NICE National Institute for Health and Care Excellence

Presentation for website (redacted)
Closed session

Rapid review - Fremanezumab for preventing chronic and episodic migraine

Chair's presentation

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Company: Teva

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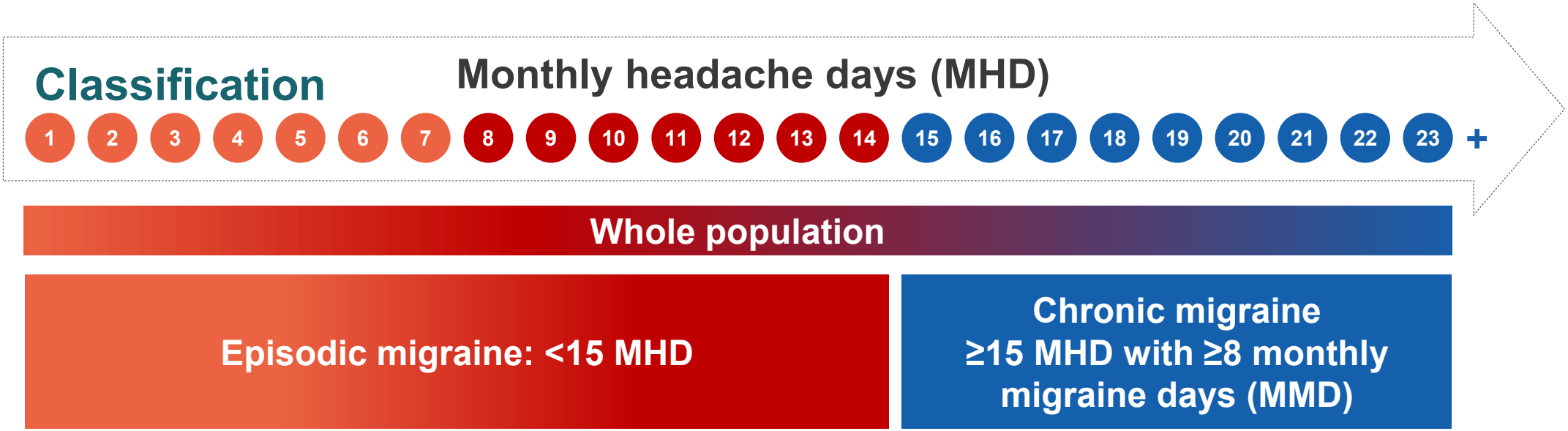
Recap: Migraine

- Headache disorder with recurring attacks usually lasting 4–72 hours
- Migraines usually produce symptoms that are more intense, painful and debilitating than headaches - 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



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. Costs may vary in different settings because of negotiated procurement discounts. A confidential commercial arrangement is in place ([redacted]).

Recap: clinical evidence. FOCUS, patients who have used at least 3 classes of preventative therapy

