Slides for public observers:
No confidential information

Chair's presentation

Fremanezumab for preventing migraine (ID1368)

2nd Appraisal Committee meeting – 6th February 2020

Committee D

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ERG: PenTAG

Company: Teva UK

[redacted]

Key issues

Clinical effectiveness:

- Is the fremanezumab trial population generalisable to NHS practice?
- What is the most plausible estimate of relative efficacy of fremanezumab and onabotulinumtoxin A (OBA): network meta-analysis or assuming they are equivalent?

Cost effectiveness:

- Is there additional utility benefit related to treatment (not captured by the mean migraine days [MMDs]): should on- and off-treatment utilities be used?
- Should the model capture treatment effect in non-responders (observed in the trial – but did not meet the threshold for response and discontinued treatment)?
- Should a positive discontinuation rule be used in the model (that is, discontinuation in responders, assuming waning of treatment effect post-discontinuation)?

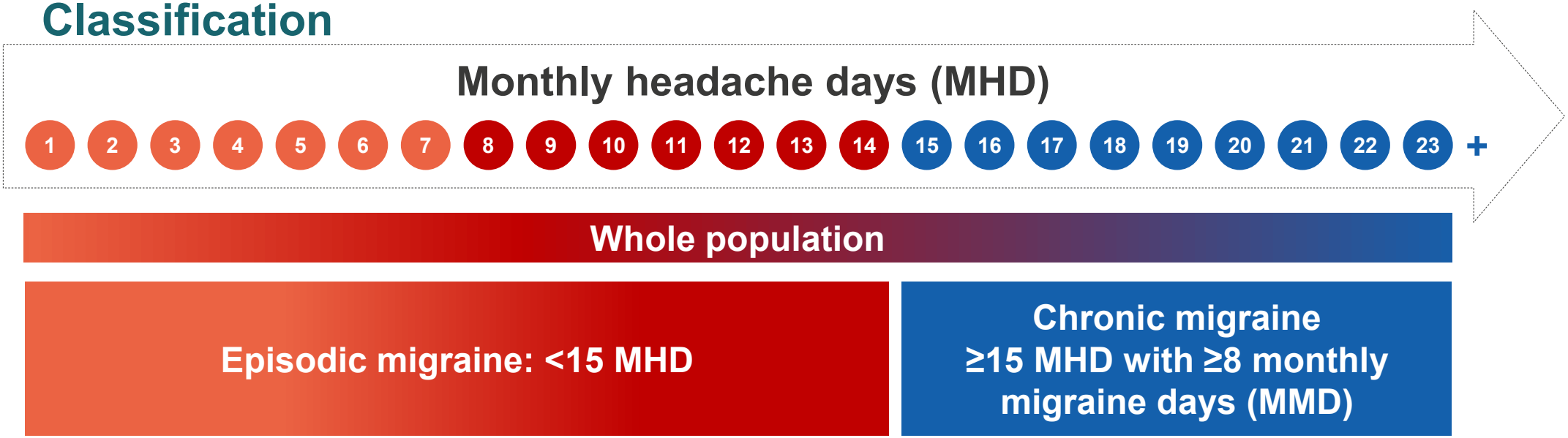
New evidence submitted:

- Revised base-case: including PAS, revised price of OBA administration and coding fixes – as well as reverting to some of the company's preferred assumptions
- Additional evidence for post-OBA population (people with chronic migraine for whom 3 oral preventive treatment and OBA have failed)

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



Fremanezumab (Ajovy, Teva)

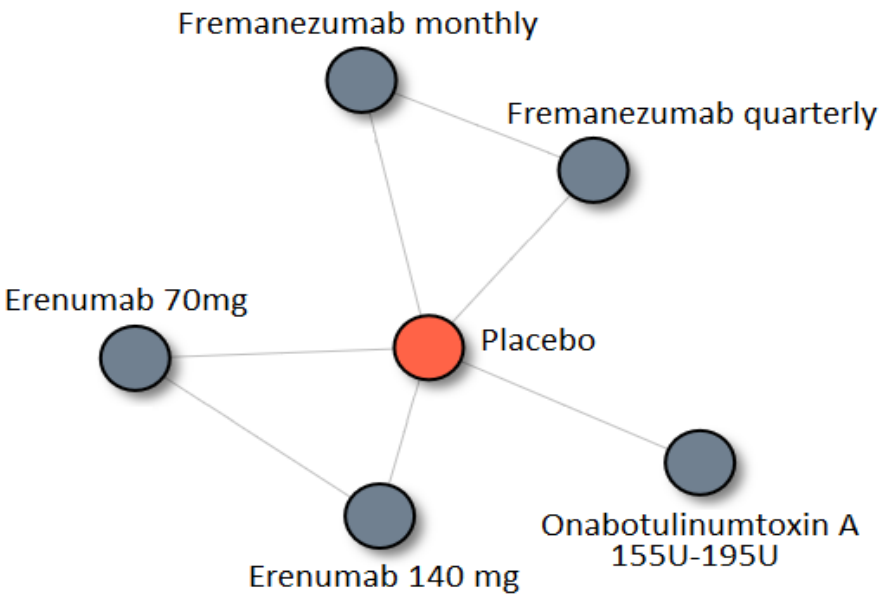
Description of technology	Fremanezumab (Ajovy, Teva) is a fully humanised monoclonal antibody that inhibits the action of calcitonin gene-related peptide (CGRP) which is believed to transmit signals that can cause severe pain
Marketing authorisation	Fremanezumab is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month
Dosage and administration	Fremanezumab is administered by subcutaneous injection and has two dosing options available: • 225 mg once monthly (monthly dosing) or, • 675 mg every three months (quarterly dosing)
List price	The list price of fremanezumab is £450 per 225 mg injection (£1350 per 675 mg). Costs may vary in different settings because of negotiated procurement discounts. Also a confidential commercial arrangement has been agreed.

