Chair's presentation

Erenumab for preventing migraine [ID1188]

3rd Appraisal Committee meeting – 21st August 2019

Committee D

Chair: Gary McVeigh

Lead team: Andrew Hitchings, Malcolm Oswald, Rob Hodgson

ERG: Kleijnen Systematic Reviews

NICE technical team: Alan Moore, Nicola Hay, Jasdeep Hayre, Linda Landells

Company: Novartis

[redacted]

Erenumab for preventing migraine [ID1188] – Timeline to date

1st Committee meeting – 6th December 2018

Appraisal Consultation Document (ACD) produced. Due to high volume of comments in response to the ACD, NICE rescheduled the 2nd committee meeting to 16th April (from 14th February) to allow full consideration of these comments

2nd Committee meeting – 16th April 2019

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

3rd Committee meeting – 21st August 2019

[redacted]

ACD preliminary recommendation – From ACM1

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

Key issues

Indirect treatment comparison

- 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

Treatment waning

- What is the most appropriate treatment waning scenario:
  - 5 years *(ERG scenario)*
  - 10 years *(ERG scenario)*
  - 10 years treatment wane after 5 years *(Company variant of ERG scenarios)*
  - No treatment waning *(company base case)*
  - 10% additional annual treatment discontinuation *(company's new scenario)*

New clinical evidence

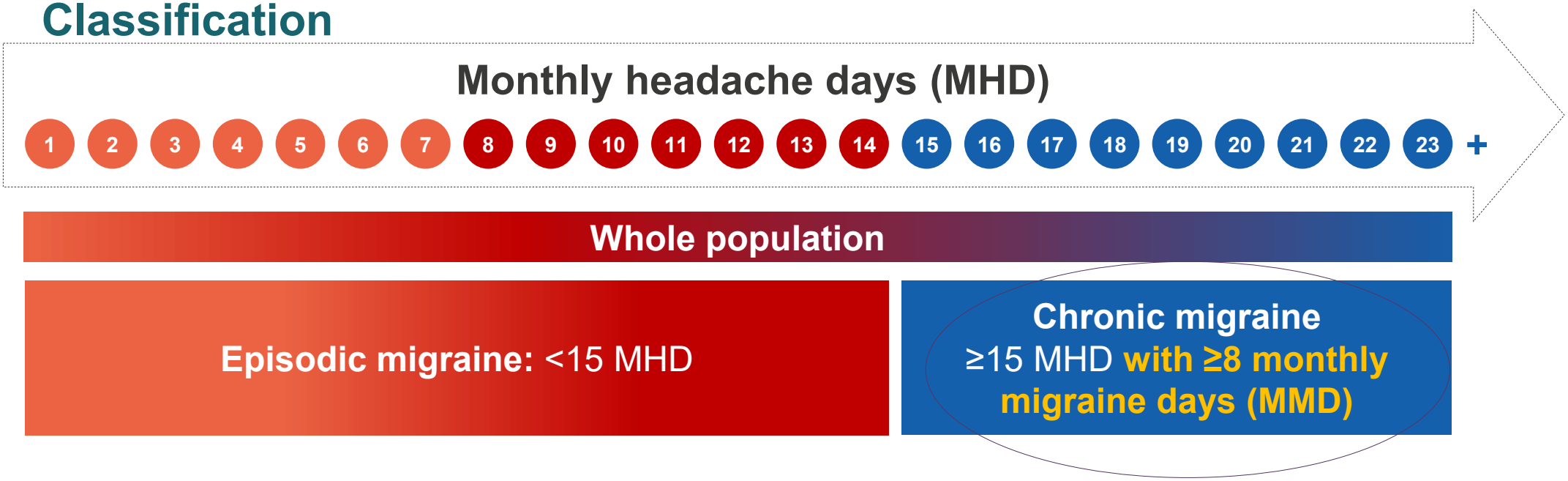
- How robust is the new evidence on the longer term clinical effectiveness of erenumab?

