IQWiG Reports – Commission No. A19-44

Fremanezumab (migraine) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.7 of the dossier assessment *Fremanezumab (Migräne) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 August 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.

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BSC	best supportive care
EMA	European Medicines Agency
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
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)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug fremanezumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 15 May 2019.

Research question

The aim of the present report was to assess the added benefit of fremanezumab in comparison with the appropriate comparator therapy (ACT) for the prophylaxis of migraine in adults who have at least 4 migraine days per month.

Table 2 shows the research questions of the benefit assessment and the ACTs specified by the G-BA.

Table 2: Research questions of the benefit assessment of fremanezumab

Research question	**Subindication**	**ACT[a]**
Adults 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 who are unsuitable for these medications	Metoprolol or propranolol or flunarizine or topiramate or amitriptyline, each under consideration of approval and prior therapy
2	Patients who do not respond to the following treatments (drug classes), are unsuitable for them or do not tolerate them: metoprolol, propranolol, flunarizine, topiramate, amitriptyline[b]	Valproic acid[c] or clostridium botulinum toxin type A[d]
3	Patients who do not respond to any of the following treatments (drug classes), are unsuitable for them or do not tolerate them: metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid[c], clostridium botulinum toxin type A[d]	BSC[e]

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.
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 company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum treatment duration of 3 months were used for the derivation of the added benefit.

Results

Research question 1

For the assessment of the added benefit of fremanezumab in patients of research questions 1, the company identified the 2 RCTs TEV48125-CNS-30049 and TEV48125-CNS-30050 (hereinafter referred to as HALO [CM] and HALO [EM]).

Both studies are unsuitable for the derivation of an added benefit of fremanezumab in comparison with the ACT in the present therapeutic indication.

The studies HALO (CM) and HALO (EM) were randomized, double-blind studies on the comparison of fremanezumab with placebo with a treatment duration of 12 weeks each. The studies investigated adults with chronic migraine (defined as ≥ 15 headache days per month, of which ≥ 8 migraine days, [HALO (CM)]) or with episodic migraine (headache on ≥ 6 to ≤ 14 days per month, of which ≥ 4 migraine days, [HALO (EM)]) according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) who had not responded to a maximum of one migraine therapy in the past. At the time of study inclusion, patients either had to be on no preventive migraine treatment (or at least 5 half-lives had to have elapsed since the last intake) or on a maximum of one preventive migraine treatment at a stable dose, which had to be continued unchanged in the study. Initiation of a new therapy in the course of the study was not planned in the study; the use of acute medications for acute migraine attacks as needed was permitted.

Implementation of the appropriate comparator therapy in the studies HALO (CM) and HALO (EM)

The studies HALO (CM) and HALO (EM) did not compare fremanezumab with the ACT (see Table 2).

Neither placebo nor the unchanged continuation of the preventive migraine treatment existing at the start of the study represents the ACT. It is therefore also irrelevant that the company formed a subpopulation for its benefit assessment in which it considered the continuation of prophylaxis of migraine as ACT. In addition, the approach chosen by the company to form the subpopulations was inadequate because it did not maintain randomization or structural equality between the treatment arms.

Research question 2

The company presented no data for the benefit assessment of fremanezumab in comparison with the ACT for research question 2.

Research question 3

For the assessment of the added benefit of fremanezumab in patients of research question 3, the company identified the TEV48125-CNS-30068 study (hereinafter referred to as FOCUS). The data presented by the company on the FOCUS study are unsuitable for the derivation of the added benefit of fremanezumab in comparison with the ACT.

The FOCUS study was a randomized, double-blind study on the comparison of fremanezumab with placebo. 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. The study included a total of 838 adult patients with chronic or episodic migraine according to ICHD-3 documented for at least 12 months. Adults with treatment failure to 2 to 4 different migraine drug classes in the past 10 years were enrolled. In the 12-week double-blind treatment phase, the patients in 3 treatment arms received either quarterly or monthly fremanezumab or placebo. The use of acute medications for acute migraine attacks as needed was permitted in the course of the study.