Recap: clinical evidence: FOCUS

	Episodic migraine			Chronic migraine		
	Placebo (n=[redacted])	Frem 3-mthly (n=[redacted])	Frem monthly (n=[redacted])	Placebo (n=[redacted])	Frem 3-mthly (n=[redacted])	Frem monthly (n=[redacted])
Mean monthly migraine days						
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with at least 50% reduction in monthly average migraine days						
Responder rate (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio vs placebo (95% CI)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean monthly days of use of any acute headache medication						
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)		[redacted]	[redacted]		[redacted]	[redacted]
LSM = log-square mean						

[redacted]

Recap: clinical evidence: indirect treatment comparison with OBA



Fremanezumab (FOCUS):

- Outcomes reported at 12 weeks
- % responder rate for monthly **migraine** days
- Placebo: a single SC injection every month or 3 SC injections every quarter

OBA (PREEMPT 1&2):

- Outcomes reported at 24 weeks
- % responder rate for monthly **headache** days
- Placebo: intramuscular injections into 31 to 39 different sites on the head and neck

Erenumab (study 295):

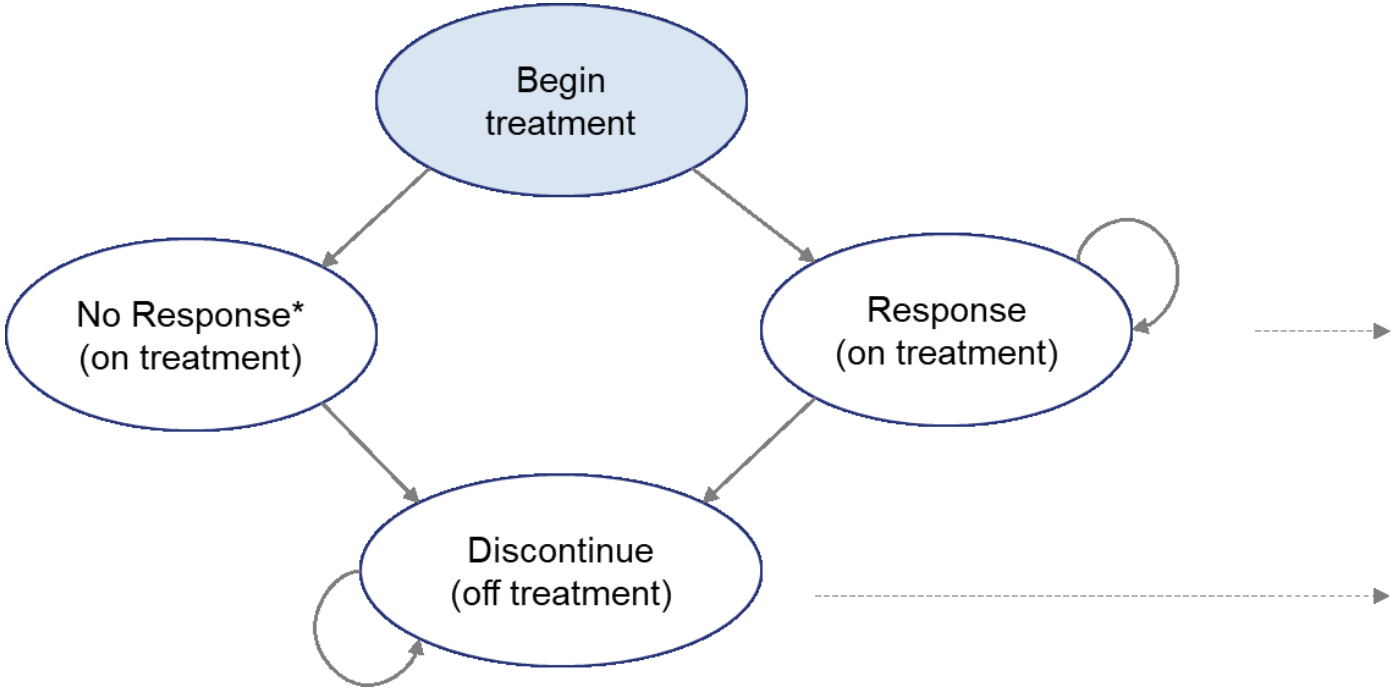
- Not clear why included in the network (how it would strengthen the network – not a comparator)

[redacted]

Point estimate favoured fremanezumab versus OBA but was not statistically significant