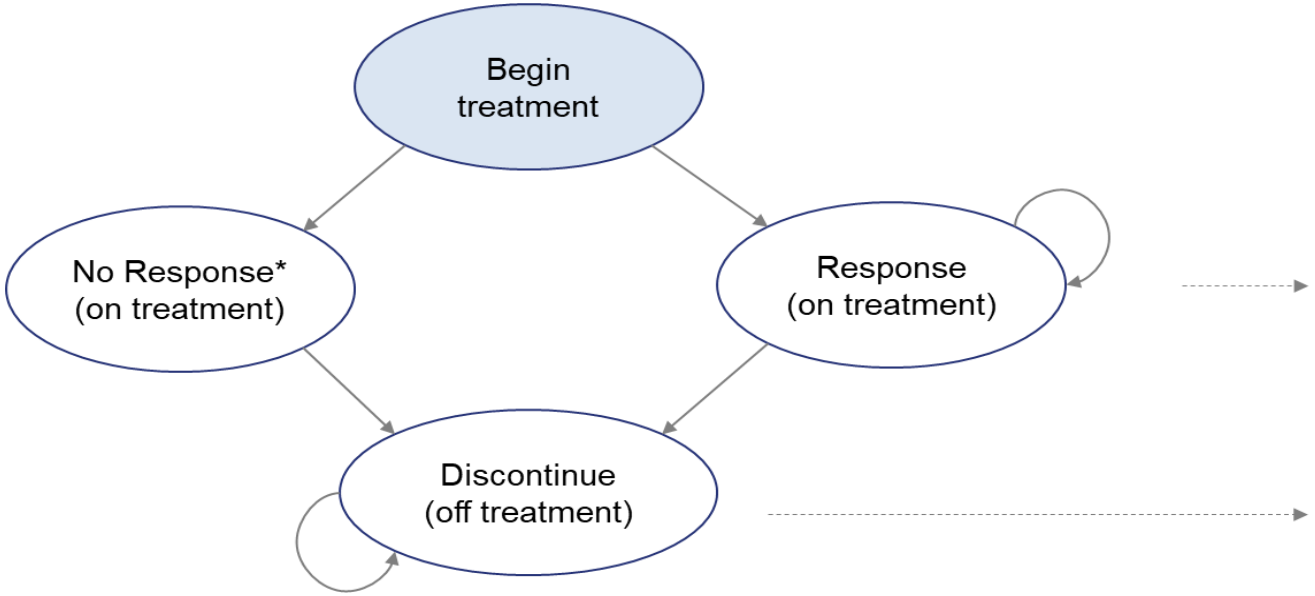
Focus for today

	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]
Patients with ≥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]
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

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

**No response defined as patients who do not achieve at least a 30% reduction in monthly migraine days (MMDs) for chronic migraine and at least a 50% reduction in MMDs for episodic migraine at 12 weeks*

Recap: FAD (TA631)

Fremanezumab recommended as an option for preventing migraine in adults, only if:

- the migraine is **chronic** (15 or more headache days a month for more than 3 months with at least 8 of those having features of migraine)
- at least 3 preventive drug treatments have failed

Stopping rule: Stop fremanezumab if the migraine frequency does not reduce by at least 30% after 12 weeks of treatment.

Context for rapid review:

- Subsequent galcanezumab (TA659) and erenumab (TA682) topics considered evidence around **differential utilities** to be used in economic modelling - use of different utility values for people on- and off-treatment.
    - *Note, both TA659 and TA682 featured episodic migraine in their recommendations, but **fremanezumab wasn't cost effective for episodic**.*
- Company invited to submit any evidence they had regarding differential utilities for fremanezumab, in the interests of fairness and making sure NICE guidance is consistent ***(company focused on episodic population)***

Issues for rapid review

- Are the company's updated analyses in episodic migraine acceptable for decision making?
- Can the fremanezumab recommendation be expanded to include episodic migraine, on the basis of the new analyses and cost-effectiveness estimates?

Company's rationale for differential utilities

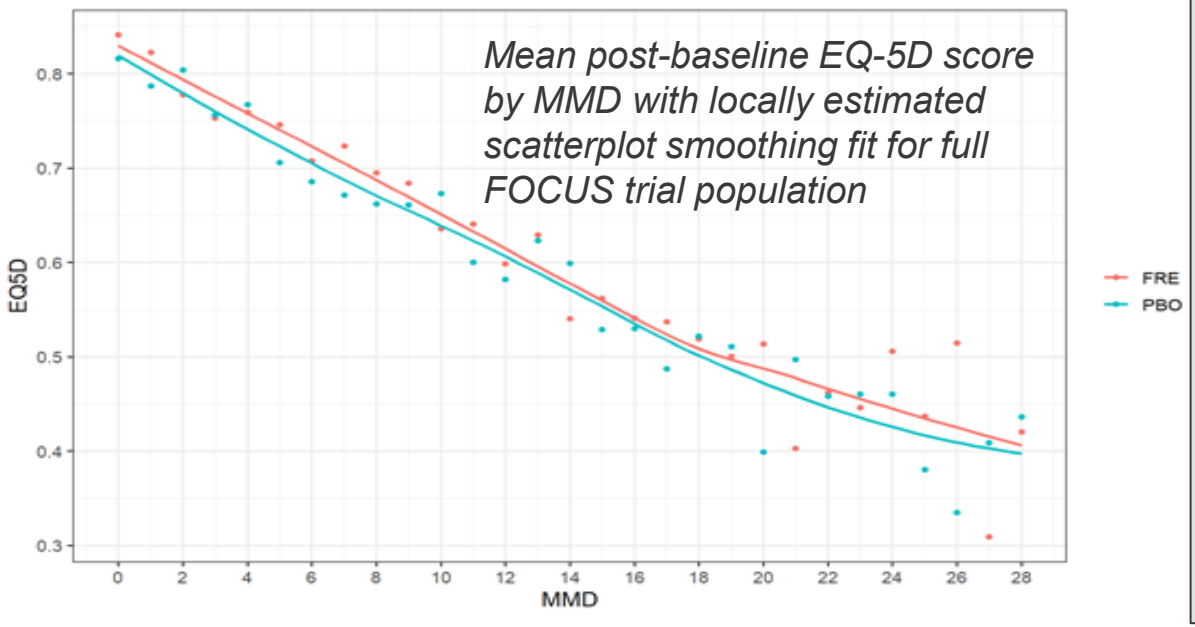
Company's clinical experts advised that improvements in utilities are well known to exceed reductions in monthly migraine days (MMDs)

