Fremanezumab for preventing chronic and episodic migraine: Rapid review of TA631 [ID3952]

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Author Contributions:	
Brian O'Toole	Critical appraisal of the economic evidence, drafted economic sections of the report, writing and editorial input
Madhusubramanian Muthukumar	Drafted economic sections, reviewed the model, carried out scenario analysis, writing and editorial input
Louise Crathorne	Reviewed and commented on the final report.
G.J. Melendez-Torres	Reviewed and commented on the final report.

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Abbreviations

ACD	appraisal consultation document
CI	confidence interval
CS	company submission
ERG	Evidence Review Group
FAD	final appraisal determination
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
MMD	monthly migraine day
NA	not applicable
NICE	National Institute for Health and Care Excellence
NR	not reported
OWSA	one-way sensitivity analysis
PSA	probabilistic sensitivity analysis
QALY	quality adjusted life year
QoL	quality of life
TA	Technology Appraisal

1. INTRODUCTION

NICE has accepted fremanezumab for use in patients with chronic migraine (after three preventative treatments have failed) (TA631).[1] However, fremanezumab was not considered cost effective in patients with episodic migraine (after three preventative treatments have failed), therefore fremanezumab was not recommended for use in this subpopulation (see p20 and p21 of the ACD document for a list of the key cost effectiveness uncertainties).

In fremanezumab (TA631),[1] the ERG noted that utility values were considered to be a key area of uncertainty within the analysis and NICE concluded that differential utility values should not be included within the economic model. Several key concerns were noted i.e. the approach did not account for possible improvements in quality of life (QoL) as a result of the placebo effect, and the baseline (before treatment) fremanezumab utility values included a benefit over best supportive care. The concerns raised by NICE were therefore linked to how the company generated and applied 'on treatment' and 'off treatment' utility values in the model, as opposed to the objective inclusion of these values. The ERG noted that in recent publications for erenumab (TA682)[2] and galcanezumab (TA659),[3] differential utilities were considered reasonable for inclusion, as company assertions of improved QoL whilst 'on treatment' were supported by data from pivotal studies and/or regression analysis.

Due to the acceptance of differential utilities within erenumab (TA682)[2] and galcanezumab (TA659), the company has provided additional justification (as part of this rapid review) to support the use of differential utility values and conducted a regression analysis to derive monthly migraine days (MMD) health state utility values. Furthermore, the company has made several additional model alterations to address key criticisms raised by NICE, with respect to the handling of placebo effect and baseline utility values (as outlined in the ACD). The ERG also noted that the company made minor alterations to some model assumptions in order to align with assumptions used in erenumab (TA682)[2] and galcanezumab (TA659).[3]

This document provides an overview of the company's revised approach and outlines the ERG's comments on the appropriateness of the company's methodology and results.

2. NICE COMMITTEE PREFERENCES AND ADDITIONAL MODEL CHANGES

For completeness, NICE committee preferences as reported in the fremanezumab (TA631)[1] ACD and the committee papers are outlined below. Only preferences relevant to episodic migraine (with three or more prior treatment class failures) are noted. Table 1 further outlines whether the revised model takes each NICE committee preference into account.

Table 1: NICE committee preferences- fremanezumab (TA631)

	NICE preferences	**Company implemented NICE preference in revised model (Yes/No)**
Time horizon	Lifetime (58 years)	Yes, a lifetime horizon has been used
Post discontinuation assumptions	NICE committee agreed with ERG's scenario analysis which assumed that people reverted to baseline migraine days after fremanezumab discontinuation (from all causes), and the treatment effect for people whose migraine responded to BSC diminished to baseline over one year. Specifically, this included • Linear waning to baseline of BSC effect (responders) • Migraine frequency for all patients on treatment returns to baseline upon discontinuing (included in revised model)	Yes, both post discontinuation assumptions were applied.
Fremanezumab costs	Applying fremanezumab costs for 10% of people	Yes, this has been applied
Positive stopping rule	Remove	Yes, this has been removed
Additional 'on treatment' utility benefit	Remove	Yes, fremanezumab baseline utility is no longer associated with a benefit over BSC in the model.
Residual fremanezumab treatment effect in non-responders	Remove	Yes

2.1. Additional changes to the model post ACD and ERG commentary

The ERG noted that the company made additional changes to the model that were not part of NICE committee preferences. As noted previously, the company has subsequently made several additional updates to their model in order to be consistent with recently published advice for erenumab (TA682)[2] and galcanezumab (TA659),[3] and to focus on the relevant subpopulation of interest. Table 2 below lists additional changes to the model and provides ERG commentary on the appropriateness of these changes.

Table 2: Full list of model changes and ERG commentary

	Original model base case	Updated model base case	ERG comment on updated model
Migraine type	Chronic migraine and episodic migraine	Episodic migraine Patients with three or more prior treatment class failures	Appropriate Fremanezumab has been accepted for use in chronic migraine. This rapid review focuses on a subpopulation of patients with episodic migraine
Patient access scheme	[redacted]	Increased to [redacted]	The PAS discount was not explicitly reported in the company submission. The company reference the fremanezumab price in the previous TA (TA631){TA631} and the price of fremanezumab in the CS in this rapid review. The ERG calculated the reported discount using these values.
Patient distribution	Beta	Normal	Appropriate A normal distribution is consistent with erenumab (TA682)[2] and galcanezumab (TA659).[3]
Utilities			
Health state utility values	Differential utilities based on 'off treatment' (BSC) and 'on treatment'	Differential utilities which include	Appropriate Differential utility values were

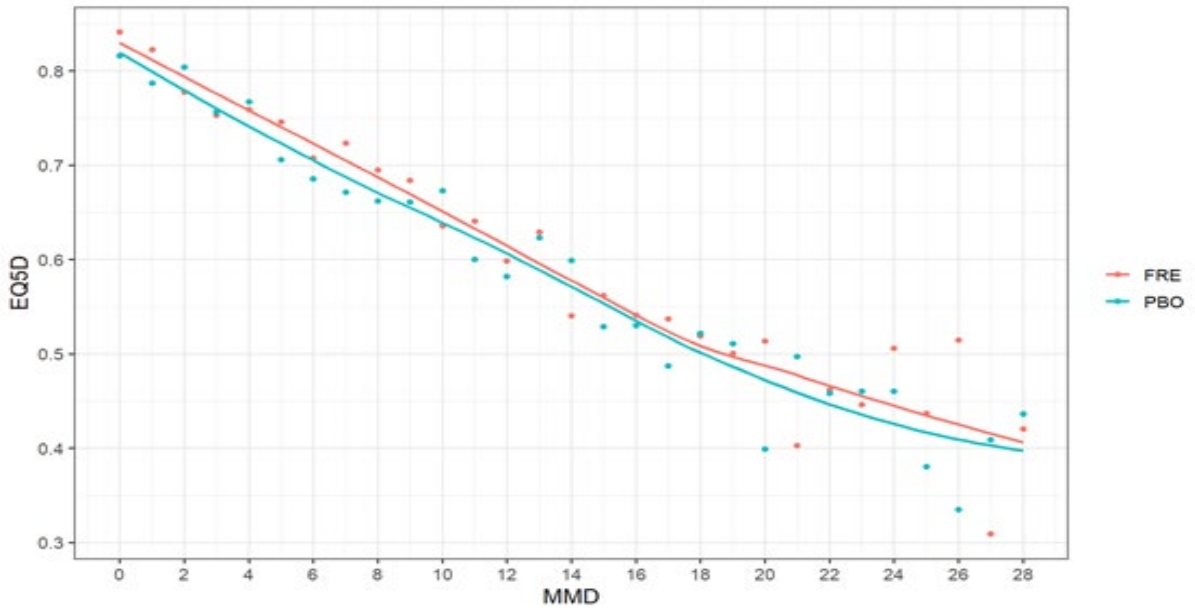
	Original model base case	Updated model base case	ERG comment on updated model
	(fremanezumab) values	baseline, BSC and fremanezumab values	considered acceptable for use in erenumab (TA682)[2] and galcanezumab (TA659).[3] Furthermore, by segregating utility into baseline and BSC, the company appears to have addressed NICE criticism 3:20 in the FAD thereby accounting for placebo effect i.e. placebo FOCUS data post-baseline are applied to BSC patients whilst they are experiencing a placebo effect
Age related disutility	Not included	Included (based on Ara and Brazier)[4]	Appropriate (included in erenumab (TA682)[2] and galcanezumab (TA659)[3]

Abbreviations: BSC, best supportive care; CS, company submission; ERG, Evidence Review Group; FAD, final appraisal determination; NICE, National Institute of Health and Care Excellence; PAS, patient access scheme; PASLU, patient access scheme liaison unit; TA, technology appraisal

3. ERG REVIEW OF THE COMPANY'S REVISED APPROACH TO ESTIMATING UTILITIES

The company provided additional visual evidence to support their decision to use differential utility values. Mean mapped EQ-5D scores were displayed in a scatter plot versus monthly migraine days (MMD), for both fremanezumab and placebo (see Figure 1). The data show that patients receiving fremanezumab tended to have a higher utility than BSC, when patients had the same MMD (albeit the difference in QoL reduced between MMD 10 to 18). Whilst Figure 1 usefully illustrates the impact of fremanezumab on HRQoL, compared to BSC, the ERG noted that these data were based on the full FOCUS population only and not the subpopulation of interest i.e. three or more prior treatment class failures population. Also, a measure of statistical significance was not provided.

Figure 1: Mean post-baseline EQ-5D score by MMD with LOESS fit for full FOCUS population



Abbreviations: FRE: fremanezumab; LOESS: locally estimated scatterplot smoothing; MMD: monthly migraine days; PBO: placebo

3.1. Approporiateness of the company's regression analysis to derive MMD utility values

The company conducted a regression analysis in patients with three or more prior preventative treatment class failures (using a normal distribution), to determine whether change in QoL can be attributed to fremanezumab. Two models were used, a baseline model which used only

baseline (Week 0) utility values and included MMD as the only covariate, and a post baseline model (utilities at Weeks 4 and 12) which was run in two forms i.e., with and without treatment type as a covariate. The company stated that the use of post-baseline model accounts for any placebo effect within the data. The ERG noted that although the company's submission provided details surrounding the regression modelling approach, a detailed statistical analysis plan was not provided.

Based on the results outlined in Table 3, fremanezumab appeared to be a significant covariate in the post baseline model ($p<0.001$), which may indicate that fremanezumab has a benefit beyond reducing MMD. The ERG noted that previous migraine appraisals including erenumab (TA682)[2] and galcanezumab (TA659)[3] have utilised similar regression models to justify the use of differential utilities. The ERG considered that the company's approach in this revised analysis addresses the limitations of previous regression models and used separate regression models for baseline and post-baseline quality of life data.

Overall, the company's regression analysis appeared to be reasonable and aligned with previous migraine appraisals.

Table 3. EQ-5D model with normal distribution in three or more previous treatment class failures population

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

Abbreviations: N numbers refer to number of observations included. AIC: Akaike information criterion; BIC: Bayesian information criterion; SE: standard error.

3.2. Face validity of revised utility values

Based on the regression models the company state that revised utilities were estimated for baseline, BSC and fremanezumab arms (see Table 4). The ERG noted that the baseline utility

values were derived using the baseline model and the fremanezumab and placebo utility values were derived using the post-baseline model with treatment covariate. For example, a baseline utility of 0.746 for MMD 1 was derived as follows: (0.762) Intercept + (-0.0162) Migraine days * (1) MMD = 0.746. Similarly, a placebo utility of 0.752 was derived as follows: 0.767 - 0.0144 * 1 + 0.0239 * 0 = 0.752 and a fremanezumab utility of 0.776 was derived as follows: 0.767 – 0.0144*1 + 0.0239 * 1 = 0.776.

Table 4: Utility values by monthly migraine days

MMD	Normal		
	Baseline	Placebo	Frem
0	0.762	0.767	0.790
1	0.746	0.752	0.776
2	0.723	0.738	0.762
3	0.713	0.723	0.747
4	0.697	0.709	0.733
5	0.681	0.694	0.718
6	0.665	0.680	0.704
7	0.649	0.666	0.689
8	0.632	0.651	0.675
9	0.616	0.637	0.661
10	0.600	0.622	0.646
11	0.584	0.608	0.632
12	0.568	0.593	0.617
13	0.551	0.579	0.603
14	0.535	0.564	0.588
15	0.519	0.550	0.574
16	0.503	0.536	0.560
17	0.487	0.521	0.545
18	0.470	0.507	0.531
19	0.454	0.492	0.516
20	0.438	0.478	0.502
21	0.422	0.463	0.487
22	0.406	0.449	0.473
23	0.389	0.435	0.459
24	0.373	0.420	0.444
25	0.357	0.406	0.430
26	0.341	0.391	0.415
27	0.325	0.377	0.401

MMD	Normal		
	Baseline	Placebo	Frem
28	0.308	0.362	0.386

Abbreviations: N numbers ref

3.3. Appropriateness of using a normal distribution

The company stated that a normal distribution was used in this revised analysis instead of the beta distribution (which was used originally in TA631),[1] given that recent appraisals for erenumab (TA682)[2] and galcanezumab (TA659)[3] used normal distributions in their regression models. The ERG acknowledged that the use of a normal distribution is consistent with aforementioned previous appraisals and therefore considered that it appropriate for use in this revised analysis. Furthermore, based on sensitivity analysis provided by the company, the use of a beta distribution did not have a material upward impact on results.

3.4. Appropriateness of including age related disutility

In fremanezumab (TA631)[1] NICE did not comment on the appropriateness of the exclusion of age related disutility. However in this rapid review the company opted to include age related disutilities based on published methodology from Ara and Brazier et al.[4] The ERG noted that the inclusion of age related disutility to be appropriate and is consistent with previous migraine appraisals including erenumab (TA682)[2] and galcanezumab (TA659).[3] Based on sensitivity analysis provided by the company, excluding age related disutility resulted in a slight decrease in the ICER. This is therefore not considered to be a key driver of cost effectiveness.

4. COMPANY REVISED BASE CASE AND SCENARIO ANALYSES RESULTS

Based on the company's updated model, fremanezumab resulted in an ICER of £17,172 compared to BSC, based on an incremental cost of £5,402 and an incremental QALY gain of 0.315 (Table 5). It should be noted that these results are based on NICE preferences (Table 1) and the additional model changes (Table 2).

Please note that in the company submission Table 7, a typo was noted in the BSC total costs [redacted] which has been corrected and aligned with the model in the table below (Table 5).

Table 5: Updated base case results (episodic migraine)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER versus BSC (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	£5,402	0.315	£17,172

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

4.1. Scenario analyses

To explore uncertainty surrounding key modelled parameters, the company provided scenario analyses (see Table 6). Scenarios included basing the analysis on the full FOCUS population using both a beta and normal distribution, excluding age related disutilities, no separation of BSC and baseline values, applying the same utilities to all states i.e., excluding differential utilities and using the previous approach to estimating utilities i.e., not separating baseline and 'off treatment' utilities' and not using off treatment utilities as baseline.

Table 6: Scenario analyses conducted by the company

Scenario number	Description
Scenario 1	Updated base case with alternative utility set, three or more treatment class failures population modelled with beta distribution
Scenario 2	Updated base case with alternative utility set, full FOCUS population with normal distribution
Scenario 3	Updated base case with alternative utility set, full FOCUS population with beta distribution
Scenario 4	Updated base case without separation of baseline and off-treatment utilities
Scenario 5	Updated base case without separation of baseline and off-treatment utilities and without off-treatment utilities used as baseline (equivalent to previous utility handing within the fremanezumab model)

Scenario number	Description
Scenario 6	Updated base case without age-related disutilities
Scenario 7	Updated base case without differential utilities (*i.e.* same utilities used for all states [based on fremanezumab three or more treatment class failures population modelled with normal distribution])

Table 7: Company scenario analyses results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus BSC (£/QALY)
Updated base case					
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	£5,402	0.315	£17,172
Scenario 1 (3+ failures with beta distribution)					
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2 (all patients with normal distribution)					
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3 (all patients with beta distribution)					
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4 (no baseline utilities)					
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5 (previous baseline/off-treatment utility handling)					
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6 (no age-related disutilities)					
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7 (no differential utilities)					
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

Based on these analyses, results appeared to be relatively robust to changes in most model parameters (with six out of seven scenarios resulting in ICERs <£20,000). However, the ERG noted that results were somewhat sensitive to Scenario 7 whereby differential utilities were not used i.e. for this scenario the company applied fremanezumab health state utilities to BSC and Baseline arms. Although this analysis resulted in an increased ICER, fremanezumab remained [redacted]. Overall, the ERG considered the scenario analyses submitted by the company to be largely appropriate.

Regarding treatment waning, the company's submission mentioned that a waning effect has not been included in the modelling due to non-availability of clinical trial wash out data as applied in the galcanezumab appraisal (TA 659).[3] Though this is a limitation related to data, the ERG noted that this is a non-issue as far as the current model update is concerned due to the following reasons:

- Waning scenarios are applied only for chronic migraine and were not conducted for episodic migraine in the original appraisal; and
- Waning scenarios are linked to the positive stopping rule (PSR); however, the committee preference is to remove PSR.

4.2. Model validation and face validity check verification

The ERG validated the changes made by the company in the updated model and found a #REF! error in 'Demographics & Costs' sheet (cell H39) which impacted the additional ERG Scenario 5. This error was fixed and the additional ERG Scenario 5 was run subsequently.

5. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

For completeness the ERG ran the additional scenario analyses applicable to the episodic migraine population and the results are presented below (Table 8).

Table 8. Alternative ERG scenarios (applicable for episodic migraine)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER Frem versus BSC (£/QALY)
Base case					
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	£5,402	0.315	£17,172
Scenario 4: 5% of Frem patients require support to administer					
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: Resource use (services) consumption rate inflation increased by 20%					
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7: Frem cycle dropout rate equal to erenumab					
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8: Triptan daily med cost adjusted to include oral and injectable					
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abrbeviations: BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

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