NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Fremanezumab for preventing migraine (Rapid Review of TA631 [ID3952])

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Fremanezumab for preventing migraine (Rapid Review of TA631 [ID3952])

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from **Teva**

2. **Evidence Review Group report** prepared by **Peninsula Technology Assessment Group (PenTAG)**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fremanezumab for preventing chronic and episodic migraine [TA631/ID3952]

Company additional evidence submission

September 2021

File name	Version	Contains confidential information	Date
ID3952_fremanezumab_submission_Sept 2021_1.1_redacted	**1.1**	**No (redacted)**	**20 October 2021**

Contents

Tables and figures

1 Background

Following publication of the National Institute for Health and Care Excellence (NICE) appraisal of fremanezumab (TA631),[1] the more recently completed appraisals of galcanezumab (TA659)[2] and erenumab (TA682)[3] have reconsidered the evidence around utility values to be used within economic modelling. This evidence relates to what is described as 'differential utilities', a term which is used here to refer to the use of different utility values for patients on- and off-treatment. Within the economic modelling of migraine, utilities have been linked to the monthly migraine days (MMDs) experienced by patients,[4] and the application of differential utilities has been implemented in order to capture quality of life (QoL) benefits from treatment beyond those capture by reductions in MMDs.

Within the appraisals of galcanezumab and erenumab, NICE concluded that differential utilities should be included within the economic modelling of migraine.[2,3] Compared to the appraisal of fremanezumab, where differential utilities were not previously accepted by the committee, this has led to a significant change in assumptions within the economic modelling and cost-effectiveness results. To allow a fair and consistent analysis across appraisals, NICE has provided Teva with the opportunity to submit additional evidence for fremanezumab focussing on differential utilities. The economic analyses presented herein will focus on EM, as this is the population for which fremanezumab is not currently recommended by NICE.

In addition, there have been a small number of other differences in the committee's preferred assumptions from the more recent galcanezumab and erenumab appraisals. Teva has conducted further analyses to match these updated assumptions and to explore their impact on the cost-effectiveness results. This will provide analyses for fremanezumab in EM conducted using the most consistent and rigorous set of assumptions possible.[2,3]

2 Differential utilities

2.1 Clinical rationale

Teva has been clear throughout all submissions to NICE that there is a strong rationale for the use of differential utilities within the economic modelling. This rationale is rooted in the clinical experience of patients with migraine and the ability to quantify the QoL experienced by these patients. The main points in this rationale will be summarised below.

- It is widely accepted that migraine is a very burdensome condition, and this has been noted by NICE during its recent appraisals in migraine.[1,2,3] Patients are extremely disabled during migraine attacks, but will also experience a reduction in QoL and depression and/or anxiety during and in between attacks (the interictal period).[5,6] QoL in the interictal period can also be negatively impacted by the fear of further migraine attacks[6]
    - This highlights the importance of measuring disability related (*e.g.* HIT-6 [Headache Impact Test]/MIDAS [Migraine Disability Assessment]) and QoL (*e.g.* MSQoL [Migraine-Specific Quality of Life Questionnaire]) outcomes during the assessment of migraine preventive treatments
    - It also highlights that QoL can be impacted by migraine both during and between migraine attacks, and, therefore, that QoL impairments extend beyond MMDs alone
- The treatment effect incorporated into the differential utilities reflect additional benefits of migraine treatment not captured within changes in MMD. This includes improvements in disability levels, nausea and/or vomiting, photophobia, phonophobia, the reduction in the severity and duration of migraine attacks, and the reduction in recovery time following a migraine attack during the interictal period
- Teva has received advice from clinical experts that states that improvements in utilities are well known to exceed reductions in MMDs, with this measure unable to capture the full burden of migraine in terms of duration, severity and all associated factors that can influence QoL

2.2 Updated analyses

2.2.1 Introduction and methodology

The final appraisal document (FAD) for fremanezumab noted that the analysis on utilities conducted at that time "*did not account for possible improvements in quality of life related to being included in a clinical trial (placebo effect)*." After the conclusion of the fremanezumab appraisal, analyses presented by galcanezumab and erenumab to NICE to support the use of differential utilities were able to account for any placebo effect in the data by having utility scores for treated and untreated patients analysed separately (*i.e.* baseline utility values were analysed separately). This approach was accepted by NICE and led to the inclusion of differential utilities based on the strength of this evidence. The analyses presented here aim to provide similar evidence for differential utilities with fremanezumab and to account for any placebo effect present.

Upon inspection of the details from the erenumab and galcanezumab appraisals,[2,3] it has been noted by Teva that both of these appraisals utilised a normal distribution rather than a beta distribution (as was used previously for fremanezumab due to this giving a better fit to the FOCUS data) within their regression models. Additionally, NICE has preferred utility data from the population of interest for these appraisals (patients with an inadequate response to three or more previous migraine preventive treatments). The use of this more targeted group rather than the full clinical trial populations reduces the sample size and hence the statistical power in analyses, but provides the most relevant data for the population of interest under these NICE appraisals. To summarise, the analyses previously presented by Teva utilised beta distributions and the full FOCUS population (2-4 treatment class failures). To provide the most consistent data compared to that produced in the other appraisals, our primary updated analyses have now been conducted matching NICE's preferences from the other migraine appraisals, namely a normal distribution and using the appraisal target population (inadequate response to three or more previous migraine preventive treatment classes). To allow continuity with the previous utilities presented for fremanezumab, analyses using a beta distribution and the full FOCUS population have also been conducted and reported.

