IQWiG Reports – Commission No. 19-82

Fremanezumab (migraine) –

Addendum to Commission A19-44[1]

Addendum

Commission: A19-82
Version: 1.0
Status: 18 October 2019

[1] Translation of addendum A19-82 *Fremanezumab (Migräne) – Addendum zum Auftrag A19-44* (Version 1.0; Status: 18 October 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Fremanezumab (migraine) – Addendum to Commission A19-44

Commissioning agency:
Federal Joint Committee

Commission awarded on:
24 September 2019

Internal Commission No.:
A19-82

Address of publisher:
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum:

- Ana Liberman
- Wiebke Sieben
- Volker Vervölgyi

Keywords: fremanezumab, migraine disorders, benefit assessment, NCT03308968

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIT-6	Headache Impact Test-6
ICHD-3	International Classification of Headache Disorders, 3rd edition
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MSQ	Migraine-Specific Quality of Life questionnaire
RCT	randomized controlled trial
SAE	serious adverse event
VAS	visual analogue scale

1 Background

On 24 September 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-44 (Fremanezumab – Benefit assessment according to §35a Social Code Book V) [1].

For the benefit assessment of fremanezumab, the pharmaceutical company (hereinafter referred to as "the company") presented data of a subpopulation of the randomized controlled trial (RCT) FOCUS in its dossier [2] to answer research question 3. Research question 3 comprises adult patients who do not respond to any of the following therapies (drug classes), who do not tolerate these therapies or for whom these therapies are unsuitable: metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid, clostridium botulinum toxin type A (the latter in compliance with the approval only for chronic migraine). The appropriate comparator therapy (ACT) for this population is best supportive care (BSC) ("research question 3" of dossier assessment A19-44 [adult patients for whom BSC is the only treatment option]; patient population c according to the company). The data presented by the company were unsuitable to answer the research question of the benefit assessment, since the subpopulation formed by the company is not an adequate representation of the target population of research question 3 [1]. With its written comments [3] and after the oral hearing [4], the company submitted further analyses of the FOCUS study [5].

The G-BA commissioned IQWiG with the assessment of the analyses on the FOCUS study subsequently submitted by the company. Moreover, the commission comprised the presentation and assessment of the outcomes (reduction of the migraine days by ≥ 75% and 100%, each from baseline, reduction of headache days/month and migraine hours/month) provided as supplementary information in the benefit assessment procedure on galcanezumab [6,7].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Assessment of the subsequently submitted data on the FOCUS study

Research question 3 of the benefit assessment of fremanezumab comprised adult patients with at least 4 migraine days per month who did not respond to any of the following therapies (drug classes), who did not tolerate these therapies or for whom these therapies were unsuitable: metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid, clostridium botulinum toxin type A. This subpopulation represented patients for whom BSC is the only treatment option.

To answer research question 3, the company presented data on the following subpopulation of the FOCUS study in its dossier: patients for whom prior use of valproic acid was documented. As described in dossier assessment A19-44 [1], this subpopulation selected by the company was no adequate representation of the target population of research question 3.

With its comments [3,5], the company submitted analyses of the FOCUS study for an assessment of research question 3 of the benefit assessment; these analyses comprised the following subpopulation: patients who did not respond to at least two of the following therapies (drug classes) or who did not tolerate these therapies: beta-blockers (propranolol or metoprolol), flunarizine, topiramate or amitriptyline.

The subpopulation formed by the company is considered suitable to answer research question 3. Therefore, the analyses of the subpopulation are relevant for the present research question.

The results on this subpopulation are described below.

2.1.1 Study characteristics

The FOCUS study was a randomized, double-blind study on the comparison of fremanezumab with placebo. Patients with chronic or episodic migraine were included in the study. The study comprised a 12-week double-blind, placebo-controlled phase and a subsequent 12-week open-label phase, in which all patients received fremanezumab. A detailed description of the study design and the interventions can be found in dossier assessment A19-44 [1].

Intervention arms of the FOCUS study

The 3-arm study FOCUS investigated a total of 2 different dosages of fremanezumab:

- monthly fremanezumab administration (225 mg for patients with episodic migraine and 675 mg/225 mg/225 mg for patients with chronic migraine)
- quarterly administration of fremanezumab (single dose: 675 mg)

In the present assessment, monthly and quarterly fremanezumab administration are considered to be equivalent. This assessment was also confirmed in the oral hearing [4]. Therefore, the

results of the two intervention arms are summarized below. Moreover, Table 1 shows the patient characteristics separately for the individual intervention arms.