[redacted]

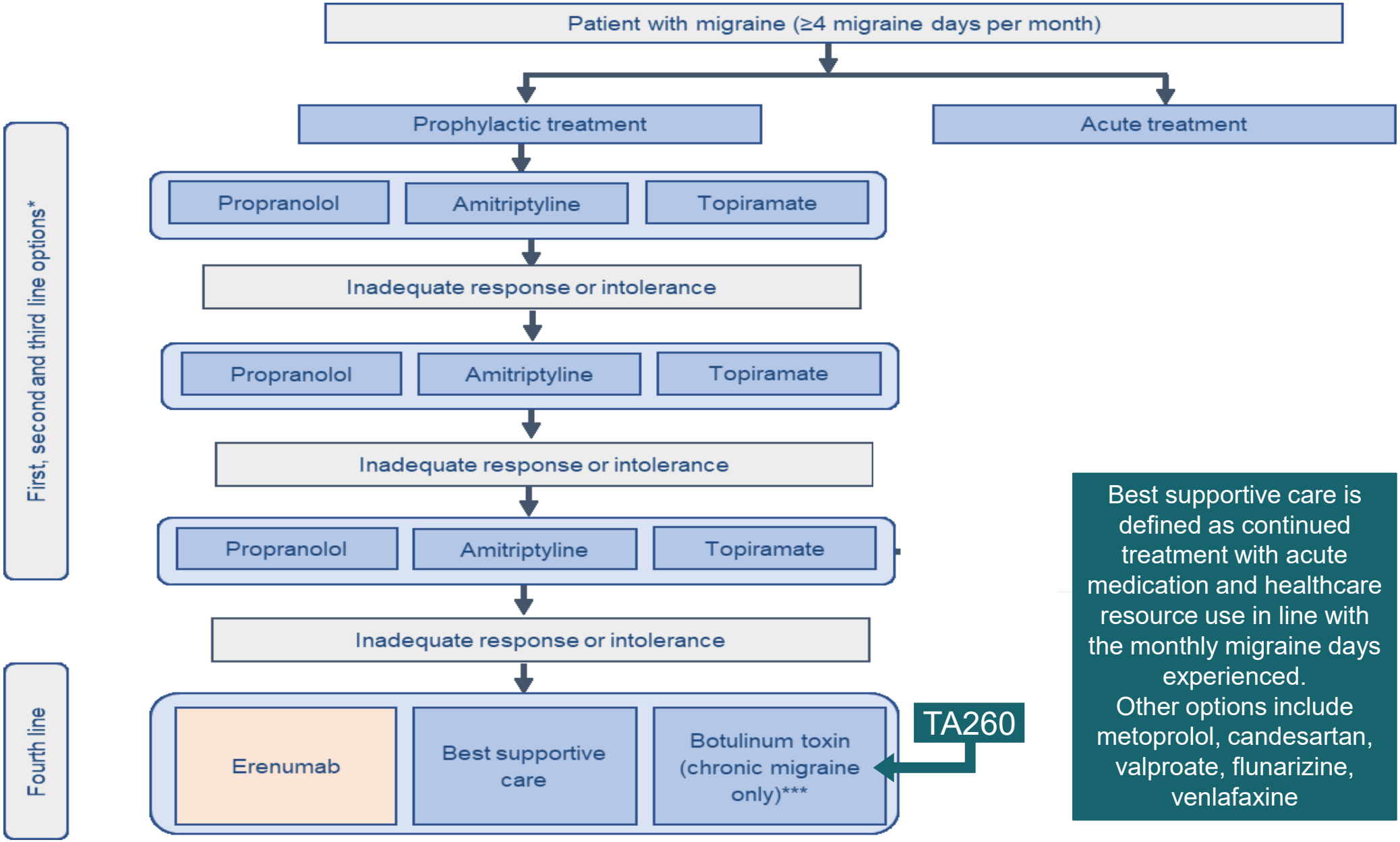
Migraine

- 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



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: results

	Chronic migraine - Clinical effectivness
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
50% reduction in Monthly Migraine Days (MMDs)	• 38.5% erenumab 140 mg • 34.8% erenumab 70 mg • 15.3% for placebo
Indirect Treatment Comparison	• ITC with botulinum toxin type A showed odds ratios that favour erenumab for both doses but the results were not statistically significant ▪ Erenumab 140mg versus Botox: Odds ratio (95% CI): [redacted] ▪ Erenumab 70mg versus Botox: Odds ratio (95% CI): [redacted]