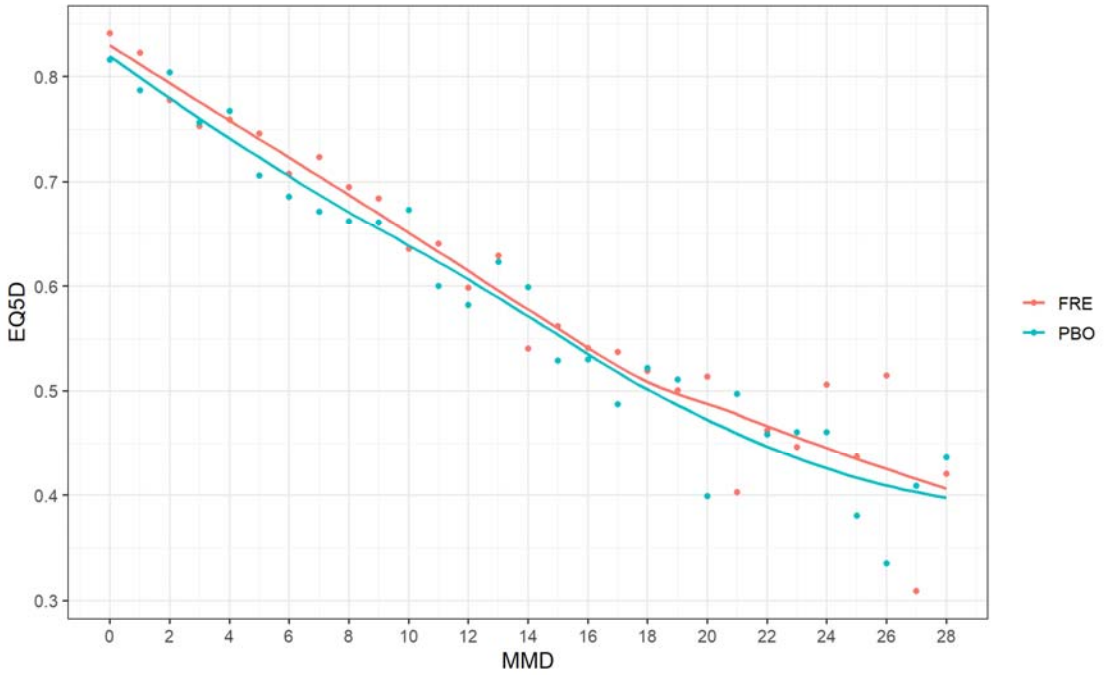
In brief, EQ-5D-3L data were used which were derived from the FOCUS clinical trial MSQoL data that mapped with the algorithm of Gillard *et al*.[7] All analyses were performed in R version 3.6.1 and all regression models were fit using the gamlss function in the GAMLSS (Generalized Additive Model for Location, Scale and Shape) package in R. The regression used a varying-intercept model, with the intercept varying by patient and an unstructured covariance matrix. Two separate models were used:

- Baseline model - used only baseline (week 0) utility values, and included MMD as the only covariate
- Post-baseline model - used post-baseline data (weeks 4 and 12); this model was run in two forms with covariates of: 1) MMD; or 2) MMD and treatment type (fremanezumab or placebo); *i.e.* models were analysed with and without treatment type as a covariate

2.2.2 FOCUS trial data

To provide an initial illustration of the effect of differential utilities within the FOCUS clinical trial data, an analysis was conducted on the mapped EQ-5D data. This consisted of producing a scatterplot of mean EQ-5D score *versus* MMD for both fremanezumab and placebo, with a LOESS (locally estimated scatterplot smoothing) fit line added. Using data from the full FOCUS population, it clearly demonstrates that fremanezumab treated patients had higher utilities at a given MMD level than placebo patients (Figure 1). This plot gives a good illustration of the utility treatment-effect within the FOCUS trial data after minimal processing, albeit does not provide a measure of statistical significance. Therefore, regression modelling was conducted to investigate this effect fully.

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



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

2.2.3 Modelling results

As has been mentioned above, the analyses previously conducted for fremanezumab focussed on the full FOCUS trial population and utilised a beta distribution within the modelling. However, these assumptions have been updated in order to best match the committee's preferences within the galcanezumab and erenumab appraisals. Therefore, the analysis is presented for the three or more prior treatment class failure population using a normal distribution. For completeness, results for the full FOCUS population and utilising the previously used beta distribution are also presented below.

2.2.3.1 Patients with failure of three or more prior preventive migraine treatment classes

The most relevant data based on previous NICE appraisals has been determined to be the three or more prior treatment class failures using a normal distribution. These results are presented in Table 1 and show that fremanezumab treatment was a significant covariate within the post-baseline model ($p<0.001$). The use of this post-

baseline model accounts for any placebo effect seen within the data and gives confidence that this is a true effect caused by fremanezumab treatment. This provides strong evidence that differential utilities are necessary to capture the additional benefits of fremanezumab treatment, and that this effect is significant within the most relevant patient population. It is encouraging that this effect can be demonstrated in this subgroup population which has a reduced statistical power compared to the full FOCUS trial population.