Recap: Economic model

- Semi-Markov model
- Episodic and chronic migraine analysed separately
- People in the model are split into treatment responders and non-responders
  - Responders remain on treatment and non-responders discontinue
- Cost and utilities are exclusive to each health state
  - Separately calculated for responders and non-responders based on the proportion of patients in each MMD health state



Markov Model
(28 MMD health states)

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

ACD preliminary recommendation

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

Recap: ACD considerations (1)

Issue	Committee's considerations
Population and outcomes (ACD 3.2)	Fremanezumab would be offered after 3 failed oral preventive treatments. Clinically meaningful response: 30% reduction (for chronic migraine) or 50% reduction (for episodic migraine) in migraine frequency.
Relevant comparator (ACD 3.3)	Episodic migraine: BSC Chronic migraine: OBA and BSC
Clinical data (ACD 3.4-3.5)	Post-hoc subgroup analysis of FOCUS study; it may not fully reflect people who would be eligible in routine clinical practice.
Clinical effectiveness (ACD 3.7-3.8)	Fremanezumab is clinically effective compared with placebo for episodic and chronic migraine. High-frequency episodic migraine is not a clinically distinct subgroup. The long-term comparative effectiveness of fremanezumab is unknown.
Indirect treatment comparison (ICD 3.10)	Uncertain whether fremanezumab is more clinically effective than OBA. Committee requested an additional scenario where fremanezumab and OBA have similar effectiveness.

[redacted]

Recap: ACD considerations (2)

Issue	Committee's considerations
Quality of life (ACD 3.11)	Using MSQ data was reasonable because the EQ-5D-5L was not sufficiently sensitive to changes in quality of life caused by migraine.
Time horizon (ACD 3.13)	Company used 10-year time horizon in their economic model. Committee preferred a lifetime horizon to capture all relevant costs and benefits associated with fremanezumab (≥30 years; 58 years used).
Discontinuation (ACD 3.14-3.15)	The fremanezumab all-cause discontinuation rate is higher than expected and could affect the cost-effectiveness results. The company's post-discontinuation assumptions are overly optimistic. Preferred ERG's scenario in which people revert to baseline monthly migraine days after discontinuing fremanezumab or best supportive care.
Stopping rule (3.16-3.17)	Applying a negative stopping rule (in non-responders) is appropriate. Applying a positive stopping rule (in responders) in not appropriate because it is implausible that treatment benefit is maintained indefinitely.
On- and off-treatment utilities	The company split the EQ-5D utility values into 'off-treatment' and 'on-treatment' groups using baseline (week 0) MSQ data for 'off-treatment utilities' and week 4 and 12 MSQ data for 'on treatment' utilities. Additional on-treatment utility value benefits should not be included.

[redacted]

MSQ = Migraine-Specific Quality of Life Questionnaire

Recap: ACD considerations (3)

Issue	Committee's considerations
Administration (ACD) 3.21	Company's model assumed all people would be able to self-administer. Committee considered that some people will need fremanezumab to be administered for them (10% assumed).
ICERs in episodic migraine (ACD 3.22)	Company base-case: £13,954 per QALY gained vs BSC Committee base-case: £48,996 per QALY gained vs BSC Fremanezumab is not cost effective compared with BSC for people with episodic migraine after 3 preventive treatments have failed.
ICERs in chronic migraine (ACD 3.23)	Company base-case: £11,825 per QALY gained vs BSC £16,227 per QALY gained vs OBA Committee base-case: £40,297 per QALY gained vs BSC Dominated by OBA Fremanezumab is not cost effective compared with OBA and BSC for people with chronic migraine after 3 preventive treatments have failed.
ICERs in post-OBA population (ACD 3.24)	The committee could not consider cost-effectiveness of fremanezumab after 3 oral preventive therapies and botulinum toxin type A have failed because no evidence was presented for this population.

[redacted]

ACD consultation responses

- Web comments (including professionals, patients, carers and public) (n=74)
- 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
  - Novartis
- Consultee comments, Teva:
  - ACD response
  - Proposed PAS
  - Revised base case and sensitivity analyses; new evidence for post-OBA population

[redacted]

Web comments

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

- The consultation received 74 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 fremanezumab is recommended, at least in selected patients initially

[redacted]

Web comments

Professionals, patients, carers and public comments (1)

Impact of migraine	Current treatments
• Everyday life negatively affected, • Can be severely disabling; bedbound • Depression, anxiety, social isolation • Feel like life is not worth living / miserable • Suicidal thoughts • Frequent health service visits • Also affects family and friends • Affects ability to work: unemployment, disability benefits, early retirement, frequent work absence, fear for job security, no career • Lack of understanding of the condition; “invisible disability”; feeling isolated and abandoned • WHO: migraine more disabling than blindness, paraplegia and acute psychosis and on the same level of disability as quadriplegia and dementia • Affects more women than men	• Existing treatments not effective and can have bad side effects • Not all treatments work for everyone – more treatment options needed • Trialling 4th ineffective, badly tolerated treatment options has severe impact on patients’ lives • Patients who did not respond to oral preventive drugs and OBA have no viable treatment options • OBA not effective for many patients, can have side effects and requires many injections and travel to clinics; long waiting lists / capacity issues • There is a high unmet need for effective and well-tolerated drug

Web comments

Professionals, patients, carers and public comments (2)