Implementation of the appropriate comparator therapy "BSC" in the FOCUS study

As already described in dossier assessment A19-44 [1], treatment with BSC also includes non-drug therapies such as psychological therapies, acupuncture or endurance sports in addition to acute medication for migraine attacks in the therapeutic indication of migraine. In the FOCUS study, the use of acute medication for the treatment of migraine attacks during treatment with the study medication was allowed. Data on the application of non-drug therapies are lacking or, according to the company's statement in the hearing [4], had not been documented in the FOCUS study. As non-drug interventions were not explicitly ruled out, however, it must be assumed that their use was basically possible. It is therefore assumed that in principle, patients had various drug and non-drug treatment options at their disposal in order to guarantee the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. The ACT "BSC" was considered to be adequately implemented in the FOCUS study.

Patient characteristics

Table 1 shows the characteristics of the patients in the relevant subpopulation of the included FOCUS study.

Table 1: Characteristics of the study population –RCT, direct comparison: fremanezumab + BSC vs. placebo + BSC

Study Characteristics Category	**fremanezumab (monthly + quarterly) +BSC**	**fremanezumab (monthly) + BSC**	**fremanezumab (quarterly) + BSC**	**placebo + BSC**
FOCUS	N[a] = 388	N[a] = 207	N[a] = 181	N[a] = 195
Age [years], mean (SD)	45 (11)	45 (11)	46 (10)	46 (11)
Sex [F/M], %	85/15	86/14	83/17	87/13
Origin, n (%)				
White	361 (93)	191 (92)	170 (94)	182 (93)
Black	2 (1)	2 (1)	0 (0)	2 (1)
Asian	3 (1)	3 (1)	0 (0)	1 (1)
Other	3 (1)[b]	1 (1)[b]	2 (1)[b]	0 (0)
Not reported	19 (5)	10 (5)	9 (5)	10 (5)
Duration of disease [years], mean (SD)	23.4 (13.1)	23.2 (13.6)	23.7 (12.5)	22.9 (13.1)
Migraine type (according to randomization), n (%)				
EM	149 (38)	82 (40)	67 (37)	76 (39)
CM	239 (62)	125 (60)	114 (63)	119 (61)
Number of migraine days [days/months], mean (SD)	14.3 (5.4)	14.2 (5.6)	14.4 (5.3)	14.2 (5.9)
Number of headache days, any severity [days/months], mean (SD)	14.2 (5.8)	14.2 (5.9)	14.1 (5.7)	14.2 (6.1)
Number of days with at least moderate headache [days/month], mean (SD)	12.6 (5.6)	12.6 (5.8)	12.6 (5.4)	12.6 (5.9)
Failed migraine prevention drugs, n (%)				
2	296 (76.3)[b]	159 (76.8%)	137 (75.7%)	143 (73.3%)
3	83 (21.4)[b]	46 (22.2%)	37 (20.4%)	49 (25.1%)
4	9 (2.3)[b]	2 (1.0%)	7 (3.9%)	3 (1.5%)
Number of days with use of acute medication for the treatment of headache [days/month], mean (SD)	12.3 (6.0)	12 (5.9)	12.7 (6.0)	12.1 (6.5)
Number of days with use of migraine-specific acute medication per month (triptan or ergotamine) [days/month], mean (SD)	9 (6.4)	8.6 (6.2)	9.3 (6.7)	9.2 (6.7)
Any non-drug prophylaxis of migraine, n (%)	ND	ND	ND	ND
Treatment discontinuation, n (%)	ND	ND	ND	ND
Study discontinuation, n (%)	ND	ND	ND	ND

a: Number of analysed patients in the relevant subpopulation. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Institute's calculation.

BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patient characteristics of the relevant subpopulation of the FOCUS study were comparable between the treatment arms: The mean age of the patients was approx. 46 years, most of them were white. The majority were women and mean disease duration was approx. 23 years. About 60% of the patients had chronic migraine; the average number of migraine days/month was approx. 14 days. Prior to inclusion in the study, about 76% of the patients in the relevant subpopulation had received two migraine prevention drugs.

There was no information on study or treatment discontinuations for the relevant subpopulation. However, the proportion of treatment discontinuations in the total population was very small (approx. 3% of patients who had received fremanezumab, and 5% of the patients in the placebo arm). The reasons for treatment discontinuation were comparably distributed in the respective study arms. In the study documents, the data pertaining to study discontinuation in the total population are identical with those relating to treatment discontinuations. However, this does not indicate whether the patients are the same.

Risk of bias across outcomes

Table 2 shows the risk of bias across outcomes (risk of bias at study level).

Table 2: Risk of bias across outcomes (study level) – RCT, direct comparison: fremanezumab + BSC vs. placebo + BSC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
FOCUS	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low.