[redacted]

Recap of consultation comments on ACD (1)

Consultees and commentators

Organisation	Comments
Patient group: The Migraine Trust	Erenumab allows people to resume normal living and working. Convenient self administration and well tolerated. Unfair to deny treatment.
Clinical expert and professional groups	Unmet need for convenient/tolerable treatment like erenumab. Duration of treatment and waning effect 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 advocate re-evaluation of need for treatment at least every 18 months
Allergan (Botox manufacturer)	Erenumab unlikely to be cost-effective compared with Botox. The economic modelling underestimates the uncertainty of the cost-effectiveness of erenumab
Novartis	“Disappointed by the draft recommendation”. Disagree with committee on the benefit of erenumab vs. Botox and erenumab’s long-term effectiveness/waning.

[redacted]

Recap of web comments on ACD (2)

Professionals, patients, carers & public comments summary

- The consultation received 280 individual comments from professionals, patients, carers and the public – summarised in detail at AMC2
- Comments generally requested that erenumab should be recommended.

Issue	Comments
Impact of Migraine	Everyday life negatively affected. Loss of independence. Frequent sick days. Depression. Low quality of life.
Current treatments	Not effective/work in short term. Botox requires many injections. Unmet need for well tolerated drug.
Erenumab effects	Erenumab improves on current treatments. Effective. Chance of leading a normal life. Can be self-administered.
Erenumab costs	Too expensive for private treatment. Could be offered to selected patients. Could reduce sickness absence.

Committee considerations summary (1)

Issue	Committee considerations	Timepoint
Appropriate comparators for chronic migraine	Botulinum toxin type A or best supportive care (BSC) were the relevant comparators in chronic migraine	ACM 2
Clinical trial populations	Clinical evidence was for a subgroup of people for whom at least 3 previous treatments had failed. However, people whose condition had no therapeutic response (defined as no reduction in headache frequency, duration or severity) to a number of previous preventive treatments were excluded from the trials. The people excluded from the trials were likely to represent the people most in need of treatment and the most clinically important subgroup	ACD section 3.5

Committee considerations summary (2)

Issue	Committee considerations	Timepoint
Is High Frequency Episodic Migraine a clinically distinct subgroup?	At consultation, the company updated its submission to focus on chronic migraine and high-frequency episodic migraine only. Clinical-effectiveness results for the High-Frequency Episodic Migraine group were highly uncertain. Committee concluded that high-frequency episodic migraine were not a distinct subgroup.	ACM 2
Long-term effectiveness of erenumab	Unclear whether erenumab works in the long term because there was no evidence that comparative efficacy was maintained beyond 12 to 24 weeks and no long-term non-comparative evidence was available beyond 52 to 64 weeks.	ACD section 3.8
Most appropriate relative treatment effect in the analysis of erenumab vs. botulinum toxin type A	There was no robust evidence that erenumab was more clinically effective than botulinum toxin type A for chronic migraine. It is appropriate to consider both the indirect treatment comparison odds ratio and a scenario in which erenumab and botulinum toxin type A have similar effectiveness (using an odds ratio of 1).	ACD section 3.9

Committee considerations summary (3)

Issue	Committee considerations	Timepoint
Adverse events	The adverse events in the trials with erenumab were generally not severe and were comparable with placebo and that erenumab was generally well tolerated in the studied populations	ACD Section 3.10
Dosing	The committee concluded that the 140 mg dose of erenumab was preferred over the 70 mg dose based on the clinical-effectiveness results and it was acceptable to consider only the 140 mg dose in the cost-effectiveness model.	ACD sections 3.6,3.7 and 3.13
Treatment waning	In the absence of evidence of long-term effectiveness, committee agreed to consider the 10- and 5-year effect waning scenarios presented by the ERG in its decision making.	ACM 2