Fremanezumab – effects	Fremanezumab – wider benefits/ costs

• Important new treatment option
• Helped when no other treatments worked (in clinical trials or private treatment)
• Few side effects
• Specifically designed to treat migraine
• Can be self-administered
• Noticeable beneficial effect in days
• Decreases frequency and severity of migraines
• Chance of leading a normal life: can return to work / social life / family life
• Impact on mental health; no longer feel suicidal
• May not be effective for everyone
	• Untreated migraine has enormous costs to the NHS and to the UK economy
	• Analysis did not consider wider benefits
	  ○ Could reduce sickness absence / disability payments / loss of productivity / enable return to work
	  ○ Could reduce NHS costs related to mental health / suicides / other services
	  ○ Could make more availability in OBA clinics for other patients
	• Too expensive for private treatment – will have greater impact on those on low incomes
	• Initially could be offered to selected patients only

Consultation comments

Patient groups: The Migraine trust

The Migraine trust recently conducted 2 surveys:

- **Patient Experience Survey:** surveyed 203 patients between 14 October and 19 November 2019 who were currently taking (or had recently taken) a CGRP drug for the prevention of their migraine. The survey asked a variety of questions about the patient experience of using CGRP inhibitors, including about effectiveness, tolerability, and comparisons with OBA.
- **Snap poll of neurologists and headache nurses:** surveyed 5 headache nurses and 11 neurologists between 22 November and 05 December 2019 about the experiences of their chronic migraine patients with OBA and CGRP drugs. In total, results speak to the experiences of 9,490 chronic migraine patients in the UK.

[redacted]

Consultation comments

Patient groups: The Migraine trust (survey results)

- **Clinical effectiveness:** patients with direct experience of OBA and CGRP medications, including fremanezumab, reported that the CGRP medication was more effective at manging their migraine than OBA.

  Neurologists/headache nurses:
  - 37%: CGRP drugs are more effective than OBA
  - 25%: CGRP drugs as effective as OBA
  - 0%: CGRP drugs less effective than OBA
  - 75%: their patients would prefer to receive CGRP drugs over OBA
- **Cost-effectiveness:** a clear majority of patients who took fremanezumab or other CGRP inhibitors were able to stop or reduce their use of other migraine medications while they were taking it. This can prevent medication overuse headache and reduce demand on resources elsewhere.
- **Equality:** % of respondents with migraine who consider themselves to have a disability as defined by the Equality Act 2010:
  - migraine (overall): 48%
  - chronic migraine with failure of 3 or more oral preventive therapies: 84%

Consultation comments

Patient groups: The Migraine trust

- The draft recommendation does not account for the significant sub-group of patients who will fail to respond to OBA
  - Significant unmet need in this patient sub-group, delivering an effective & well-tolerated treatment that many report as ‘life changing’.
  - Of patients surveyed who had failed to respond to OBA (n=125), 76% agree or strongly agree that the CGRP drug has improved quality of life.
- The draft recommendation does not account for the difficulties some patients are currently experiencing in accessing OBA therapy
  - 12% of eligible patients surveyed had to wait over one year to receive their first course of OBA injections from the time they were first prescribed it.
  - 27% of respondents who had received OBA had to pay privately in order to do so.
- The Migraine trust would like to ask the committee to take all necessary steps to consider this technology for use for a smaller group of patients than outlined in the marketing authorisation.

[redacted]

Consultation comments

Professional groups (ABN, BASH)

There is an unmet need for a convenient and tolerable treatment

- Focus study – definition of failure aligned with clinical practice
- Responder rates of ≥50% reduction in monthly migraine days are a truer reflection of the efficacy of treatments in everyday clinical practice
- 4th oral agent not effective and poorly tolerated – not an appropriate comparator.
- Patients who have tried and failed 3 oral preventives and OBA have particularly high unmet need – high disability and limited treatment options (which may be more expensive and more invasive than fremanezumab) – should be reconsidered by the committee

Duration of treatment and waning effect

- Positive stopping rule should be applied as this is expected in clinical practice and aligned with clinical guidelines which recommend ‘drug holidays’ in responding patients to confirm whether or not continued treatment is needed; in clinical practice, few people take prophylactic agents for longer than 6-18 months
- Sustained efficacy following discontinuation shown for other treatments (OBA)

[redacted]

Consultation comments

Professional groups (ABN, BASH)

- Data from patients receiving OBA for chronic migraine from a UK headache centre presented at the International Headache Congress in Dublin 2019 (Ahmed et al, IHC-PO-419); proportion is more difficult to estimate for episodic migraine - likely very few will need fremanezumab as many would respond to first line treatments

OBA	2-year data	5-year data
Discontinuation rate (responders)	~60% (228/380)	~86% (160/186)
Main reason for discontinuation	Reverted to episodic migraine	Reverted to episodic migraine
Relapse rate	61/228 – all restarted OBA	18/160; relapse period ranged from 4-36 months

- Treatment duration of 2 years would be reasonable for modelling purposes; treatment could be stopped earlier (after an annual review, for example) if the patient improves and this improvement is maintained off treatment (e.g. for 3 months); for chronic migraine, this improvement should be:
  - At least a reversion to episodic migraine
  - Possibly a reversion to episodic migraine with <10 headache days/month