2.1.2 Results on added benefit

2.1.2.1 Outcomes included

- Mortality
  - all-cause mortality
- Morbidity
  - symptoms, measured with migraine days/month
  - general impairment from headache, recorded using the Headache Impact Test-6 (HIT-6)

- health status measured with the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D) questionnaire

- health-related quality of life
  - health-related quality of life, measured with the Migraine-Specific Quality of Life questionnaire (MSQ)
- Side effects
  - serious adverse events (SAEs)
  - discontinuation due to adverse events (AEs)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes. Appendix B (of the full dossier assessment) provides explanatory comments on further outcomes presented by the company.

Operationalizations on the outcome "symptoms" presented as supplementary information

The G-BA's commission also comprised the presentation and assessment of the operationalizations on the outcome "symptoms" listed below. These were presented as supplementary information in the present benefit assessment. This is justified below.

Reduction of migraine days/month by ≥ 75% and 100% from the baseline phase

For the outcome "reduction of migraine days/month", the company submitted responder analyses on the reduction by ≥ 50%, by ≥ 75% and by 100%, each in comparison with the baseline phase. These response criteria are patient-relevant. The population considered in research question 3 included patients with at least 4 migraine days/month in whom drug treatment options for prophylaxis of migraine had been exhausted and for whom therefore BSC was the only treatment option. Against the background of the patients' symptom burden, reduction by ≥ 50% already represents an appropriate response criterion, regardless of whether the patient has episodic or chronic migraine. Therefore, reduction of the migraine days/month by ≥ 50% is used for the derivation of the added benefit. The analyses on the reduction by ≥ 75% and 100% are presented as supplementary information. Regardless of this, the results on the various response criteria do not contradict each other.

Migraine hours/month

Analyses on the number of migraine hours/month are not available. The comments on patient relevance are therefore omitted.

Headache days/month: reduction by ≥ 50% from the baseline phase; mean change from the baseline phase

In the FOCUS study, a headache day was defined as a calendar day on which a patient had headache of any severity for ≥ 4 subsequent hours. Moreover, headache of any severity and duration requiring the use of migraine-specific acute medication (triptans or ergot derivatives) was documented as a headache day.

Headache days/month were not used for the benefit assessment, because the migraine days/month reflect the patients' burden of disease more accurately than the unspecific recording of the number of days with headache of any type. The migraine headache or probable migraine headache of interest in the present therapeutic indication according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) classification [8] was already reflected by the migraine days/month. Differentiated analyses on migraine headache, probable migraine headache and non-migraine headache are lacking.

Table 3 shows for which outcomes data were available in the included FOCUS study.

Table 3: Matrix of outcomes – RCT, direct comparison: fremanezumab + BSC vs. placebo + BSC

Study	Outcomes						
	All-cause mortality	Symptoms (migraine days/month; additionally: headache days/month)	General impairment from headache (HIT-6)	Health status (EQ-5D VAS)	Health-related quality of life (MSQ)	SAEs	Discontinuation due to AEs
FOCUS	Yes	Yes	Yes	Yes	Yes	Yes	Yes

AE: adverse event; BSC: best supportive care; EQ-5D: European Quality of Life-5 Dimensions; HIT-6: Headache Impact Test-6; MSQ: Migraine-Specific Quality of Life; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.1.2.2 Risk of bias

Table 4 describes the risk of bias for the results of the relevant outcomes.

Table 4: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: fremanezumab + BSC vs. placebo + BSC

Study	Study level	Outcomes						
		All-cause mortality	Symptoms (migraine days/month; additionally: headache days/month)	General impairment from headache (HIT-6)	Health status (EQ-5D VAS)	Health-related quality of life (MSQ)	SAEs	Discontinuation due to AEs
FOCUS	L	L	H[a]	L	L	L	L	L

a: No information on frequency or distribution of missing values in the electronic diary on the basis of which the effect is calculated.

AE: adverse event; BSC: best supportive care; EQ-5D: European Quality of Life-5 Dimensions; HIT-6: Headache Impact Test-6; MSQ: Migraine-Specific Quality of Life; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The risk of bias of the outcomes “all-cause mortality”, “general impairment from headache (HIT-6)”, “health status (EQ-5D VAS)” as well as the harm outcomes “SAEs” and “discontinuation due to AEs” was rated as low.

The risk of bias of the outcome “symptoms” (migraine days/month as well as headache days/month [presented as supplementary information]) was rated as high. The outcome “symptoms” was derived from the daily recordings in the electronic diary. The reason for the high risk of bias in the results is that due to a lack of information it remains unclear for how many patients there were missing entries in the electronic diary to a relevant extent. The monthly migraine days were calculated according to the proportion of migraine days among the documented days and apportioned to the total period. Lacking documentation on many days can result in significant bias in the calculation of the monthly migraine days. Assessment of a possible extent of a resulting bias of the effect estimation would, for instance, require frequency tables showing for the entire observation period for how many patients there were no entries for how many days within a given month. Even after the oral hearing, the company provided no adequate data to assess the extent of the missing entries in the electronic diary. In the submitted subsequently documents, the company only described that calculations on the operationalization of symptoms for entries ≥ 10 days/month were extrapolated to 28 days based on the available data, and that the missing values for entries on < 10 days/month were updated using last observation carried forward (LOCF). However, these data are insufficient.