Table 1 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

N numbers refer to number of observations included (see Appendix for details). AIC: Akaike information criterion; BIC: Bayesian information criterion; SE: standard error.

For completeness in relation to the previously utilised beta distributions, Table 2 shows the same analyses conducted using a beta distribution. These results show a strong similarity to those produced with a normal distribution, with fremanezumab being a significant covariate within the post-baseline model ($p<0.001$).

Table 2 EQ-5D model with beta distribution in three or more previous treatment class failures population

Coefficient	Estimate	SE	p-value
Baseline model (N = 416; BIC = -410)			
Intercept	1.1327	0.0807	<0.001
Migraine days	-0.0651	0.0054	<0.001
Post-baseline model with treatment covariate (N = 818; AIC = -1574; BIC = -94)			
Intercept	1.2452	0.0296	<0.001
Migraine days	-0.0635	0.0015	<0.001
Fremanezumab	0.0958	0.0234	<0.001
Post-baseline model without treatment covariate (N = 818; AIC = -1574; BIC = -97)			
Intercept	1.3221	0.0222	<0.001
Migraine days	-0.0645	0.0015	<0.001

N numbers refer to number of observations included (see Appendix for details). AIC: Akaike information criterion; BIC: Bayesian information criterion; SE: standard error.

2.2.3.2 All FOCUS patients

Analyses have also been conducted in the full FOCUS population, which matches the population utilised in previous utility analyses for fremanezumab. These analyses are presented in Table 3 for normal distribution and in Table 4 for a beta distribution. These data show that, in both of these analyses, fremanezumab was a significant covariate within the post-baseline model (p<0.001).

Table 3 EQ-5D model with normal distribution in all FOCUS population

Coefficient	Estimate	SE	p-value
Baseline model (N = 827; BIC = -831)			
Intercept	0.7784	0.0129	<0.001
Migraine days	-0.0163	0.0010	<0.001
Post-baseline model with treatment covariate (N = 1630; AIC = -3081; BIC = 483)			
Intercept	0.7818	0.0040	<0.001
Migraine days	-0.0145	0.0002	<0.001
Fremanezumab	0.0196	0.0034	<0.001
Post-baseline model without treatment covariate (N = 1630; AIC = -3079; BIC = 479)			
Intercept	0.7973	0.0028	<0.001
Migraine days	-0.0147	0.0002	<0.001

N numbers refer to number of observations included (see Appendix for details). AIC: Akaike information criterion; BIC: Bayesian information criterion; SE: standard error.

Table 4 EQ-5D model with beta distribution in all FOCUS population

Coefficient	Estimate	SE	p-value
Baseline model (N = 827; BIC = -934)			
Intercept	1.2053	0.0533	<0.001
Migraine days	-0.0657	0.0038	<0.001
Post-baseline model with treatment covariate (N = 1630; AIC = -3396; BIC = 52)			
Intercept	1.3144	0.0188	<0.001
Migraine days	-0.0642	0.0010	<0.001
Fremanezumab	0.0843	0.0157	<0.001
Post-baseline model without treatment covariate (N = 1630; AIC = -3395; BIC = 49)			
Intercept	1.3809	0.0137	<0.001
Migraine days	-0.0652	0.0010	<0.001

N numbers refer to number of observations included (see Appendix for details). AIC: Akaike information criterion; BIC: Bayesian information criterion; SE: standard error.

2.2.4 Utility values utilised in economic modelling

Using the above-described regression models, utilities for each MMD state were derived for use in the economic model. These utilities are reproduced in Table 5 for the three or more prior treatment class failures population and Table 6 for the full FOCUS population.

Table 5 Utility values derived from regression models for three or more prior treatment class failures population

MMD	Normal			Beta		
	Baseline	Placebo	Frem	Baseline	Placebo	Frem
0	0.762	0.767	0.790	0.744	0.765	0.782
1	0.746	0.752	0.776	0.731	0.754	0.771
2	0.723	0.738	0.762	0.718	0.741	0.760
3	0.713	0.723	0.747	0.705	0.729	0.748
4	0.697	0.709	0.733	0.691	0.716	0.735
5	0.681	0.694	0.718	0.676	0.702	0.722
6	0.665	0.680	0.704	0.661	0.689	0.709
7	0.649	0.666	0.689	0.646	0.675	0.696
8	0.632	0.651	0.675	0.631	0.660	0.682
9	0.616	0.637	0.661	0.615	0.646	0.668
10	0.600	0.622	0.646	0.599	0.630	0.653
11	0.584	0.608	0.632	0.583	0.615	0.638
12	0.568	0.593	0.617	0.566	0.600	0.623
13	0.551	0.579	0.603	0.550	0.584	0.607
14	0.535	0.564	0.588	0.533	0.568	0.592