[redacted]

Consultation comments

Commentator comments: Allergan (OBA manufacturer)

- General agreement with the committee's conclusions:
  - No robust evidence that fremanezumab is more clinically effective than OBA
  - Long-term effectiveness of fremanezumab is uncertain
  - Analysis based on post-hoc subgroup analysis of FOCUS trial
  - High uncertainty in the model; cost per QALY likely higher
  - Unlikely that patients who stop treatment due to positive response would never recommence the treatment when the symptoms return – evidence for OBA showed 20% of responders who discontinued treatment relapsed and restarted treatment (Andreou et al.)
  - Unlikely people who discontinue will maintain treatment benefit
  - Not all people may be able to self-administer
  - Allergan provided a summary of new studies for OBA

[redacted]

Consultation comments

Commentator comments: Novartis (erenumab manufacturer)

- Study 295 should be removed from NMA as per NICE DSU TSD1
- No on-treatment utility benefit was applied in erenumab appraisal (but was applied in OBA assessment)
- Lifetime horizon should be used, as for erenumab assessment
- Exclusion criteria of HALO studies not accurately described – some patients might meet the criteria of 3 prior treatment failures with the broader definition of treatment failure used in the assessment
- Agrees that per cycle all-cause discontinuation rate for fremanezumab appears high, and this can affect cost-effectiveness results; ERG's scenario in which patients revert to baseline monthly migraine days after all-cause discontinuation should be used

[redacted]

ACD consultation comments (Teva)

Summary of company's comments & updated evidence

- FOCUS population generalisable to UK routine practice
- NMA remains the best available evidence for the relative efficacy of fremanezumab and OBA
- Positive stopping rule should be applied as it will be used in NHS clinical practice (expert opinion, clinical guidelines)
- On-treatment utilities should be used – treatment impact on utilities known to exceed reductions in MMDs; seen in FOCUS and other migraine trials
- Treatment effect in non-responders should be restored: based on clinical trial data
- The same assumptions should be used to model efficacy of fremanezumab and OBA (coding errors: on-treatment utilities, efficacy in non-responders)
- Revised base-case submitted: new PAS price, updated OBA administration costs, coding errors fixed + restoring some company preferred assumptions (mentioned above)
- New evidence submitted for population for whom OBA has failed

[redacted]

ACD consultation comments (Teva)

Relevance of FOCUS population to UK routine practice

Committee considerations (ACD section 3.5)

- Conclusion: Subgroup whose treatment with 3 or 4 treatment classes was considered to have failed in FOCUS may not fully reflect those eligible for fremanezumab in clinical practice
- In clinical practice contraindication would not necessarily represent a treatment failure (FOCUS: part of definition of inadequate response)
- Failure of 3 or more preventive treatments may correspond to failure of 2 treatment classes (FOCUS: valproic acid and topiramate in separate drug classes)

Company response (ACD response points 1 - 3)

- Only 1.9% recorded treatment failures in FOCUS were due to contraindication
- If a treatment is contraindicated, then this treatment is not available for use so surmounts to a failure to be successfully treated
- Previous NICE guidance and all major clinical guidelines refer to number of failed treatments and not failed classes of treatment – so inadequate response to both valproic acid and topiramate meets the standard definition of 2 failed treatments
- Treatment failure history was before FOCUS enrollment so represents real-world practice

ACD consultation comments (Teva)

Relative efficacy of fremanezumab and OBA

Committee considerations (ACD section 3.10)

- Conclusion: Appropriate to consider a scenario in which equivalent efficacy was assumed and another in which the results of the NMA were incorporated
- Concerns over NMA; uncertainty whether fremanezumab was more clinically effective than OBA for chronic migraine
- There was real-world evidence supporting the effectiveness, tolerability and safety of OBA from a UK perspective, but not for fremanezumab

Company response (ACD response points 5 - 6)

- NMA remains the best available data for comparison between fremanezumab and OBA: it shows a benefit for fremanezumab across all endpoints analysed, despite conservative assumptions with respect to its relative efficacy
- NMA does not consider further benefits of fremanezumab, e.g. administration
- Most OBA data collected using a treatment protocol that does not follow NICE guidelines, and comes from a single centre analysis: limited generalisability

[redacted]

NMA data used in Teva's revised base case

ACD consultation comments (Teva)

Positive stopping rule

Committee considerations (ACD section 3.17)

- Conclusion: Positive stopping rule assumptions are not appropriate because it is implausible that treatment benefit is maintained indefinitely

Company response (ACD response point 9)

- Positive stopping rule will be utilised within NHS clinical practice as confirmed by clinical experts contacted by Teva
- Treatment would not be continued indefinitely in routine clinical practice - patients who show a sufficient response and who no longer require treatment would have this treatment positively stopped
- Positive stopping of preventive treatment within migraine is also recommended within SIGN and BASH guidelines
- European Headache Federation guidelines on anti-CGRP: continuation on treatment should be managed in the same way as for other migraine preventives
- SmPC of fremanezumab: "Evaluation of the need to continue treatment is recommended regularly thereafter [after initial assessment of efficacy]"

[redacted]