2.1.2.3 Results

Table 5 and Table 6 summarize the results on the comparison of fremanezumab + BSC with placebo + BSC in patients with ≥ 4 migraine days/month who had not responded to ≥ 2 prior therapies (drug classes) with beta-blockers (propranolol, metoprolol) or flunarizine, topiramate or amitriptyline or who had not tolerated these therapies. Where necessary, calculations by the Institute are provided in addition to the data.

Table 5: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: fremanezumab + BSC vs. placebo + BSC

Study Outcome category Outcome	Fremanezumab + BSC		Placebo + BSC		Fremanezumab + BSC vs. placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
FOCUS					
Mortality					
All-cause mortality	388	0 (0)	195	0 (0)	–
Morbidity					
Symptoms: migraine days/month[b]					
Reduction by ≥ 50%	388	144 (37)	195	19 (10)	3.82 [2.44; 5.97]; < 0.001
Reduction by ≥ 75% (supplementary information)	388	46 (12)	195	5 (3)	4.64 [1.87; 11.48]; < 0.001
Reduction by 100% (supplementary information)	388	4 (1)	195	0 (0)	4.54 [0.25; 83.91]; 0.161
Headache days/month, any severity, reduction by ≥ 50%[c] (supplementary information)		ND		ND	ND
Side effects					
AEs (supplementary information)	388[d]	208 (53.61[d])	195	101 (52)	–
SAEs	388[d]	4 (1[d])	195	3 (1)	0.67 [0.15; 2.96]; 0.625
Discontinuation due to AEs	388[d]	3 (0.8[d])	195	2 (1)	0.75 [0.13; 4.47]; 0.829

a: Institute's calculation (unconditional exact test, CSZ method according to [9]).
b: Defined as a calendar day on which a patient documented a migraine headache or a probable migraine headache on ≥ 4 subsequent hours or use of migraine-specific headache medication.
c: Defined as calendar day on which headache of any severity occurred for ≥ 4 subsequent hours or use of migraine-specific headache medication was necessary (documented in the electronic diary).
d: Incorrect information in the submitted documents, Institute's calculation.
AE: adverse event; BSC: best supportive care; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 6: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: fremanezumab + BSC vs. placebo + BSC

Study Outcome category Outcome	Fremanezumab + BSC			Placebo + BSC			Fremanezumab + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Change at end of study mean (SD)	N[a]	Values at baseline mean (SD)	Change at end of study mean (SD)	MD [95% CI]; p-value
FOCUS							
Morbidity							
Health status (EQ-5D VAS)[b]	388	69.6 (21.2)	6.28 (20.14)	195	70.1 (20.1)	1.72 (17.6)	4.22 [1.28; 7.17]; 0.005 Hedges' g: 0.24 [0.06; 0.41]
General impairment from headache (HIT-6)[c]	388	64.2 (4.4)	−6.43 (7.16)	195	64.0 (5.2)	−2.96 (6.18)	−3.37 [−4.45; −2.30]; < 0.001 Hedges' g: −0.57 [−0.74; −0.39]
Migraine hours/month (supplementary information)			ND		ND		ND
Headache days/month, any severity[d] (supplementary information)	388	14.2 (5.8)	−4.72 (4.59)	195	14.2 (6.1)	−1.28 (4.19)	−3.47 [−4.32; −2.62]; < 0.001
Health-related quality of life							
MSQ[e]							
Limitation of role functioning	388	47.6 (17.4)	18.33 (20.44)	195	47.6 (19.0)	9.74 (17.15)	9.06 [5.77; 12.35]; < 0.001 Hedges' g: 0.44 [0.27; 0.62]
Prevention of role functioning	388	63.2 (20.4)	14.51 (18.52)	195	64.2 (21.0)	8.56 (17.35)	5.81 [2.82; 8.80]; < 0.001 Hedges' g: 0.33 [0.16; 0.50]
Emotional state	388	60.6 (23.9)	16.55 (22.6)	195	60.6 (25.3)	8.1 (21.88)	9.14 [5.52; 12.77]; < 0.001 Hedges' g: 0.38 [0.204; 0.55]

(continued)

Table 6: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: fremanezumab + BSC vs. placebo + BSC (continued)

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
f: Higher values reflect a better health status; a positive group difference corresponds to an advantage of fremanezumab.
c: Higher values indicate deterioration of the general impairment from headache, a negative group difference corresponds to an advantage of fremanezumab.
d: Defined as calendar day on which headache of any severity occurred on ≥ 4 subsequent hours or use of migraine-specific headache medication was necessary (documented in the electronic diary).
e: Higher values reflect a better health-related quality of life; a positive group difference corresponds to an advantage of fremanezumab.
BSC: best supportive care; CI: confidence interval; EQ-5D: European Quality of Life5 Dimensions; HIT-6: Headache Impact Test-6; MD: mean difference; MSQ: Migraine-Specific Quality of Life; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

Mortality

All-cause mortality

Deaths occurred in none of the study arms of the FOCUS study. Thus, there was no hint of an added benefit of fremanezumab + BSC in comparison with BSC for the outcome "all-cause mortality"; an added benefit is therefore not proven.