MMD	Normal			Beta		
	Baseline	Placebo	Frem	Baseline	Placebo	Frem
15	0.519	0.550	0.574	0.516	0.551	0.576
16	0.503	0.536	0.560	0.499	0.535	0.560
17	0.487	0.521	0.545	0.482	0.519	0.543
18	0.470	0.507	0.531	0.465	0.502	0.527
19	0.454	0.492	0.516	0.448	0.485	0.510
20	0.438	0.478	0.502	0.431	0.469	0.494
21	0.422	0.463	0.487	0.414	0.452	0.477
22	0.406	0.449	0.473	0.397	0.435	0.460
23	0.389	0.435	0.459	0.381	0.419	0.444
24	0.373	0.420	0.444	0.364	0.402	0.427
25	0.357	0.406	0.430	0.348	0.386	0.411
26	0.341	0.391	0.415	0.332	0.370	0.394
27	0.325	0.377	0.401	0.316	0.354	0.378
28	0.308	0.362	0.386	0.301	0.339	0.362

Frem: fremanezumab.

Table 6 Utility values derived from regression models for full FOCUS population

MMD	Normal			Beta		
	Baseline	Placebo	Frem	Baseline	Placebo	Frem
0	0.778	0.782	0.801	0.758	0.778	0.792
1	0.762	0.767	0.787	0.745	0.766	0.781
2	0.746	0.753	0.772	0.733	0.754	0.770
3	0.730	0.738	0.758	0.719	0.742	0.758
4	0.713	0.724	0.744	0.706	0.729	0.746
5	0.697	0.709	0.729	0.692	0.716	0.733
6	0.681	0.695	0.715	0.677	0.703	0.720
7	0.664	0.681	0.700	0.662	0.689	0.707
8	0.648	0.666	0.686	0.647	0.675	0.693
9	0.632	0.652	0.671	0.631	0.660	0.679
10	0.615	0.637	0.657	0.616	0.645	0.665
11	0.599	0.623	0.642	0.599	0.630	0.650
12	0.583	0.608	0.628	0.583	0.614	0.635
13	0.567	0.594	0.613	0.566	0.598	0.619
14	0.550	0.579	0.599	0.550	0.582	0.603
15	0.534	0.565	0.584	0.533	0.566	0.587
16	0.518	0.550	0.570	0.516	0.550	0.571
17	0.501	0.536	0.556	0.498	0.533	0.555
18	0.485	0.521	0.541	0.481	0.516	0.538
19	0.469	0.507	0.527	0.464	0.500	0.522

MMD	Normal			Beta		
	Baseline	Placebo	Frem	Baseline	Placebo	Frem
20	0.452	0.493	0.512	0.447	0.483	0.505
21	0.436	0.478	0.498	0.430	0.466	0.488
22	0.420	0.464	0.483	0.413	0.449	0.471
23	0.404	0.449	0.469	0.396	0.432	0.454
24	0.387	0.435	0.454	0.379	0.416	0.437
25	0.371	0.420	0.440	0.362	0.399	0.421
26	0.355	0.406	0.425	0.346	0.383	0.404
27	0.338	0.391	0.411	0.330	0.366	0.388
28	0.322	0.377	0.396	0.314	0.350	0.371

Frem: fremanezumab.

2.2.4.1 Face validity

The face validity of these utility values has been assessed in relation to external sources. Firstly, the validity in relation to the utilities of the general population was assessed using data as reported by Ara and Brazier.[8] Based on the data from this publication and the baseline characteristics of the modelled population (based on the demographics of the FOCUS clinical trial – average age of 46.8 years and 84% female), the utility of the general population would be expected to be around 0.865. As the utilities used within the model are for a diseased health state, the utility values used within the model are all below this value for the general population. The most comparable value to the general population is the 0 MMD health state as this includes patients with the lowest disease activity modelled. However, any comparison here must consider that although the patients in the 0 MMD health state have no monthly migraine days, by definition, these patients are likely to still be experiencing some headache days and other impacts related to migraine even when they are experiencing no headaches that meet the criteria for classification as migraine. In addition, co-morbidities are common for patients with migraine and these may continue to impact QoL even when MMDs have reduced to zero. Both of these issues were noted within the ERG report for the galcanezumab appraisal, where the external validity of the utilities used in that appraisal were assessed.[2] These effects make the face validity harder to assess compared to the general population. That said, the modest size of the difference between the 0 MMD health state in our model and that expected in the general population confirms the general face validity of the derived utilities, especially given the justifications outlined above.