Updated positive stopping rule* used in Teva's revised base-case

*15% of patients stop treatment after each annual assessment and treatment effect wanes to baseline over 1 year after treatment cessation

ACD consultation comments (Teva)

On- and off-treatment utilities

Committee considerations (ACD section 3.19)

- Conclusion: Additional on-treatment utility value benefits should not be included in the model
- No evidence supporting on-treatment utility value benefits for people with migraine

Company response (ACD response point 10)

- This is not a clinically valid interpretation of the available evidence
- Data based on FOCUS clinical trial data which showed that, for a patient with a given number of monthly migraine days, their QoL was higher when being treated with fremanezumab
- Similar effects were shown in other migraine clinical trials, including erenumab (Lipton et al. 2018) and OBA (Batty et al. 2013)
- Clinical experts advice that differences in utilities are well known to exceed reductions in MMDs – which do not capture the full burden of headaches in terms of duration, severity and associated factors (nausea etc.)
- NICE appraisal of OBA concluded that the most plausible ICER included separate on- and off- treatment utilities

[redacted]

On- and off-treatment utilities restored in Teva's revised base-case

ACD consultation comments (Teva)

Treatment effect adjustments not applied for OBA

Committee considerations (ACD section 3.23)

- Using committee preferred assumptions (including removal of on-treatment utility benefit), scenario assuming relative efficacy based on NMA results, ICER value was £40,297 per QALY gained versus OBA

Company response (ACD response point 11)

- On-treatment utility benefits were not removed for OBA (as for fremanezumab); when corrected, ICER is £32,295 per QALY gained vs OBA.
- Additional change applied in the model that was not justified in the ACD, labelled as "removal of residual fremanezumab effect in non-responders."
  - This change removes any MMD reductions for fremanezumab non-responders during their 12-week treatment trial.
  - Change goes against the clinical trial evidence used to model this population (real treatment effect seen in the trial – but did not reach the threshold of a clinically meaningful response of at least 30%/50% reduction in MMD).
  - After the 12-week trial these patients stopped treatment and reverted to baseline MMDs
  - This change was applied for fremanezumab but not for OBA

[redacted] Equal assumptions for treatment effects used in Teva's revised base-case

ACD consultation comments (Teva)

Post-OBA population

Committee considerations (ACD sections 3.24)

- Could not consider the use of fremanezumab after OBA because it had not been presented with cost-effectiveness estimates for this group.

Company response (ACD response point 11)

- Teva has submitted additional evidence to demonstrate the clinical effectiveness and cost-effectiveness of fremanezumab in patients who have failed OBA.

[redacted]

New evidence submitted for post-OBA population

Committee preferences and company's new analysis

Committee preference:	Did company include?	
	Revised base-case	Scenario analyses
Minor ERG model corrections	✓	✓
Applying a lifetime (at least a 30-year) model horizon (ACD section 3.13)	✓ **(58 years)**	✓ **(58 years)**
Applying the ERG's post-discontinuation scenario (treatment effect waning post-discontinuation, return to baseline MDD; ACD section 3.15)	✓	✓
Removing a positive stopping rule (ACD section 3.17)	**X***	✓
Removing additional on-treatment utility benefits (ACD section 3.19)	**X**	✓
Applying fremanezumab administration costs for 10% of people (ACD section 3.21)	✓	✓
Considering 2 scenarios (ACD section 3.10): • Equal effectiveness of fremanezumab and OBA • Comparative effectiveness estimates from the network meta-analysis	 **X** ✓	 **X** ✓

[redacted]

*** Updated positive stopping rule applied**

New evidence submitted

Company revised base case & additional population

The revised base case presented: using the committee's preferred assumptions, with the following changes made:

- New PAS price for fremanezumab included
- Updated OBA administration costs (£125 per administration*)
- The same assumptions used to model the efficacy of fremanezumab and OBA (on-treatment utility benefits; treatment effect in non-responders - previously removed for fremanezumab but not OBA)
- Restoring relative OBA efficacy as per network meta-analysis results
- Restoring fremanezumab efficacy in non-responders
- Restoring on-treatment utilities
- Updated positive stopping rule where 15% of responders stop treatment after each annual assessment and treatment effect wanes to baseline over 1 year after treatment cessation

<u>Evidence submitted for a subgroup of patients for whom 3 oral preventive therapies and OBA have failed</u>

[redacted]

* as per NICE and NHS England budget impact analysis

New evidence submitted

Scenario analyses

Scenario	Explanation of scenario
A	All assumptions set to the committee's preferences Updated PAS price for fremanezumab, Updated OBA administration costs For chronic migraine: OBA efficacy based on the NMA results
B	As scenario A but with the original on- and off-treatment utilities restored
C	As scenario B but with treatment effect of on- utilities reduced by half
D	As scenario A but with fremanezumab effectiveness in non-responder patients restored (also restores efficacy in OBA to reverse change of coding correction)
E	As scenario A but with inclusion of an updated positive stopping rule whereby 15% of treated patients permanently stop treatment each year
F	As scenario A but with inclusion of an updated positive stopping rule whereby 10% of treated patients permanently stop treatment each year
G	As scenario A but with inclusion of an updated positive stopping rule whereby 15% of treated patients stop treatment each year and 50% of patients restart treatment after half of treatment effect is lost