Morbidity

Symptoms (migraine days/month)

Reduction of migraine days/month by ≥ 50% from the baseline phase

There is a statistically significant difference in favour of fremanezumab + BSC for the reduction of migraine days/month by ≥ 50% from the baseline phase, averaged over the treatment period. Because of the high risk of bias based on outcomes, there is a hint of an added benefit of fremanezumab + BSC in comparison with BSC for this outcome.

Operationalizations on the outcome "symptoms" presented as supplementary information

Migraine days/month

Reduction of migraine days/month by ≥ 75% from the baseline phase

There is a statistically significant difference in favour of fremanezumab + BSC for the reduction of migraine days/month by ≥ 75% from the baseline phase, averaged over the treatment period.

Reduction of migraine days/month by 100% from the baseline phase

For the reduction of the migraine days/month by 100% from the baseline phase, averaged over the treatment period, there is no statistically significant difference between the treatment groups.

Migraine hours/month

There are no data on migraine hours/month.

Headache days/month

Reduction by ≥ 50% from the baseline phase

There are no data on the reduction of headache days/month by ≥ 50% from the baseline phase.

Mean changes of headache days/month from the baseline phase

There is a statistically significant advantage of fremanezumab + BSC versus placebo + BSC for the change of the average monthly headache days/month from the baseline phase, averaged over the treatment period of 12 weeks.

General impairment from headache (HIT-6)

The mean differences were used for the outcome "general impairment from headache" (HIT-6). There was a statistically significant difference in favour of fremanezumab + BSC. The standardized mean difference (SMD) in the form of Hedges' g was considered to check the relevance of the result. The 95% confidence interval (CI) of the SMD is fully outside the irrelevance range of −0.2 to 0.2. This was interpreted to be a relevant effect. This resulted in an indication of an added benefit of fremanezumab + BSC in comparison with BSC for this outcome.

Health status (EQ-5D VAS)

For the outcome "health status" (EQ-5D VAS), a statistically significant difference in favour of fremanezumab + BSC was shown for the mean change. The SMD in the form of Hedges' g was considered to check the relevance of the result. However, the 95% CI of the SMD was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. There was no hint of an added benefit of fremanezumab + BSC in comparison with placebo + BSC for this outcome; an added benefit is therefore not proven.

Health-related quality of life

MSQ

The mean differences were used for the outcome "health-related quality of life" measured using the MSQ. For each of the domains "limitation of role functioning", "prevention of role functioning" and "emotional state" of the MSQ, there was a statistically significant difference in favour of fremanezumab + BSC. Each SMD in the form of Hedges' g was considered to check the relevance of the results. However, the 95% CI of the SMD was fully outside the irrelevance range of −0.2 to 0.2 for the two domains "limitation of role functioning" and "emotional state". This was interpreted to be a relevant effect in each case. This resulted in an indication of an added benefit of fremanezumab + BSC in comparison with BSC for each of these domains. However, for the domain "prevention of role functioning", the 95% CI of the SMD was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. There was no hint of an added benefit of fremanezumab + BSC in comparison with BSC for this domain; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

There was no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". Hence, there was no hint of greater or lesser harm from fremanezumab + BSC in comparison with BSC for any of these outcomes; greater or lesser harm is therefore not proven for these outcomes.

Specific AEs

Specific AEs for the benefit assessment were chosen according to the events that occurred in the relevant study on the basis of frequency and differences between the treatment arms and under consideration of the patient relevance. Specific AEs of particular importance for the disease or for the drugs used in the study could also be chosen.

In the subsequently submitted documents, the company only presented data on AEs at system organ class (SOC) level for the relevant subpopulation. There are not data on the preferred terms (PTs). This data situation permits no choice of specific AEs. It is assumed that the results on specific AEs do not raise doubts about the results on side effects and the total assessment on the added benefit. Overall, there are not statistically significant differences in the overall rates of the outcomes on side effects. In the FOCUS study, the AEs occurred in about half of the patients included; only very few of them were serious (Table 5).

Common AEs at SOC level are presented in Appendix A.