When turning to assess the face validity of theses utilities within a directly comparable patient population, the ability to do this is limited by a lack of available published data. There have been three other NICE appraisals focussed within this patient population of interest;[2,3,9] however, the utility values used within the galcanezumab and erenumab appraisals were designated as confidential meaning that they are not available to Teva for use in this comparison.[2,3] The other NICE appraisal conducted in migraine was that of onabotulinumtoxin A,[9] with the utilities from this appraisal also being published by Batty et al.[10] These utilities were reported only within bands of MMDs and not for individual MMD values and (in the three or more prior treatment group) show a range of utilities of 0.691 to 0.461.[9,10] These values are both lower than the values derived from the FOCUS study. However, the values derived for the onabotulinumtoxin A appraisal did show some unexpected features, most notably with the utilities being lower in the 20-23 MMD group than in the 24-28 MMD group in the treated population.[9,10] This effect was partly explained by the low N numbers in that analysis.[9] This factor combined with the age of these data (PREEMPT studies were utilised which were completed in 2008)[9,11,12] make it hard to draw conclusions when comparing to the FOCUS derived utility values. The other identified available publication was one that includes utilities for erenumab; however, this was in a population that have experienced fewer previous treatment failures and so is not directly comparable.[13] The utility values in this publication were reported for all MMD states between 0 and 28, and had a range of 0.823 to 0.324.[13] In comparison, the numbers reported in our analyses were lower for the 0 MMD health state and slightly higher for the 28 MMD health state. As the FOCUS trial included patients with multiple previous preventive treatment class failures, it might be expected that the utilities would be lower than those in a more general migraine population. This was generally observed, but with small differences between the two utility sets. Overall, these results confirm the face validity of the utilities derived from the FOCUS as the utility values were broadly comparable to those previously reported.[13]

2.3 Correlation analysis

The FOCUS clinical trial provided evidence of the benefits of fremanezumab using a number of measures in order to try and demonstrate the full value of this treatment on both migraine attacks (with change from baseline in MMDs being the primary endpoint for this study) and the wider impact of migraine on patients through the use of a number of patient-reported outcome (PRO) measures. The evidence previously presented to NICE showed that fremanezumab was able to provide significant improvements in these PRO measures when compared to placebo. However, to simplify the economic analysis, this has been based primarily on changes in MMDs (as the primary outcome of the clinical trial data). There is a risk in these analyses that this approach may not fully capture the entirety of the impact of migraine, such as that measured through PROs, and any impact on the interictal period. To investigate this further, correlation analyses have been conducted to explore how well changes in MMDs are likely to have been able to capture any wider impacts of treatment, especially on the interictal period where MMDs do not provide any coverage (being an aggregate measure of the ictal period).

A correlation analysis was conducted between migraine/headache days/hours, migraine symptoms and PRO instruments measured within the FOCUS trial utilising Spearman's Rank Correlation Coefficient. Spearman's correlation is similar to Pearson's correlation, but instead of measuring the strength and direction of a linear relationship between two variables, Spearman's correlation determines the strength and direction of a monotonic relationship between two variables.

The following ictal measures and PRO instruments were included this analysis:

1. Monthly migraine days
2. Monthly headache days
3. Headache Impact Test (HIT-6)
4. Migraine Disability Assessment (MIDAS)
5. Acute medication use days
6. Nausea/vomiting days
7. Photophobia/phonophobia days
8. Headache hours

9. Migraine-Specific Quality of Life Questionnaire (MSQ)
10. Work Productivity and Activity Impairment (WPAI) Questionnaire
11. Patient Global Impression of Change Scale (PGIC)
12. 9-Item Patient Health Questionnaire (PHQ-9)

The results of these correlation analysis are presented in Figure 2 and Figure 3. These demonstrate that most measures have negligible to moderate correlations to MMDs. The measures with the highest correlation to MMDs are those that are alternative gauges of the ictal period (and hence these correlations would be expected). Overall, the strength of correlations suggests that MMD alone is insufficient to capture the full QoL burden inflicted on patients by migraine. The correlation between the ictal period measures implies that the QoL and PRO measures show meaningful influence from the interictal period. This strongly supports the contention that the full improvement in QoL due to preventive treatment (particularly effects in the interictal period) are not fully captured when utilities are driven by MMDs alone. This disparity in the correlation pattern of baseline outcome measures with MMD (Figure 2) and week 12 outcome measures with MMD (Figure 3) further strengthens the rationale for the use of differential utilities within the economic modelling.

Figure 2 Correlations between outcomes in FOCUS data at baseline

	MMD	MHD	HIT6	MIDAS	Acute Med	Nausea-Vomit	Photo-Phono	HH	MSQoL EMOT	MSQoL PREV	MSQoL REST	MSQoL TOT	WPAI Absent	WPAI Present	WPAI Overall
MHD	0.88														
HIT6	0.20	0.16													
MIDAS	0.37	0.33	0.53												
Acute Med	0.62	0.63	0.06	0.12											
Nausea-Vomit	0.30	0.23	0.30	0.34	0.08										
Photo-Phono	0.58	0.45	0.33	0.40	0.25	0.36									
HH	0.58	0.67	0.23	0.41	0.23	0.33	0.44								
MSQoL EMOT	-0.22	-0.19	-0.49	-0.45	-0.05	-0.27	-0.25	-0.25							
MSQoL PREV	-0.30	-0.27	-0.59	-0.60	-0.07	-0.34	-0.38	-0.35	0.58						
MSQoL REST	-0.34	-0.31	-0.65	-0.65	-0.09	-0.35	-0.41	-0.42	0.63	0.79					
MSQoL TOT	-0.31	-0.28	-0.64	-0.63	-0.07	-0.36	-0.38	-0.37	0.86	0.87	0.89				
WPAI Absent	0.18	0.17	0.28	0.42	0.06	0.23	0.23	0.25	-0.30	-0.54	-0.43	-0.47			
WPAI Present	0.23	0.17	0.45	0.49	0.06	0.27	0.31	0.25	-0.40	-0.53	-0.57	-0.57	0.48		
WPAI Overall	0.23	0.18	0.45	0.53	0.06	0.29	0.32	0.28	-0.42	-0.59	-0.60	-0.60	0.70	0.94	
PHQ9	0.30	0.28	0.43	0.41	0.14	0.24	0.33	0.31	-0.50	-0.47	-0.54	-0.56	0.32	0.39	0.41