Implementation of the appropriate comparator therapy best supportive care (BSC)

During treatment with the study medication, the use of acute medications was permitted in the FOCUS study for the treatment of migraine attacks. Non-drug treatments that are also part of a BSC (such as psychological therapies, acupuncture or endurance sports) were not explicitly mentioned in the FOCUS study.

Subpopulation formed by the company does not concur with research question 3

In accordance with the G-BA's notes already made for earlier commissions in the therapeutic indication of migraine (A18-71 [erenumab], A19-28 [galcanezumab]), from this study, patients with treatment failure or intolerance under ≥ 2 prior therapies with drugs from the drug classes named as ACTs in research question 1 are to be regarded as relevant for the present benefit assessment.

From the total population of the FOCUS study, the company formed the subpopulation of patients for whom prior use of valproic acid was documented and designated it as mITTc population. The mITTc population formed by the company is not an adequate representation of the target population of research question 3. On the one hand, the mITTc population includes a relevant proportion of patients who do not meet the requirement of treatment failure or intolerance to ≥ 2 prior therapies with drugs from the drug classes for research question 1. It can be inferred from the study documents that about 40% of the patients in the mITTc population received either no or at most one drug from the drug classes (drugs) of research question 1. The remaining 60% of the mITTc population may also include further patients who have received several prior therapies, which do not necessarily comprise at least 2 from the group of the therapies (drug classes) mentioned above, however. On the other hand, it can be assumed that the total population of the FOCUS study includes further patients not comprised by the mITTc population who are relevant for research question 3 (treatment failure/intolerance

under ≥ 2 prior therapies with drugs from the above-mentioned drug classes without valproic acid administration in the prior therapy). However, the company did not provide sufficient documentation on treatment failure, intolerances and contraindications from which the relevance of the patients for research question 3 can be inferred.

Overall, the mITTc population formed by the company is not an adequate representation of the target population of research question 3. It can be assumed, however, that the total population of the FOCUS study comprised relevant patients for research question 3. The company presented no analyses on this subpopulation of interest. For this reason, overall, no suitable data from the FOCUS study were available for the present benefit assessment.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of fremanezumab.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Fremanezumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
Adults 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 who are unsuitable for these medications	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), are unsuitable for them or do not tolerate them: 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), are unsuitable for them or do not tolerate them: metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid[c], clostridium botulinum toxin type A[d]	BSC[e]	Added benefit not proven

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.
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 G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of fremanezumab in comparison with the ACT for the prophylaxis of migraine in adults who have at least 4 migraine days per month.

Table 4 shows the research questions of the benefit assessment and the ACTs specified by the G-BA.

Table 4: Research questions of the benefit assessment of fremanezumab

Research question	Subindication	ACT[a]
Adults 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 who are unsuitable for these medications	Metoprolol or propranolol or flunarizine or topiramate or amitriptyline, each under consideration of approval and prior therapy
2	Patients who do not respond to the following treatments (drug classes), are unsuitable for them or do not tolerate them: metoprolol, propranolol, flunarizine, topiramate, amitriptyline[b]	Valproic acid[c] or clostridium botulinum toxin type A[d]
3	Patients who do not respond to any of the following treatments (drug classes), are unsuitable for them or do not tolerate them: metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid[c], clostridium botulinum toxin type A[d]	BSC[e]

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.
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

Research questions 1, 2 and 3 of the present benefit assessment correspond to the company's research questions a, b and c. For easier presentation and better readability, the present benefit assessment uses the following terms for the 3 research questions in the running text:

- research question 1: adult patients for whom treatment with metoprolol or propranolol or flunarizine or topiramate or amitriptyline is an option
- research question 2: adult patients for whom treatment with valproic acid or clostridium botulinum toxin type A is an option
- research question 3: adult patients for whom BSC is the only treatment option

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum treatment duration of 3 months were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

For the 3 research questions, the study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on fremanezumab (status: 18 March 2019)
- bibliographical literature search on fremanezumab (last search on 19 March 2019)
- search in trial registries for studies on fremanezumab (last search on 18 March 2019)

To check the completeness of the study pool:

- search in trial registries for studies on fremanezumab (last search on 24 May 2019)

No relevant studies were identified for research questions 1 and 2, and no additional relevant study was identified for research question 3. This deviates from the assessment of the company, which included 2 studies for research question 1 and one study for research question 3 in its benefit assessment.