New evidence submitted

ERG comments

- **Relative efficacy based on NMA:** ERG maintains that NMA results may not be reliable due to multiple issues with the analysis and reporting
- **On-treatment utility benefit:** ERG maintains its original views that there is no evidence to suggest an additional utility benefit beyond that from reducing migraine days, as there are limitations in how on- and off-treatment utility benefits were estimated
  - The scenario analysis where treatment effect on utilities is reduced by half should be disregarded as not supported by any data
- **Treatment effect in non-responders:** ERG accepts the changes implemented by Teva
- **Positive stopping rule:** ERG agrees that a range of scenario analyses is useful to consider given uncertainty in the model structure and data inputs;
  - The scenario where 50% of patients who discontinued treatment restart it after half of treatment effect is lost should be disregarded as not supported by data

[redacted]

Company's revised model:

Episodic migraine – after failure of 3 or more preventive treatments

Company preferred assumptions

Base-case results	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs BSC (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG: Committee preferred assumptions

Base-case results	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs BSC (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] ([redacted])

Scenario analyses	ICER vs BSC
A – Committee preferred assumptions (updated costs)	[redacted]
B – Scenario A + original on- and off- treatment utilities	[redacted]
C – Scenario B but treatment effect on utilities reduced by 50%	[redacted]
D – Scenario A + restoring fremanezumab effect in non-responders	[redacted]
E – Scenario A + 15% responders permanently stop every year	[redacted]
F – Scenario A + 10% responders permanently stop every year	[redacted]
G – Scenario E + 50% of patients restart treatment after half of treatment effect is lost	[redacted]

[redacted]

BSC: best supportive care; probabilistic ICERs in brackets
Source: Teva's additional evidence (Tables 12-13); ERG additional analyses (Table 10)

Company's revised model:

Chronic migraine – after failure of 3 or more preventive treatments; Scenario 1: relative efficacy with OBA based on NMA results

Company preferred assumptions

Base-case results	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs BSC (£/QALY)	Incremental ICER (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
OBA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG: Committee preferred assumptions

Base-case results	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs BSC (£/QALY)	Incremental ICER (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
OBA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] ([redacted])	[redacted] ([redacted])

Scenario	ICER vs BSC	ICER vs OBA
A – Committee preferred assumptions (updated costs)	[redacted]	[redacted]
B – Scenario A + original on- and off- treatment utilities	[redacted]	[redacted]
C – Scenario B but treatment effect on utilities reduced by 50%	[redacted]	[redacted]
D – Scenario A + restoring fremanezumab effect in non-responders	[redacted]	[redacted]
E – Scenario A + 15% responders permanently stop every year	[redacted]	[redacted]
F – Scenario A + 10% responders permanently stop every year	[redacted]	[redacted]
G – Scenario E + 50% of patients restart treatment after half of treatment effect is lost	[redacted]	[redacted]

[redacted]

BSC: best supportive care; probabilistic ICERs in brackets

Source: Teva's additional evidence (Tables 10-11); ERG additional analyses (Table 2)

Company's revised model:

Chronic migraine – after failure of 3 or more preventive treatments; Scenario 2: equal efficacy of fremanezumab and OBA (ERG)

ERG: Company assumptions

Base-case results	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs OBA (£/QALY)
OBA	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ERG: Committee assumptions

Base-case results	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs OBA (£/QALY)
OBA	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Scenario	iCosts	iQALYs	ICER vs OBA
A – Committee preferred assumptions (updated costs)	[redacted]	[redacted]	Dominated
B – Scenario A + original on- and off- treatment utilities	[redacted]	[redacted]	Dominated
C – Scenario B but treatment effect on utilities reduced by 50%	[redacted]	[redacted]	Dominated
D – Scenario A + restoring fremanezumab effect in non-responders	[redacted]	[redacted]	Dominated
E – Scenario A + 15% responders permanently stop every year	[redacted]	[redacted]	Dominated
F – Scenario A + 10% responders permanently stop every year	[redacted]	[redacted]	Dominated
G – Scenario E + 50% of patients restart treatment after half of treatment effect is lost	[redacted]	[redacted]	Dominated

[redacted]

Negative values for QALYs due to the difference in assessment period for OBA vs fremanezumab (24 weeks vs 12 weeks, respectively). At 12 weeks fremanezumab non-responders discontinue and revert to their baseline MMD and individuals treated with OBA accrue treatment benefit for an additional 12 weeks.
BSC: best supportive care; Source: ERG additional analyses (Tables 4-5)

Company's new evidence

Clinical effectiveness of fremanezumab post-OBA

- Post-hoc subgroup analysis of FOCUS - [redacted] patients with chronic migraine who had inadequate response to 3 oral preventive treatments and OBA

	Placebo	Fremanezumab quarterly	Fremanezumab monthly	Placebo	Fremanezumab pooled
Patient numbers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endpoint	Mean monthly migraine days				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)		[redacted]	[redacted]		[redacted]
P-value vs placebo		[redacted]	[redacted]		[redacted]
Endpoint	Patients with at least 30% reduction in monthly average migraine days				
Number achieving endpoint (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio vs placebo (95% CI)		[redacted]	[redacted]		[redacted]
P-value vs placebo		[redacted]	[redacted]		[redacted]