2.1.2.4 Subgroups and other effect modifiers

The following potential effect modifiers are basically relevant for the benefit assessment:

- age (18 to 45 years/> 45 years)
- sex (female/male)
- region (USA/Europe)
- migraine type (chronic/episodic)
- medication overuse at baseline (yes/no)
- number of prior migraine prevention drugs with treatment failure (2/3/4)

All subgroup characteristics used in the present benefit assessment were prespecified.

Contrary to the oral hearing [4], the company did not submit the complete results on subgroup analyses in its comments [5]. In the subsequently submitted documents, the company only provided a brief description of the methodology applied and furnished no particulars on whether the intervention arms were considered jointly or separately in the analyses. Overall, the results on subgroup analyses presented by the company are not reproducible. Therefore, the presented subgroup analyses are unusable for the relevant subpopulation. The available data did not

permit an Institute's calculation of subgroup analyses, since results on the subgroup characteristics were only available for subgroups, for which the company had observed a significant interaction between treatment and subgroup characteristic (p-value < 0.05) on the basis of its calculations.

Overall, the available data are unsuitable to draw conclusions on effect modifications in the FOCUS study.

2.1.3 Probability and extent of added benefit

Probability and extent of the added benefit under consideration of the data subsequently submitted by the company in the commenting procedure are deduced below at outcome level. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [10].

2.1.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.1.2.3 of the present addendum (see Table 7).

Determination of the outcome category for the outcomes on morbidity

Symptoms (migraine days/month)

The outcome "migraine days/month" was allocated to the outcome category "serious/severe symptoms/late complications". This is largely derived from the available baseline values on "general impairment from headache (HIT-6)" of the relevant subpopulation. For the analysis of the HIT-6, a total score is formed that can assume values between 36 and 78. Higher values indicate more pronounced impairment from headache. A total score ≤ 49 indicates little or no impact, 50 to 55: some impact, 56 to 59: substantial impact; a total score ≥ 60 indicates very severe impact from headache [11]. The values show that the patients in the FOCUS study had very severe impairment from headache at the start of the study (see Table 6). Although the HIT-6 instrument is used to assess headache in general and not specifically migraine headache, the present benefit assessment is based on the assumption that the burden of disease from migraine headache in the group of patients for whom "BSC" is the ACT makes HIT-6 suitable for assessing the outcome category for the outcome "migraine days/month".
General impairment from headache (HIT-6)

The outcome "general impairment from headache (HIT-6)" is allocated to the outcome category "serious/severe symptoms/late complications". For reasons, see the arguments for the classification of the outcome category of the outcome "migraine days/month".

Table 7: Extent of added benefit at outcome level: fremanezumab + BSC vs. placebo + BSC

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Fremanezumab + BSC vs. placebo + BSC** **Proportion of events (%) or MD** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser benefit/added benefit not proven
Morbidity		
Symptoms Migraine days/month; reduction by ≥ 50%	37% vs. 10% RR: 3.82 [2.44; 5.97] RR: 0.26 [0.17; 0.41][c] p < 0.001 Probability: "hint"	Outcome category: "serious/severe symptoms/late complications" CI_u < 0.75 and risk ≥ 5% Added benefit, extent: "major"
General impairment from headache (HIT-6)	-6.43 vs. -2.96 MD: -3.37 [-4.45; -2.30] p < 0.001 Hedges' g[d]: -0.57 [-0.74; -0.39] Probability: "indication"	Outcome category: "serious/severe symptoms/late complications" added benefit, extent: "non-quantifiable"
Health status (EQ-5D VAS)	6.28 vs. 1.72 MD: 4.22 [1.28; 7.17] p = 0.005 Hedges' g[d]: 0.24 [0.06; 0.41]	Lesser benefit/added benefit not proven
Health-related quality of life		
MSQ Limitation of role functioning	18.33 vs. 9.74 MD: 9.06 [5.77; 12.35]; p < 0.001 Hedges' g[d]: 0.44 [0.27; 0.62] Probability: "indication"	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"
Prevention of role functioning	14.51 vs. 8.56 MD: 5.81 [2.82; 8.80] p < 0.001 Hedges' g[d]: 0.33 [0.16; 0.50]	Lesser benefit/added benefit not proven
Emotional state	16.55 vs. 8.1 MD: 9.14 [5.52; 12.77] p < 0.001 Hedges' g[d]: 0.38 [0.204; 0.55] Probability: "indication"	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"
SAEs	1% vs. 1% RR: 0.67 [0.15; 2.96]; p = 0.625	Greater/lesser harm not proven
Discontinuation due to AEs	0.8% vs. 1% RR: 0.75 [0.13; 4.47]; p = 0.829	Greater/lesser harm not proven

(continued)