Data presented by the company

Table 5 shows the studies included by the company in its benefit assessment.

Table 5: Study pool of the company – presented RCTs with fremanezumab

Research question	Study	Study category		
		Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
1	TEV48125-CNS-30049 (HALO (CM)[b]) [3-5]	Yes	Yes	No
	TEV48125-CNS-30050 (HALO (EM)[b]) [6-8]	Yes	Yes	No
2	No data presented			
3	TEV48125-CNS-30068 (FOCUS[b]) [9,10]	Yes	Yes	No
The company listed the following studies in its study pool without allocation to any of the 3 research questions. According to the company, it presented the results of these studies as supportive information and did not use them for the derivation of the added benefit of fremanezumab (Section 4.4, Module 4 A): ▪ TV48125-CNS-30051 [11] ▪ LBR-101-021 [12-17] ▪ LBR-101-022 [14-16,18-20]				
a: Study for which the company was sponsor. b: Hereinafter, the study is referred to with this abbreviated form. RCT: randomized controlled trial; vs.: versus				

Deviating from the company, the data presented by the company are not considered suitable for the present benefit assessment to derive an added benefit of fremanezumab in comparison with the respective ACTs of research questions 1 to 3. Detailed reasons can be found in Section 2.4 (research question 1) and in Section 2.6 (research question 3).

The company presented the studies TV48125-CNS-30051, LBR-101-021 and LBR-101-022 as supportive information without allocating them to any of the 3 research questions. It also did not provide any information on the extent to which the studies may include relevant subpopulations for individual research questions. With these studies, the company presented no data relevant for the benefit assessment. More details on the 3 studies can be found in Section 2.8.3.2 of the full dossier assessment.

2.4 Research question 1: adult patients for whom treatment with metoprolol or propranolol or flunarizine or topiramate or amitriptyline is an option

The company presented the results of the studies HALO (CM) and HALO (EM) for research question 1.

The studies HALO (CM) and HALO (EM) were randomized, double-blind studies on the comparison of fremanezumab with placebo with a treatment duration of 12 weeks each. See

Table 10 and Table 11 in Appendix A of the full dossier assessment for a description of the study design and of the interventions, including concomitant medications.

The studies investigated adults with chronic migraine (≥ 15 headache days per month, of which ≥ 8 migraine days, [HALO (CM)]) or with episodic migraine (headache on ≥ 6 to ≤ 14 days per month, of which ≥ 4 migraine days, [HALO (EM)]) according to ICHD-3 [21]. Patients who had not responded to a maximum of one preventive migraine treatment in the past were enrolled. At the time of study inclusion, patients either had to be on no preventive migraine treatment (or at least 5 half-lives had to have elapsed since the last intake) or on a maximum of one preventive migraine treatment at a stable dose. The prerequisite was that they had been taking this treatment at a stable dose for 2 months before the 28-day run-in phase. The proportion of this patient group with a maximum of one preventive treatment was not to exceed 30% in each study according to the study planning. During the study, these patients were not allowed to change the dosage or the treatment regimen of their prophylaxis of migraine used at baseline. It was not planned that any of the patients included initiated a new therapy in the course of the study; the use of acute medications for acute migraine attacks as needed was permitted.

Implementation of the appropriate comparator therapy in the studies HALO (CM) and HALO (EM)

As described above, the studies HALO (CM) and HALO (EM) enrolled patients with a history of treatment failure to no more than one preventive migraine treatment who thus concur with the target population of research question 1. For these patients, treatment with the drug classes (drugs) beta-blocker (metoprolol, propranolol), flunarizine, topiramate or amitriptyline was the ACT (Section 2.8.1 of the full dossier assessment).