Committee considerations summary (4)

Issue	Committee considerations	Timepoint
Negative stopping rule	A negative stopping rule at 3 months in the economic model if there is no response to treatment (>30% reduction in monthly migraine days at the 12-week assessment time point) is appropriate	ACM 2
Positive stopping rule	The company's 2 positive stopping rule scenarios were not appropriate for consideration.	ACM 2
Utility values	Utility values used in the model (the Migraine-Specific Quality of Life Questionnaire (MSQ) mapped to the EQ-5D-3L) may be reasonable but are uncertain.	ACD section 3.14

Committee considerations summary (5)

Issue	Committee considerations	Timepoint
Applying a mode of administration utility decrement to botulinum toxin type A	Applying a administration utility decrement to botulinum toxin type A resulted in the QALYs gained for botulinum toxin type A being lower than for BSC, therefore applying the decrement is not appropriate.	ACM 2
Costs of erenumab in the company's modelling	In response to consultation on the ACD, the company updated its economic model to include the appropriate triptan injection price which the committee accepted. Committee concluded that all relevant costs were captured in the modelling.	ACM 2
Equalities considerations	The committee considered issues around migraine being common in the working population and more common in women compared with men. It also noted that there may be unequal access to specialist headache clinics but concluded that there were no specific adjustments required to the NICE methods in this circumstance	ACD section 3.20

[redacted]

Committee preferences from 2nd Meeting

Committee's preferred assumptions from ACM2
Fully incremental analysis comparing erenumab 140mg with botulinum toxin type A and BSC in chronic migraine
Including odds ratio from the indirect treatment comparison and an odds ratio of 1 for comparison with botulinum toxin type A
Negative stopping rule (less than a 30% response to treatment)
Treatment waning effect of 5 and 10 years

Following ACM2, NICE agreed that the company could submit new evidence: This included an alternative treatment waning scenario analysis, an updated model and further long-term clinical data

[redacted]

Company's alternative treatment waning scenario

- Under waning scenarios considered – health state costs and utilities were linearly waned over time for responder patients for ereumab and botulinum toxin type A, until the benefit was equal to that of BSC.

- However, treatment was not discontinued as efficacy waned; therefore, treatment costs continued to occur over the long term

- Clinical expert opinion has stated that people who no longer experienced a clinically meaningful benefit would discontinue treatment with erenumab

- The company therefore felt that the waning scenarios do not reflect what would happen in clinical practice.

- **The company submitted an alternative scenario, which uses a discontinuation rate instead of a waning assumption, along with longer term clinical evidence**

[redacted]

Updated company model

Model for ACM2

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

- After ACM2, the company provided an updated model, which included implementing **additional discontinuation** along with the original 2.38% rate for all-cause discontinuations
- Company state that the model structure does not allow tracking of monthly migraine days (MMDs) in individual patients
- Therefore the company applied a loss of efficacy annual discontinuation rate of 10%, based on clinical opinion that patients would be reviewed annually
- Due to the lack of evidence to inform an appropriate discontinuation rate, the company selected 10% which is similar to rates used in previous NICE TAs* for chronic conditions
- This loss in efficacy was applied to both erenumab and botox treatment arms
- In one-way sensitivity analyses, this was altered this rate to 5% and 20%

*(asthma TA431, psoriasis TA521, ankylosing spondyloarthritis TA383, multiple sclerosis TA585)

[redacted]

ERG comment – company's alternative waning scenario

- The Evidence Review Group (ERG) agrees that a waning effect may lead to treatment discontinuation once a clinically meaning benefit is not detected
- The ERG does not agree that the company's modelling approach reflects the potential impact of treatment waning
- The company's approach takes patients off treatment without a previous loss of effectiveness; this does not reflect the gradual loss of effectiveness and the continuation of treatment costs entailed by treatment effect waning
- ERG believes that waning of treatment effect and treatment discontinuation are two separate, though potentially related, issues
- Adjusting discontinuation probabilities does not reflect the uncertainty of potential waning of treatment effect that was expressed by the committee.
- The ERG prefers the treatment waning scenarios as previously implemented by the ERG: In these scenarios, health state costs and utilities for responders gradually revert to BSC non-responder values (starting at 12 weeks- waning over 5 or 10 years) to reflect the loss of treatment effect while treatment costs continued to accumulate.

[redacted]

Additional long-term clinical analysis

- The company submitted evidence from 3 and 4.5 year interim analysis of a 5 year episodic migraine open-label extension study (NCT01952574)

Source	Results
3 year data: *Ashina, M. et al. Long-term safety and tolerability of erenumab: Three-plus year results from a five-year open-label extension study in episodic migraine*. Cephalalgia. 2019 May	383 people entered the open-label treatment phase on erenumab 70mg, all those remaining on treatment after a median of 2 years (n=250) were switched to erenumab 140mg. Of the 250 patients on erenumab 140mg, 236 patients remained on treatment at the time of the 3 year interim safety analysis. 5.6% of people discontinued from 140mg dose, 0% due to lack of efficacy
4.5 year data: *Ashina, M. et al. Sustained Efficacy and Long-Term Safety of Erenumab in Patients With Episodic Migraine: 4+-Year Results of a 5-Year, Open-Label Treatment Period*. Presentation at American Headache Society, 61st Annual Meeting; Philadelphia	250 people received erenumab 140mg during the open-label treatment phase and 221 patients remained on treatment at the time of the 4.5 year pre-planned analysis. 7.6% of people discontinued from 140mg dose treatment in 4.5 year the open-label treatment phase, 0% due to lack of efficacy

ERG comment - additional long-term clinical evidence

- The ERG considers the long-term clinical evidence to support long-term maintenance of erenumab to be weak.
- Open-label uncontrolled design of the trial means that no comparative effectiveness data of erenumab vs. comparators were obtained.
- The ERG does not consider this open-label study to be directly applicable to the current submission.
- The specified population for the submission was patients with chronic migraine who had ≥3 failed prior prophylactic treatments, whereas the open-label study was conducted in patients with episodic migraine and did not specify prior treatment failure.
- The majority (56%) of patients included in the open-label study were treatment naïve and 36% were classified as having prior treatment failure (number of prior treatments not specified), including discontinuations due to lack of efficacy and/or adverse events.

[redacted]

Updated company model base case

Parameter	Assumption
Population	Adults with chronic migraine for whom ≥3 prior prophylactic treatments have failed
Analysis	Incremental
Comparators	Best supportive care and botulinum toxin
Erenumab dose	140mg
Time horizon	Lifetime
Relative efficacy vs botulinum toxin	Indirect treatment comparison (ITC), Mid-point and Odds ratio = 1
Response assessment	30% reduction in monthly migraine days (MMDs)
Additional treatment discontinuation due to loss of efficacy	9.24% discontinuation rate applied every 4 cycles (every 48 weeks) (discontinuation rates are equivalent to an annual discontinuation of 10%) starting at week 48 (only applied in scenario 2 on next slide)

Updated cost effectiveness analysis (1)

Incremental analysis - deterministic

Scenario Type		Loss of Efficacy/Waning	Relative efficacy versus Botulinum type A assumption		
			ITC	Mid-point	No benefit
1	All-cause discontinuation (small proportion due to loss of efficacy)	2.38% all-cause discontinuation per 12 week cycle **Company base case**	[redacted]	[redacted]	[redacted]
2	As per scenario 1 plus additional discontinuation of treatment due to loss of efficacy	Additional discontinuation every 4 cycles (based on 10% annual rate) **New company scenario**	[redacted]	[redacted]	[redacted]

ICERs include simple confidential PAS discount

[redacted] ** ICER for erenumab 140mg compared with Botox

*** ICER for erenumab 140mg compared with BSC

Updated cost effectiveness analysis (2)