Negligible (>0 to ≤0.3)
Low (>0.3 to ≤0.5)
Moderate (>0.5 to ≤0.7)
High (>0.7)

Absent: absenteeism; Acute Med: acute medication use; EMOT: emotional; HH: headache hours; HIT6: Headache Impact Test; MHD: monthly headache days; MIDAS: Migraine Disability Assessment; MMD: monthly migraine days; MSQoL: Migraine-Specific Quality of Life Questionnaire; Photo-Phono: photophobia and phonophobia; PHQ9: Patient Health Questionnaire; Present: presenteeism; PREV: preventive; REST: restrictive; TOT: total; WPAI: Work Productivity and Activity Impairment.

Figure 3 Correlations between outcomes in FOCUS data at week 12

	MMD	MHD	HIT6	MIDAS	Acute Med	Nausea-Vomit	Photo-Phono	HH	MSQoL EMOT	MSQoL PREV	MSQoL REST	MSQoL TOT	WPAI Absent	WPAI Present	WPAI Overall	PGIC
MHD	0.92															
HIT6	0.56	0.53														
MIDAS	0.60	0.60	0.73													
Acute Med	0.71	0.71	0.40	0.40												
Nausea-Vomit	0.45	0.40	0.41	0.43	0.29											
Photo-Phono	0.64	0.53	0.50	0.55	0.36	0.43										
HH	0.77	0.84	0.54	0.64	0.49	0.48	0.56									
MSQoL EMOT	-0.56	-0.53	-0.73	-0.64	-0.40	-0.40	-0.44	-0.52								
MSQoL PREV	-0.57	-0.55	-0.77	-0.76	-0.39	-0.41	-0.51	-0.58	0.72							
MSQoL REST	-0.64	-0.62	-0.84	-0.80	-0.44	-0.43	-0.54	-0.63	0.76	0.86						
MSQoL TOT	-0.64	-0.61	-0.84	-0.79	-0.44	-0.44	-0.54	-0.62	0.89	0.92	0.95					
WPAI Absent	0.31	0.31	0.42	0.48	0.15	0.26	0.27	0.36	-0.44	-0.51	-0.46	-0.50				
WPAI Present	0.48	0.48	0.63	0.65	0.32	0.40	0.39	0.51	-0.58	-0.64	-0.67	-0.68	0.50			
WPAI Overall	0.49	0.48	0.63	0.66	0.32	0.39	0.39	0.52	-0.59	-0.67	-0.68	-0.70	0.65	0.97		
PGIC	-0.64	-0.65	-0.60	-0.51	-0.54	-0.29	-0.34	-0.54	0.55	0.51	0.60	0.61	-0.26	-0.43	-0.43	
PHQ9	0.48	0.48	0.61	0.60	0.33	0.34	0.36	0.46	-0.62	-0.60	-0.66	-0.68	0.39	0.57	0.57	-0.44

Negligible (>0 to ≤0.3)
Low (>0.3 to ≤0.5)
Moderate (>0.5 to ≤0.7)
High (>0.7)

Absent: absenteeism; Acute Med: acute medication use; EMOT: emotional; HH: headache hours; HIT6: Headache Impact Test; MHD: monthly headache days; MIDAS: Migraine Disability Assessment; MMD: monthly migraine days; MSQoL: Migraine-Specific Quality of Life Questionnaire; PGIC: Patient Global Impression of Change; Photo-Phono: photophobia and phonophobia; PHQ9: Patient Health Questionnaire; Present: presenteeism; PREV: preventive; REST: restrictive; TOT: total; WPAI: Work Productivity and Activity Impairment.

2.4 Summary

The evidence presented above provides a strong rationale for the use of differential utilities within the economic modelling. The key points are:

- Migraine is a highly burdensome condition, with impacts on QoL during migraine attacks and between attacks (the interictal period)
- Differential utilities reflect additional benefits of migraine treatment not captured within MMD changes; including improvements in disability levels, nausea and/or vomiting, photophobia, phonophobia, the reduction in the severity and duration of migraine attacks, and the reduction in recovery time following a migraine attack
- Clinical experts agree that improvements in QoL often exceed reductions in MMDs
- Utilities analysis conducted on the FOCUS clinical trial data shows a clear and significant treatment effect for fremanezumab. Patients with a given number of MMDs demonstrated a higher QoL when being treated with fremanezumab compared to placebo
- Differential utility values incorporated into the economic model come directly from the FOCUS clinical trial and are the most robust data to utilise within the model. These data show a real effect on QoL above improvements in MMDs following treatment with fremanezumab
- Similar effects have been demonstrated within QoL data from a number of clinical trials in migraine, with benefits from treatment in patients with similar migraine/headache day frequencies. This effect has been reported for both erenumab,[13] and onabotulinumtoxin A.[10] Both of these studies are focussed on economic modelling and utilise data from the key clinical trials of these treatments. In both cases, these analyses resulted in the use of differential utilities based on the available clinical data
- The correlation analyses revealed that negligible to moderate correlations exist between MMDs and PRO instruments, which suggests that MMDs alone are insufficient to capture the changes in QoL burden for patients with migraine receiving preventive treatment