For the patients in the comparator arms of both studies, however, there was no treatment optimization by initiating a therapy with the above-mentioned drug classes (drugs) comprised by the ACT. Instead, the patients received placebo or unchanged continuation of their stable prophylaxis of migraine existing at baseline. It can be assumed, that the continued treatment also included drug classes (drugs) comprised by the ACT. However, the unchanged continuation of the existing migraine prevention treatment is not a representation of the ACT, i.e. initiation of treatment not yet received. In the study design chosen in this way, the aim in the intervention arm – unlike in the comparator arm – was to improve the symptoms since the existing need for treatment was met by the use of fremanezumab. In contrast, the patients in the comparator arms received no optimization of their treatment regimens despite existing need for treatment.

The studies HALO (CM) and HALO (EM) are therefore unsuitable for research question 1 for the assessment of the added benefit of fremanezumab in comparison with the ACT.

Subpopulation formed by the company is inadequate

For the assessment of the added benefit of fremanezumab, the company formed a subpopulation of each of the studies HALO (CM) and HALO (EM). It selected from both studies the following patients as subpopulations:

- fremanezumab arms of both studies: patients without concomitant medication for the prophylaxis of migraine during the study
- comparator arms of both studies: patients with unchanged continuation of their prophylaxis of migraine with metoprolol or propranolol or flunarizine or topiramate or amitriptyline initiated before the start of the study as concomitant medications during the study

The company's approach was inadequate because the original randomization of the study and thus the structural equality of the treatment groups can only be maintained in a subsequent selection of subpopulations if the same selection criteria are applied in both study arms that were already established at the beginning of the study. It cannot be excluded for the sub-populations formed by the company that structural equality of the treatment groups was not maintained.

Overall, the subpopulations formed by the company are not relevant for the benefit assessment, irrespective of the possible lack of structural equality, as the ACT was not implemented.

2.4.1 Results on added benefit (research question 1)

For research question 1, no suitable data were available for the assessment of the added benefit of fremanezumab in comparison with the ACT. This resulted in no hint of an added benefit of fremanezumab in comparison with the ACT. An added benefit is therefore not proven.

2.4.2 Probability and extent of added benefit (research question 1)

The company presented no suitable data for the assessment of the added benefit of fremanezumab in comparison with the ACT in adult patients with migraine for whom treatment with metoprolol or propranolol or flunarizine or topiramate or amitriptyline is an option. An added benefit of fremanezumab in comparison with the ACT is therefore not proven for these patients.

This deviates from the assessment of the company, which derived an added benefit from the studies it included for research question 1.

2.4.3 List of included studies (research question 1)

Not applicable as the company presented no relevant data for research question 1 for the benefit assessment.

2.5 Research question 2: adult patients for whom treatment with valproic acid or clostridium botulinum toxin type A is an option

2.5.1 Results on added benefit (research question 2)

The company presented no data for the assessment of the added benefit of fremanezumab in comparison with the ACT for research question 2. This resulted in no hint of an added benefit of fremanezumab in comparison with the ACT. An added benefit is therefore not proven.

2.5.2 Probability and extent of added benefit (research question 2)

The company presented no data for the assessment of the added benefit of fremanezumab in adult patients for whom treatment with valproic acid or clostridium botulinum toxin type A is an option. An added benefit of fremanezumab in comparison with the ACT is therefore not proven for these patients.

This concurs with the assessment of the company, which claimed no added benefit for this patient group.

2.5.3 List of included studies (research question 2)

Not applicable as the company presented no relevant data for research question 2 for the benefit assessment.

2.6 Research question 3: adult patients for whom BSC is the only treatment option

The company presented the results of the FOCUS study for research question 3.

The FOCUS study was a randomized, double-blind study on the comparison of fremanezumab with placebo. 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. See Table 12 and Table 13 in Appendix B of the full dossier assessment for a description of the study design and of the interventions, including concomitant medications.