- MMD measure unable to capture full burden of migraine in terms of duration, severity, factors that influence QoL

QoL can be impacted by migraine both during and between migraine attacks, so QoL impairments extend beyond MMDs alone

Treatment effect incorporated into differential utilities reflect additional benefits of treatment not captured within changes in MMD, including:

- Improvements in – disability levels, nausea/vomiting, photophobia
- Reductions in – severity/duration of migraine attacks, recovery time



Company:
Visual evidence to support use of differential utilities - people having fremanezumab tended to have a higher utility than BSC, when people had same MMD

ERG:
- not from subpopulation of interest (≥3 prior treatment class failures)
- no measure of statistical significance

FRE: fremanezumab; PBO: placebo

Company's new analyses (1)

Company
Previous analyses for differential utilities using beta distributions and full FOCUS population (2-4 treatment class failures) not accepted
Primary updated analyses for episodic migraine match NICE's preferences from the other migraine appraisals: • Normal distribution • Using appraisal target population (inadequate response to ≥3 previous migraine preventive treatment classes)   • Use of more targeted group rather than the full clinical trial population reduces sample size and statistical power, but provides most relevant data for population of interest
Amended analyses to reflect committee preferred assumptions from FAD, and align with assumptions in the galcanezumab and erenumab appraisals • Waning of treatment effect after discontinuation applied in galcanezumab appraisal based on clinical trial wash-out data. No such data currently available to demonstrate similar effect in fremanezumab so effect has not been included in modelling

ERG viewed waning as non-issue for current model update (waning scenarios applied only for chronic and not conducted for episodic in original appraisal; waning scenarios linked to positive stopping rule but committee preference to remove this rule

Company's new analyses (2)

EQ-5D model with normal distribution in ≥3 previous treatment class failures population (N numbers refer to number of observations included)			
Coefficient	Estimate	SE	p-value
Baseline model (N = 416; BIC = -365)			
Intercept	0.7619	0.0200	<0.001
Migraine days	-0.0162	0.0014	<0.001
Post-baseline model with treatment covariate (N = 818; AIC = -1449; BIC = 87)			
Intercept	0.7666	0.0063	<0.001
Migraine days	-0.0144	0.0003	<0.001
Fremanezumab	0.0239	0.0051	<0.001
Post-baseline model without treatment covariate (N = 818; AIC = -1448; BIC = 84)			
Intercept	0.7858	0.0045	<0.001
Migraine days	-0.0147	0.0003	<0.001

Company interpretation:

- Fremanezumab treatment was significant covariate in post-baseline model ($p<0.001$).
- Using post-baseline model accounts for any placebo effect seen in data, gives confidence this is true effect caused by fremanezumab treatment.
- Strong evidence that differential utilities are necessary to capture additional benefits of fremanezumab, and this effect is significant within most relevant population.