Table 7: Extent of added benefit at outcome level: fremanezumab + BSC vs. placebo + BSC (continued)

a: Probability provided if there is a statistically significant and relevant effect.
b: Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c: Institute's calculation, reversed direction of effect to enable use of limits in the derivation of the extent of the added benefit.
d: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2]; this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HIT-6: Headache Impact Test-6; MD: mean difference; MSQ: Migraine-Specific Quality of Life; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.1.3.2 Overall conclusion on added benefit

Table 8 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 8: Positive and negative effects from the assessment of fremanezumab + BSC compared with placebo + BSC

Positive effects	**Negative effects**
Outcome category: serious/severe symptoms/late complications: ▪ migraine days/month, reduction by ≥ 50%: hint of an added benefit, extent: "major" ▪ general impairment from headache (HIT-6): indication of an added benefit, extent: "non-quantifiable"	-
Outcome category: health-related quality of life ▪ MSQ (limitation of role functioning): indication of an added benefit, extent: "non-quantifiable" ▪ MSQ (emotional state): indication of an added benefit, extent: "non-quantifiable"	
BSC: best supportive care; HIT-6: Headache Impact Test-6; MSQ: Migraine-Specific Quality of Life	

In the overall assessment based on the FOCUS study, there are only positive effects for adult patients who have at least 4 migraine days/month and for whom BSC is the only treatment option. These were observed in each of the outcome categories "morbidity" and "health-related quality of life".

In summary, there is an indication of a non-quantifiable added benefit of fremanezumab + BSC versus BSC for adult patients who have at least 4 migraine days/month and for whom BSC is the only treatment option.

2.1.4 List of included studies

Ferrari MD, Diener HC, Ning X, Galic M, Cohen JM, Yang R et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. Lancet 2019; 394(10203): 1030-1040.

Teva Branded Pharmaceutical Products. An efficacy and safety study of fremanezumab in adults with migraine (FOCUS): study details [online]. In: ClinicalTrials.gov. 22.05.2019 [Accessed: 29.05.2019]. URL: https://ClinicalTrials.gov/show/NCT03308968.

Teva Branded Pharmaceutical Products R&D. A multicenter, randomized, double-blind, parallel-group, placebo-controlled study with an open-label period to evaluate the efficacy and safety of fremanezumab for the prophylactic treatment of migraine in patients with inadequate response to prior preventive treatments [online]. In: EU Clinical Trials Register. [Accessed: 29.05.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-002441-30.

Teva Branded Pharmaceutical Products R&D. A multicenter, randomized, double-blind, parallel-group, placebo-controlled study with an open-label period to evaluate the efficacy and safety of fremanezumab for the prophylactic treatment of migraine in patients with inadequate response to prior preventive treatments: study TEV48125-CNS-30068; clinical study protocol amendment 01 [unpublished]. 2017.

Teva Branded Pharmaceutical Products R&D. A multicenter, randomized, double-blind, parallel-group, placebo-controlled study with an open-label period to evaluate the efficacy and safety of fremanezumab for the prophylactic treatment of migraine in patients with inadequate response to prior preventive treatments: study TEV48125-CNS-30068; statistical analysis plan [unpublished]. 2018.

Teva Branded Pharmaceutical Products R&D. A multicenter, randomized, double-blind, parallel-group, placebo-controlled study with an open-label period to evaluate the efficacy and safety of fremanezumab for the prophylactic treatment of migraine in patients with inadequate response to prior preventive treatments: study TEV48125-CNS-30068; interim clinical study report [unpublished]. 2019.

Teva. Stellungnahme zum IQWiG-Bericht Nr. 802: Fremanezumab (Migräne); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-44. Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/462/#beschluesse im Dokument "Zusammenfassende Dokumentation".

Teva. Zusätzliche Analysen gemäß den Anforderungen des G-BA; Studien: TEV48125-30068 (FOCUS), TEV48125-30049 (HALO CM), TEV48125-30050 (HALO EM) [unpublished]. 2019.

2.2 Summary

The data subsequently submitted by the company in the commenting procedure changed the conclusion on the added benefit of fremanezumab from dossier assessment A19-44 for research question 3: "adult patients for whom BSC is the only treatment option". For the other research questions, there was no change in comparison with dossier assessment A19-44.

The following Table 9 shows the result of the benefit assessment of fremanezumab under consideration of dossier assessment A19-44 and the present addendum.