Scenario Type		Loss of Efficacy/Waning	Relative efficacy versus Botulinum type A assumption		
			ITC	Mid-point	No benefit
3	As per scenario 1 plus treatment waning i.e. loss of efficacy and no additional discontinuation	**5 year waning** *ERG scenario* (2.38% all-cause discontinuation per 12 week cycle)	[redacted]	[redacted]	[redacted]
		10 year waning *ERG scenario* (2.38% all-cause discontinuation per 12 week cycle)	[redacted]	[redacted]	[redacted]
		10 years of waning after 5 years *Novartis scenario* (2.38% all-cause discontinuation per 12 week cycle)	[redacted]	[redacted]	[redacted]

ICERs include simple confidential PAS discount

[redacted] ** ICER for erenumab 140mg compared with Botox

*** ICER for erenumab 140mg compared with BSC

Updated cost effectiveness analysis (3)

Pairwise analysis- deterministic

Scenario Type		Loss of Efficacy/Waning	BSC	Relative efficacy versus Botulinum type A assumption		
			BSC	ITC	Mid-point	No benefit
1	All-cause discontinuation (small proportion due to loss of efficacy)	2.38% all-cause discontinuation per 12 week cycle **Company base case**	[redacted]	[redacted]	[redacted]	[redacted]
2	As per scenario 1 plus additional discontinuation of treatment due to loss of efficacy	Additional discontinuation every 4 cycles (based on 10% annual rate) **New company scenario**	[redacted]	[redacted]	[redacted]	[redacted]

ICERs include simple confidential PAS discount

[redacted]

Updated cost effectiveness analysis (4)

Scenario Type		Loss of Efficacy/Waning		Relative efficacy versus Botulinum type A assumption		
			BSC	ITC	Mid-point	No benefit
3	As per scenario 1 plus treatment waning i.e. loss of efficacy and no additional discontinuation	**5 year waning** *ERG scenario* (2.38% all-cause discontinuation per 12 week cycle)	[redacted]	[redacted]	[redacted]	[redacted]
		10 year waning *ERG scenario* (2.38% all-cause discontinuation per 12 week cycle)	[redacted]	[redacted]	[redacted]	[redacted]
		10 years of waning after 5 years *Novartis scenario* (2.38% all-cause discontinuation per 12 week cycle)	[redacted]	[redacted]	[redacted]	[redacted]

ICERs include simple confidential PAS discount

[redacted]

Updated cost effectiveness analysis (5)

Sensitivity analysis – Incremental, deterministic

Scenario Type		Loss of Efficacy/Waning	Relative efficacy versus Botulinum type A assumption		
			ITC	Mid-point	No benefit
1	Additional discontinuation of treatment due to loss of efficacy	Additional discontinuation every 4 cycles (based on 5% annual rate)	[redacted]	[redacted]	[redacted]
2	Additional discontinuation of treatment due to loss of efficacy	Additional discontinuation every 4 cycles (based on 20% annual rate)	[redacted]	[redacted]	[redacted]
3	As above, but with additional discontinuation starting at 192 weeks (based on new data)	Additional discontinuation every 4 cycles (based on 10% annual rate) starting at 192 weeks	[redacted]	[redacted]	[redacted]

ICERs include simple confidential PAS discount

[redacted] ** ICER for erenumab 140mg compared with Botox

*** ICER for erenumab 140mg compared with BSC

ERG critique of the company's updated cost effectiveness analyses

- The ERG confirmed that they could reproduce the company's cost-effectiveness estimates – *Table 1 ERG addendum*

[redacted]

Key issues

Indirect treatment comparison

- 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

Treatment waning

- What is the most appropriate treatment waning scenario:
  - 5 years *(ERG scenario)*
  - 10 years *(ERG scenario)*
  - 10 years treatment wane after 5 years *(Company variant of ERG scenarios)*
  - No treatment waning *(company base case)*
  - 10% additional annual treatment discontinuation *(company's new scenario)*

New clinical evidence

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

[redacted]