- Previous NICE appraisals of galcanezumab and erenumab have concluded that there is a strong justification for the use of differential utilities and have used this methodology within their economic modelling[2,3]

3 Updated cost-effectiveness results

3.1 Changes in modelling assumptions

Since the previously considered cost-effectiveness results produced for fremanezumab, there have been some changes in assumptions preferred by NICE and that has subsequently been utilised in the galcanezumab and erenumab appraisals.[2,3] These changes in assumptions can be summarised as:

- The use of differential utilities
- The use of baseline *versus* treated utilities
- Age-related disutility based on Ara and Brazier[8]
- Waning of treatment effect after treatment discontinuation

In the section above the evidence for differential utilities for fremanezumab has been presented. Given the strong evidence presented for this effect, differential utilities will be included in the updated economic analyses. These analyses will also include an updated treatment of baseline *versus* treated utilities to account for any placebo effect in utilities; this will match the approach taken in other NICE appraisals. Age-related disutilities are not a factor that was considered previously within the fremanezumab appraisal. Therefore, this factor will also be included into these updated analyses. The last of these differences, the waning of treatment effect after treatment discontinuation, was applied in the galcanezumab appraisal based on clinical trial wash-out data.[2] However, no such data are currently available to demonstrate a similar effect in fremanezumab and hence this effect has not been included in the modelling.

In addition to the above factors, Teva has included a revised Patient Access Scheme (PAS) within this modelling. Teva has applied for an update to its current PAS, which has been approved by PASLU for use associated with this evidence submission. The modelling results presented below include this PAS which makes fremanezumab available [redacted].

In addition to the updated PAS price, the following changes have been made from the previous committee preferred case as outlined in the fremanezumab FAD:

A. Inclusion of updated utilities based on differential utility analysis as reported above (with the application of differential utilities restored in the model) and using utilities derived from the three or more prior treatment class failures population with a normal distribution
B. Off-treatment utilities used at baseline (correction of a coding error that led to the on-treatment utility value being applied at baseline in actively treated patients)
C. Age-related disutilities applied (using the method of Ara and Brazier,[8] applied in the same manner as in the galcanezumab and erenumab appraisals)[2,3]
D. Separation of baseline and off-treatment utilities (this added baseline utility values to the model that were applied to all baseline states in the model, fremanezumab treated patients who had discontinued treatment and best supportive care [BSC] patients who had baseline MMD values [*i.e.* these were applied after the placebo effect had dissipated and when the patients were receiving no benefit from BSC treatment]). Under this scenario, the utilities labelled as 'off-treatment' within the model are the utilities derived from the placebo FOCUS data post-baseline and are applied to BSC patients whilst they are experiencing a placebo effect

3.2 Results of updated cost-effectiveness analysis

The results of the updated base case analysis are presented in Table 7. These results show that fremanezumab is highly cost effective in this scenario with an incremental cost-effectiveness ratio (ICER) of less than £20,000 *per* quality-adjusted life year (QALY).

Table 7 Updated base case results in 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**

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

To investigate the impact that each of these changed assumptions makes on the ICER value, a series of scenario analyses were conducted. The details on these scenarios are detailed in Table 8.

Table 8 Details of scenarios analyses

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 (changes A, B and C only)
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) (changes A and C only)
Scenario 6	Updated base case without age-related disutilities (changes A, B and D only)
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]) (change C only, with updated utilities)

The results of these scenario analyses are presented in Table 9. The results of these analyses showed that most of these changes had only minor impacts on the ICER, with only the no differential utilities scenario incurring an ICER of above £20,000 *per* QALY. These results also confirm that the four different utility sets derived all provided similar results within the economic model. Overall, these results confirm the importance of the use of differential utilities within the assessment of the

cost-effectiveness of migraine treatments and that fremanezumab can be considered a cost-effective treatment in the population of interest for all these analyses (episodic migraine patients with an inadequate response to three or more previous migraine preventive treatments).

Table 9 Results of scenario analyses

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]

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

For completeness, Teva also investigated the impact that these updated assumptions had in CM. Analyses confirmed that under the updated assumptions fremanezumab is a highly cost-effective treatment for CM (all ICERs were less than £10,000 *per* QALY).

3.3 Summary

Overall, the economic analyses presented here demonstrate that fremanezumab is a highly cost-effective treatment for patients with episodic migraine. These analyses include an investigation of the modelling assumptions that have varied across recent NICE migraine appraisals and have shown that, under a comparable set of assumptions and with an updated PAS, fremanezumab is a cost-effective treatment option for both chronic and episodic migraine.

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Appendix

Numbers of observations used in regression modelling

Table 10 Number of observations included in the regression modelling for three or more previous treatment class failures population

MMD	Baseline		Post-baseline	
	Fremanezumab	Placebo	Fremanezumab	Placebo
0	-	-	17	2
1	-	-	20	1
2	-	-	23	4
3	-	-	30	4
4	2	2	28	3
5	5	3	31	9
6	6	3	44	10
7	6	5	17	8
8	14	8	27	16
9	12	5	25	10
10	14	7	38	10
11	15	10	29	15
12	17	9	19	11
13	28	7	17	11
14	26	10	18	18
15	15	4	20	15
16	23	5	23	13
17	6	9	18	10
18	14	7	9	15
19	12	9	14	12
20	14	7	12	12
21	11	3	12	13
22	9	6	10	9
23	5	4	9	6
24	6	3	5	7
25	3	4	7	1
26	4	4	8	6
27	5	2	8	3
28	7	1	14	12

MMD: monthly migraine days

Table 11 Number of observations included in the regression modelling for all FOCUS population

MMD	Baseline		Post-baseline	
	Fremanezumab	Placebo	Fremanezumab	Placebo
0	-	-	41	7
1	-	-	47	3
2	-	-	69	7
3	-	-	83	16
4	7	2	69	18
5	13	9	70	24
6	15	9	73	33
7	23	8	59	25
8	29	22	53	26
9	34	19	54	23
10	33	17	71	34
11	44	19	57	28
12	37	14	36	26
13	47	17	28	30
14	44	18	30	26
15	37	17	32	25
16	36	11	32	23
17	16	14	27	11
18	22	10	23	24
19	17	12	21	14
20	22	9	19	16
21	16	6	16	17
22	13	6	12	11
23	8	4	12	7
24	9	7	8	9
25	7	4	9	7
26	8	5	11	10
27	6	6	9	9
28	11	8	22	28

MMD: monthly migraine days

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

October 2021

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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
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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

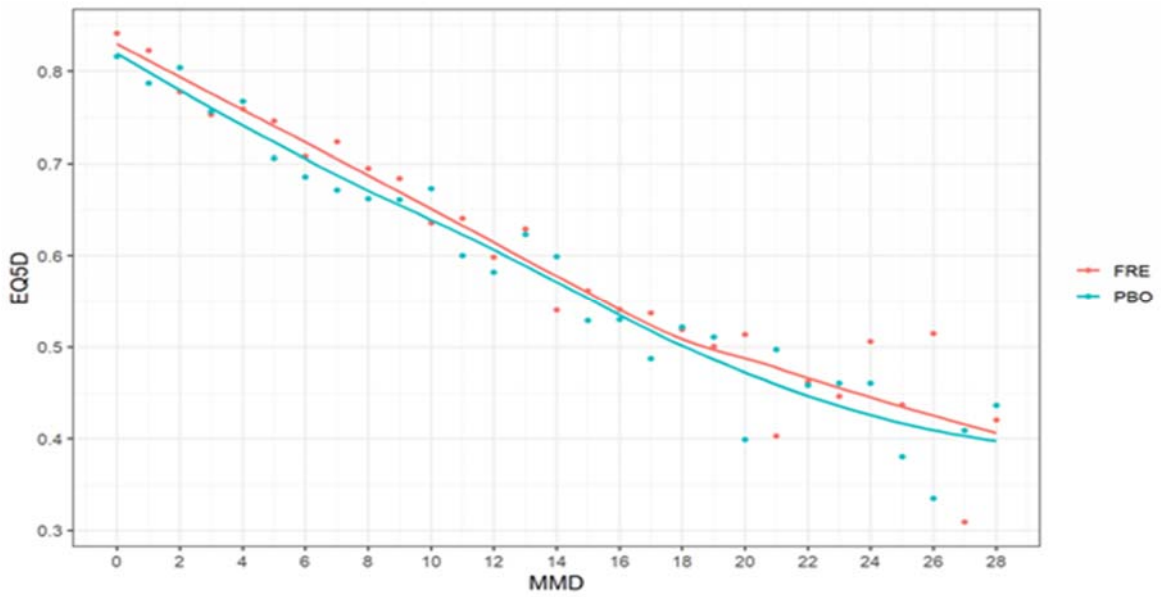
	Original model base case	Updated model base case	ERG comment on updated model
	(fremanezumab) values	baseline, BSC and fremanezumab values	considered acceptable for use in erenumab (TA682)[2] and galcanezumab (TA659).[3] Furthermore, by segregating utility into baseline and BSC, the company appears to 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

References

1. National Institute of Health and Care Excellence. Fremanezumab for preventing migraine Technology appraisal guidance [TA631]. https://www.nice.org.uk/guidance/ta631 (last accessed October 2021)
2. National Institute of Health and Care Excellence. Erenumab for preventing migraine Technology appraisal guidance [TA682]. https://www.nice.org.uk/guidance/ta682 (last accessed October 2021)
3. National Institute of Health and Care Excellence. Galcanezumab for preventing migraine Technology appraisal guidance [TA659]. https://www.nice.org.uk/guidance/ta659 (last accessed October 2021)
4. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value in Health* 2010; **13:** 509-518.