Table 9: Fremanezumab – probability and extent of added benefit

Research question	**Subindication**	**ACT[a]**	**Probability and extent of added benefit**
Adult patients who have at least 4 migraine days per month			
1	Treatment-naive patients and patients with inadequate response or intolerance to at least 1 prophylactic medication or for whom this medication is unsuitable	Metoprolol or propranolol or flunarizine or topiramate or amitriptyline, each under consideration of approval and prior therapy	Added benefit not proven
2	Patients who do not respond to the following treatments (drug classes), who do not tolerate them or for whom these treatments are unsuitable: metoprolol, propranolol, flunarizine, topiramate, amitriptyline[b]	Valproic acid[c] or clostridium botulinum toxin type A[d]	Added benefit not proven
3	Patients who do not respond to any of the following treatments (drug classes), who do not tolerate them or for whom these treatments are unsuitable: metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid[c] or clostridium botulinum toxin type A[d]	BSC[e]	Indication of a non-quantifiable added benefit

a: Presentation of the respective ACT specified by the G-BA.
b: All 4 drug classes specified as ACTs for research question 1 (beta-blockers, flunarizine, topiramate or amitriptyline) must have been considered before the patients fall under research question 2. Neither valproic acid nor clostridium botulinum toxin type A are regular options for all patients.
c: According to Appendix VI to Section K of the Pharmaceutical Directive: if treatment with all other drugs approved for this indication has been unsuccessful or is contraindicated.
d: In compliance with the approval only for chronic migraine.
e: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Fremanezumab (Migräne): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-44 [online]. 13.08.2019 [Accessed: 15.08.2019]. (IQWiG-Berichte; Volume 802). URL: https://www.iqwig.de/download/A19-44_Fremanezumab_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. Teva. Fremanezumab (AJOVY): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 15.05.2019 [Accessed: 19.08.2019]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/462/#dossier.

3. Teva. Stellungnahme zum IQWiG-Bericht Nr. 802: Fremanezumab (Migräne); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-44. Demnächst verfügbar unter: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/462/#beschluesse im Dokument "Zusammenfassende Dokumentation".

4. Gemeinsamer Bundesausschuss. Wirkstoff Fremanezumab: mündliche Anhörung gemäß 5. Kapitel § 19 Abs. 2 Verfahrensordnung des Gemeinsamen Bundesausschusses; stenografisches Wortprotokoll [online]. 24.09.2019 [Accessed: 15.10.2019]. URL: https://www.g-ba.de/downloads/91-1031-462/2019-09-24_Wortprotokoll_Fremanezumab_D-460.pdf.

5. Teva. Zusätzliche Analysen gemäß den Anforderungen des G-BA; Studien: TEV48125-30068 (FOCUS), TEV48125-30049 (HALO CM), TEV48125-30050 (HALO EM) [unveröffentlicht]. 2019.

6. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Galcanezumab (Migräne): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-28 [online]. 27.06.2019 [Accessed: 17.07.2019]. (IQWiG-Berichte; Volume 787). URL: https://www.iqwig.de/download/A19-28_Galcanezumab_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

7. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Galcanezumab (Migräne): Addendum zum Auftrag A19-28; Auftrag A19-63 [online]. 21.08.2019 [Accessed: 25.09.2019]. (IQWiG-Berichte; Volume 805). URL: https://www.iqwig.de/download/A19-63_Galcanezumab_Addendum-zum-Auftrag-A19-28_V1-0.pdf.

8. Headache Classification Committee of the International Headache Society (IHS): the International Classification of Headache Disorders; 3rd edition. Cephalalgia 2018; 38(1): 1-211.

9. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

10. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden: Version 5.0. Köln: IQWiG; 2017. URL: https://www.iqwig.de/download/Allgemeine-Methoden_Version-5-0.pdf.

11. Yang M, Rendas-Baum R, Varon SF, Kosinski M. Validation of the Headache Impact Test (HIT-6) across episodic and chronic migraine. Cephalalgia 2011; 31(3): 357-367.

Appendix A – Results on side effects (study FOCUS)

Table 10: Common AEs – RCT, direct comparison: fremanezumab + BSC vs. placebo + BSC

Study	**Patients with event n (%)**	
SOC[a, b]	**Fremanezumab + BSC N = 388[c]**	**Placebo + BSC N = 195**
FOCUS		
Overall rate AEs	208 (53.6)[c]	101 (52)
Infections and infestations	59 (15.2)[c]	39 (20)
Psychiatric disorders	18 (4.6)[c]	2 (1)
Nervous system disorders	25 (6.4)[c]	22 (11)
Vascular disorders	11 (2.8)[c]	4 (2)
Gastrointestinal disorders	27 (7.0)[c]	22 (11)
Skin and subcutaneous tissue disorders	16 (4.1)[c]	7 (4)
Musculoskeletal and connective tissue disorders	41 (10.6)[c]	9 (5)
General disorders and administration site conditions	70 (18.0)[c]	35 (18)
Investigations	23 (5.9)[c]	4 (2)
Injury, poisoning and procedural complications	17 (4.4)[c]	9 (5)

a: MedDRA-Version 18.1; deviating from the study report, Module 4 A indicates version 16.1.
b: There was no information on PTs for the relevant subpopulation.
c: Institute's calculation based on data on patient numbers in individual fremanezumab arms.

AE: adverse event; BSC: best supportive care; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus