Chronic migraine: Botox • High-frequency episodic migraine (10–14 MHDs): BSC
Treatment effect	• Wanes over 5 years or 10 years	• Maintained over time
Scenario analyses	• Odds ratio of 1 for Botox vs erenumab	• Midpoint OR and OR of 1 for Botox vs erenumab • Positive discontinuation • Treatment waning over 10 years from week 12 and from 5 years • Botox mode of administration utility decrements
Response rate	• 30% response rate for chronic migraine • 50% response rate for episodic migraine	• 30% response rate for chronic migraine • 50% response rate for HFEM

[redacted]

Company's revised base case

Deterministic results for chronic migraine, no waning, full treatment effect, 30% response					
Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Botox	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic ICER – chronic migraine: erenumab 140 mg vs. Botox					[redacted]

Deterministic results for HFEM, no waning, full treatment effect, 50% response					
Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Deterministic results for whole population (HFEM and chronic migraine), no waning					
Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC vs CM & BSC vs Botox	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

- An updated confidential PAS discount has been incorporated in the analysis

Source: Tables 3, 4, 5 & 6 in company response appendix

Company's deterministic scenario analyses

No benefit over Botox and positive discontinuation

- No difference in benefit between erenumab and Botox

Deterministic results for chronic migraine, no waning, no difference in benefit (OR=1)					
Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Botox	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- Positive discontinuation scenario

Deterministic results incorporating positive discontinuation scenario (ICERs)				
	Chronic migraine		High Frequency Episodic Migraine	
	Maintain MMD improvement	Change to 12 week placebo MMDs	Maintain MMD improvement	Change to 12 week placebo MMDs
Including positive discontinuation	[redacted]	[redacted]	[redacted]	[redacted]

Source: Tables 7 & 10 in company response appendix

[redacted]

Company's probabilistic scenario analyses results

- PSA results in chronic migraine incorporating different efficacy vs. Botox, treatment waning and utility decrement associated with mode of Botox administration

	Without applying mode of action utility decrement		Applying mode of action utility decrement	
	Comparison with Botox assumption		Comparison with Botox assumption	
Treatment waning assumption	Base case ITC	Mid-point ITC	Base case ITC	Mid-point ITC
No waning (Novartis submission assumption)	[redacted]	[redacted]	[redacted]	[redacted]
10 years of waning after 12 weeks (ACD scenario)	[redacted]	[redacted]	[redacted]	[redacted]
10 years of waning after 5 years treatment (revised ACD scenario)	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Source: Table 9 in company response appendix

ERG base-case for chronic migraine

ERG results incorporating the company's adjustments

The ERG :

- Added BSC as comparator for chronic migraine
- Provided fully incremental analyses including both BSC and Botox as comparators using a 30% response rate.
- Triptan injection price: was assumed to be reflected by the triptan injection price (Originally this was assumed to be reflected by the triptan oral price).
- MMD frequency after treatment discontinuation: all treatment discontinuers are assumed to have the week 12 non-responder MMD frequency (Originally, the MMD frequency for discontinuers was dependent on the nature of treatment discontinuation)

ERG Probabilistic results (erenumab 140 mg)	ICER (£/QALY)
1. Constant treatment effectiveness (no waning)	[redacted]
2. Treatment waning over 5 years	[redacted]
3. Treatment waning over 10 years	[redacted]

* Compared with BSC

[redacted]

ERG base-case for HFEM

Results incorporating the company's adjustments

- ERG results 4-6 include original definition of HFEM from company's trials (8-14 monthly headache days [MHDs])
- Results also include a 50% response rate for discontinuation

ERG deterministic results (erenumab 140 mg)	ICER (£/QALY)**	Probabilistic ICERs*
1. HFEM = 10-14 MHDs, constant treatment effectiveness (no waning)	[redacted]	[redacted]
2. HFEM = 10-14 MHDs, waning over 5 years	[redacted]	[redacted]
3. HFEM = 10-14 MHDs, waning over 10 years	[redacted]	[redacted]
4. HFEM = 8-14 MHDs, constant treatment effectiveness (no waning)	[redacted]	[redacted]
5. HFEM = 8-14 MHDs, waning over 5 years	[redacted]	[redacted]
6. HFEM = 8-14 MHDs, waning over 10 years	[redacted]	[redacted]

*ERG caution against using probabilistic ICERs due to the spurious results.

** Updated with corrected ICERs post ACM2

[redacted]

Source: Amended from company's response to FAC & ERG addendum 4

ERG scenario analyses (1)

- Deterministic results for: Chronic migraine incorporating:
  - Without mode of administration related utility decrement
  - Different efficacy vs. Botox
  - Treatment waning scenarios
  - Positive discontinuation scenario (maintaining MMD improvement)
  - Incremental ICERs (Botox and BSC included as comparators)
  - 30% response rate for discontinuation

ICER*	Without mode of administration related utility decrement			
	Without positive discontinuation assumption		With positive discontinuation assumption	
Treatment waning assumption	Botox OR based on ITC	Botox OR = 1	Botox OR based on ITC	Botox OR = 1
No treatment waning	[redacted]	[redacted]	[redacted]	[redacted]
5 year treatment waning	[redacted]	[redacted]	[redacted]	[redacted]
10 year treatment waning	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

** ICER for erenumab 140mg compared with botox
*** ICER for erenumab 140mg compared with BSC

ERG scenario analyses (2)

- Deterministic results for: Chronic migraine incorporating:
  - With mode of administration related utility decrement*
  - Different efficacy vs. Botox
  - Treatment waning scenarios
  - Positive discontinuation scenario (maintaining MMD improvement)
  - Incremental ICERs (Botox and BSC included as comparators)
  - 30% response rate for discontinuation

ICER*	With mode of administration related utility decrement			
	Without positive discontinuation assumption		With positive discontinuation assumption	
Treatment waning assumption	Botox OR based on ITC	Botox OR = 1	Botox OR based on ITC	Botox OR = 1
No treatment waning	[redacted]	[redacted]	[redacted]	[redacted]
5 year treatment waning	[redacted]	[redacted]	[redacted]	[redacted]
10 year treatment waning	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

*MOA decrement not fully validated by ERG, results to be interpreted with caution
** ICER for erenumab 140mg compared with botox
*** ICER for erenumab 140mg compared with BSC

Scenario analyses: Chronic migraine

- Deterministic results* for: Chronic migraine incorporating:
  - Different efficacy vs. Botox
  - Treatment waning scenarios
  - Positive discontinuation scenario (Change to 12 week placebo MMDs**)
  - Incremental ICERs (Botox and BSC included as comparators)

	Without applying positive treatment discontinuation			Applying positive treatment discontinuation		
	Comparison with Botox assumption			Comparison with Botox assumption		
Treatment waning assumption	ITC	Mid-point	OR=1	ITC	Mid-point	OR=1
No waning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 year waning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 year waning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years of waning after 5 years (company new scenario)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

*All results run by NICE technical team

** This assumption has not been validated by the ERG therefore results should be interpreted with caution

Scenario analyses: HFEM migraine

- Deterministic results* for HFEM incorporating positive treatment discontinuation scenario (Change to 12 week placebo MMDs**)

HFEM deterministic (erenumab 140 mg)	ICER (£/QALY)
1. Constant treatment effectiveness (no waning)	[redacted]
2. Treatment waning over 5 years	[redacted]
3. Treatment waning over 10 years	[redacted]
4. years of waning after 5 years (company new scenario)	[redacted]

[redacted]

*All results run by NICE technical team

** This assumption has not been validated by the ERG therefore results should be interpreted with caution

Key issues (1)

High Frequency Episodic Migraine (HFEM)

- Is HFEM a clinically distinct subgroup?
- Is it defined as 8-14 MMD or 10-14 MHD?
- Do the STRIVE and LIBERTY trials adequately capture the effectiveness of erenumab in HFEM defined by the company as 10-14 MHDs?

Comparators

- Is a 4th oral prophylactic used in NHS practice?
- Should a 4th oral preventative treatment be included as a comparator?
- What are the appropriate comparators for chronic migraine and HFEM?
- What is the most appropriate relative treatment effect to use in the analysis of Botox vs erenumab:
  - OR from ITC
  - Midpoint OR
  - OR of 1
  - Is the Botox mode of administration utility decrement (-0.059) scenario applied by the company reasonable?

[redacted]

Key issues (2)

Treatment effect

- What is the most appropriate treatment waning scenario:
  - 5 years
  - 10 years
  - 10 years treatment wane after 5 years (company's new scenario)
  - No treatment waning (company preferred)

Stopping rules

- Is it reasonable to apply a negative stopping rule at 3 months if there is no response to treatment (non-responders defined as those experiencing a <30% reduction in MMDs in the chronic group and <50% reduction in MMDs for the HFEM group)?
- Is the positive treatment discontinuation scenario where treatment is stopped in 20% of patients (who continue to benefit from erenumab at 64.5 weeks) reasonable?

Costs

- Have all the costs of erenumab been captured in the company's modelling?

Equalities considerations

- Are there any additional equalities considerations to address?

[redacted]

Additional slides

HFEM clinical evidence

	STRIVE		LIBERTY	
	Placebo (n=19)	Erenumab 140mg (n=17)	Placebo (n=72)	Erenumab 140mg (n=76)
Change from baseline in MMDs				
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at Week 12 (SE)*	NR (NR)	NR (NR)	[redacted]	[redacted]
Difference versus placebo (95% CI)	NA	[redacted]	NA	[redacted]
p-value	NA	[redacted]	NA	[redacted]
≥50% responder rate (MMDs)				
n (%)*	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	NA	[redacted]	NA	[redacted]
p-value	NA	[redacted]	NA	[redacted]

Source: Page 53 ERG report table 4.11

*Week 24 for STRIVE

CI = confidence interval; MMD = mean migraine days; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error

ACD consultation comments

Other issues raised by experts

Clinical expert comments

In the clinical expert and professional response to ACD consultation (see slide 12) it was noted that people with chronic migraine and psychiatric illness were also excluded from study 295*.

- Clinical experts were asked to what extent does comorbid psychiatric illness (e.g. depression) affect response to treatment in migraine?
  - "Significant"
  - "have not really observed any appreciable effect of treating anxiety/depression on migraine frequency…nor the response to migraine treatment"
  - "Unless the treatment itself is a contributing factor to the development of psychiatric illness, there will be no effect"
- How prevalent is psychiatric illness in patients with migraine?
  - "Chronic migraine 70%+ have anxiety or depression"
  - "expected that some people will experience low mood or depression as migraine is a debilitating illness"
  - "Anxiety is very common. Depression is also a comorbidity"

*Study 295 exclusion criteria: History of major psychiatric disorder or current evidence of depression based on a Beck depression inventory II score >24 at screening