Company's new analyses (3)

ERG view
Although company's submission provided details surrounding regression modelling approach, a detailed statistical analysis plan was not provided. Overall, company's regression analysis appeared reasonable and aligned with previous migraine appraisals.
Based on results in previous slide, fremanezumab appeared to be a significant covariate in post baseline model ($p<0.001$) – may indicate fremanezumab has benefit beyond reducing MMD.
Previous migraine appraisals including erenumab (TA682) and galcanezumab (TA659) used similar regression models to justify use of differential utilities. Company's approach in this revised analysis addresses limitations of previous regression models and used separate regression models for baseline and post-baseline quality of life data.

ERG confirmed company revised model implemented committee's preferences from original topic for:

Lifetime horizon; post discontinuation assumptions (linear waning to baseline of BSC effect for responders, migraine frequency for all people on treatment returns to baseline on discontinuing); fremanezumab costs applied for 10% of people; positive stopping rule removed, no benefit over BSC for fremanezumab baseline utility, removed residual fremanezumab treatment effect in non-responders

Revised utility values

Section of the revised utility values table. Full table of utility values up to 28 monthly migraine days is on pages 13-14 of ERG critique, and reproduced in back up slide at the end of this presentation

MMD	Normal		
	Baseline	Placebo	Frem
0	0.762	0.767	0.790
1	0.746	0.752	0.776

ERG

Baseline utility values derived using baseline model, fremanezumab and placebo utility values derived using post-baseline model with treatment covariate.

E.g. baseline utility of 0.746 for MMD 1 derived: (0.762) Intercept + (-0.0162) Migraine days * (1) MMD = 0.746

Company

Face validity:

- Compared to Ara and Brazier general population utility (0.865) for population with similar baseline characteristics to modelled population.
  - Utility values used in model are all below this value.
  - Most comparable value to general population is for 0 MMD, but likely to still be experiencing some headache days and other migraine-related impacts even when experiencing no headaches meeting criteria for classification as migraine.
  - Modest size of difference between utility for 0 MMD health state in model and that in general population confirms general face validity of the derived utilities
- Lack of available published data for a directly comparable patient population (galcanezumab and erenumab utilities confidential so not available to company)

Model changes to match committee preferences

	Original model base case	Updated model base case	ERG view on change
Migraine type	Chronic migraine and episodic migraine	Episodic migraine, ≥3 prior treatment class failures	**Appropriate.** Fremanezumab accepted for use in chronic, review focuses on subpopulation with episodic migraine.
Patient distribution	Beta	Normal	**Appropriate.** Normal consistent with erenumab (TA682) and galcanezumab (TA659).
Health state utility values	Differential utilities based on 'off treatment' (BSC) and 'on treatment' (fremanezumab) values	Differential utilities which include baseline, BSC and fremanezumab values	**Appropriate.** Differential utilities considered appropriate for use in erenumab (TA682) and galcanezumab (TA659). By segregating utility into baseline and BSC, company appears to have addressed committee criticism (FAD section 3.20), thereby accounting for placebo effect i.e. placebo FOCUS data post-baseline applied to BSC patients whilst they are experiencing placebo effect.
Age related disutility	Not included	Included (based on Ara and Brazier)	**Appropriate.** Included in erenumab (TA682) and galcanezumab (TA659).

Cost effectiveness results

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY) frem. vs BSC
Company base case	[redacted]	[redacted]	£5,402	0.315	**£17,172**
Scenarios (company)					
1) ≥3 treatment class failures, beta distribution	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2) All patients, normal distribution	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3) All patients, beta distribution	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4) No baseline utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5) Previous baseline/off-treatment utility handling	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6) No age-related disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7) No differential utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Company also investigated impact these updated assumptions had in chronic migraine for completeness, all ICERs less than £10,000 per QALY.

ERG alternative scenarios

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY) frem. vs BSC
Company base case	[redacted]	[redacted]	£5,402	0.315	**£17,172**
Scenarios (ERG)					
8) 5% of people on fremanezumab require support to administer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9) Resource use (services) consumption rate inflation increased by 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10) Fremanezumab cycle dropout rate equal to erenumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11) Triptan daily med cost adjusted to include oral and injectable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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