Source: Teva's additional evidence (Tables 1-2)

- Supportive analyses for additional 2 subgroups showing similar results :
  - People for whom 3 or more prior treatments have failed, of which one was OBA (n = [redacted])
  - All people with CM for whom OBA has failed (n = [redacted])

- ERG comment: while there is some evidence of effectiveness for the proposed fifth-line positioning, the evidence is tenuous and should be treated with caution

Company's new evidence

Clinical data used in the model (post-OBA population)

	Responders	Non-responders
Initial migraine days per 28 days	[redacted]	[redacted]
Mean reduction in monthly migraine days for fremanezumab versus placebo at 12 weeks	[redacted]	[redacted]
Modelled absolute monthly migraine days value for fremanezumab at efficacy assessment (12 weeks)	[redacted]	[redacted]
Modelled absolute monthly migraine days value for BSC at efficacy assessment (12 weeks)	[redacted]	[redacted]

Responder rates at 12 weeks:

- Fremanezumab: [redacted]
- BSC: [redacted]

[redacted] Source: Teva's additional evidence (Tables 5-6); Teva also presented supportive analysis for patients who have had an inadequate response to 4 preventive treatments

Company's new evidence:

Cost-effectiveness of fremanezumab post-OBA

Company preferred assumptions

Base-case results	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs BSC (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]*

ERG: Committee preferred assumptions

Base-case results	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs BSC (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	ICER vs BSC
A – Committee preferred assumptions (updated costs)	[redacted]*
B – Scenario A + original on- and off- treatment utilities	[redacted]*
C – Scenario B but treatment effect on utilities reduced by 50%	[redacted]*
D – Scenario A + restoring fremanezumab effect	[redacted]*
E – Scenario A + 15% responders permanently stop every year	[redacted]*
F – Scenario A + 10% responders permanently stop every year	[redacted]*
G – Scenario E + 50% of patients restart treatment after half of treatment effect is lost	[redacted]*

*ICER values lower by £2-£3 when re-run by the ERG

- Supportive analysis for patients who have had an inadequate response to <u>any</u> 4 preventive treatments – similar results to post-OBA population

[redacted] Source: Teva's additional evidence (Tables 14-15)

Key issues

Clinical effectiveness:

- Is the fremanezumab trial population generalisable to NHS practice?
- What is the most plausible estimate of relative efficacy of fremanezumab and onabotulinumtoxin A (OBA): network meta-analysis or assuming they are equivalent?

Cost effectiveness:

- Is there additional utility benefit related to treatment (not captured by the mean migraine days [MMDs]): should on- and off-treatment utilities be used?
- Should the model capture treatment effect in non-responders (observed in the trial – but did not meet the threshold for response and discontinued treatment)?
- Should a positive discontinuation rule be used in the model (that is, discontinuation in responders, assuming waning of treatment effect post-discontinuation)?

New evidence submitted:

- Revised base-case: including PAS, revised price of OBA administration and coding fixes – as well as reverting to some of the company's preferred assumptions
- Additional evidence for post-OBA population (people with chronic migraine for whom 3 oral preventive treatment and OBA have failed)

[redacted]

Additional slides

Recap: indirect treatment comparison

	Placebo	Fremanezumab monthly	Fremanezumab quarterly	OBA
Placebo	-	[redacted]	[redacted]	[redacted]
Fremanezumab monthly	[redacted]	-	[redacted]	[redacted]
Fremanezumab quarterly	[redacted]	[redacted]	-	[redacted]
OBA	[redacted]	[redacted]	[redacted]	-
Percentage of patients with ≥50% reduction in monthly migraine days (odds ratios)				
Placebo	-	[redacted]	[redacted]	[redacted]
Fremanezumab monthly	[redacted]	-	[redacted]	[redacted]
Fremanezumab quarterly	[redacted]	[redacted]	-	[redacted]
OBA	[redacted]	[redacted]	[redacted]	-

[redacted]

On- and off-treatment utilities

After mapping from MSQ to EQ-5D-3L, the company split the EQ-5D utility values into ‘on-treatment’ and ‘off-treatment’ groups.

- Off-treatment health state utility values were estimated using baseline (week 0) MSQ data
- On-treatment utility values were estimated from the week 4 and week 12 MSQ data.
- Off-treatment utility values were applied to best supportive care.
- On-treatment utility values were used for fremanezumab and botulinum toxin type A strategies until people stopped treatment.

[redacted]

On- and off-treatment utilities

Utility values for each MMD health state (≥2 prior prophylactic therapies)

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

[redacted]

Company's new evidence

Chronic migraine – after failure of 3 oral preventives and OBA

Additional endpoints

	Placebo	Fremanezumab quarterly	Fremanezumab monthly	Placebo	Fremanezumab pooled
Patient numbers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endpoint	Mean headache days of at least moderate severity				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)		[redacted]	[redacted]		[redacted]
P-value vs placebo		[redacted]	[redacted]		[redacted]
Endpoint	Mean monthly days of use of any acute headache medication				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)		[redacted]	[redacted]		[redacted]
P-value vs placebo		[redacted]	[redacted]		[redacted]

[redacted]