The study included a total of 838 adult patients with chronic or episodic migraine (defined according to ICHD-3 [21]) documented for at least 12 months. Patients with episodic migraine had to have an average of ≥ 6 and < 15 headache days during the run-in phase, of which ≥ 4 migraine days. Patients with chronic migraine had to have an average of ≥ 15 headache days during the run-in phase, of which ≥ 8 migraine days. Patients with headache on ≥ 80% of their waking phase and without headache on < 4 days/month were not included in the study. Patients with preventive migraine treatment in the screening phase or with opioid or barbiturate use for migraine treatment on > 4 days were also not included in the study. The use of acute medications for acute migraine attacks as needed was permitted in the course of the FOCUS study.

The extent to which the inclusion criterion on the number of headache or migraine days/month was met was checked by the patients' entries in their electronic migraine diaries during the

4-week run-in phase. At the same time, the compliance of patients for filling out the diary was also checked. Compliance in the run-in phase had to be ≥ 85% for transition to the randomized treatment phase.

Adults with treatment failure to 2 to 4 of the following migraine drug classes in the past 10 years were enrolled. A group of at least 120 patients to be included had to present with treatment failure to 2 to 3 of these drug classes and an inadequate response to valproic acid. The following drug classes (drugs) were defined:

- beta-blockers (metoprolol, propranolol, atenolol, bisoprolol)
- anticonvulsants (topiramate)
- tricyclic antidepressants (amitriptyline)
- calcium channel blockers (flunarizine)
- angiotensin II receptor blockers (candesartan)
- clostridium botulinum toxin type A
- valproic acid

Treatment failure was defined as no clinically meaningful improvement after at least 3 months of preventive migraine treatment at a stable dose, treatment discontinuation because of adverse events, or treatment contraindicated or unsuitable for preventive treatment of migraine of the patient.

In the 12-week double-blind treatment phase, patients with episodic or chronic migraine were randomly assigned in a ratio of 1:1:1 to quarterly fremanezumab, monthly fremanezumab or placebo.

The quarterly administration of fremanezumab consisted of a dosage of 675 mg fremanezumab for all patients in the study. The dosing regimen of the monthly administration depended on whether the patients had episodic or chronic migraine. The patient group with episodic migraine received a total of 3 monthly doses, each with 225 mg fremanezumab. Patients with chronic migraine, in contrast, received an initial dose of 675 mg fremanezumab and 2 subsequent monthly doses of 225 mg each.

In the study, the administration of fremanezumab in patients with episodic migraine was in compliance with the approval. The dosing regimen of fremanezumab used in patients with chronic migraine (initial administration of 675 mg followed by 2 further doses of 225 mg) deviated from the dosage described in the Summary of Product Characteristics (SPC). The SPC provides for either a monthly dose of 225 mg or a quarterly dose of 675 mg of fremanezumab for all patients, regardless of whether they have episodic or chronic migraine [22].

It can be inferred from the information provided by the company and the registration documents that the company has filed an application with the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for an adjustment of the dosage of fremanezumab for all patients in the therapeutic indication as part of the approval process. The application of the company was based primarily on analyses of the subpopulation of patients with high-frequency episodic migraine (≥ 12 and < 15 headache days per month) and modelling of pharmacokinetic and clinical data on selected efficacy and safety outcomes [23]. The EMA considers the 2 dosing regimens (with and without an initial dose of 675 mg in patients with chronic migraine) to be comparable in the present therapeutic indication. The present benefit assessment regards the dosing regimen as adequate.

Implementation of the appropriate comparator therapy BSC

During treatment with the study medication, the use of acute medications was permitted in the FOCUS study for the treatment of migraine attacks. The acute medication used individually for each patient (indication, dosage, period of use) was documented in the electronic migraine diary. In addition to acute medication for migraine attacks, treatment with BSC in the therapeutic indication of migraine also includes non-drug therapies such as psychological therapies, acupuncture or endurance sports [24-26]. The FOCUS study did not explicitly mention such interventions. The company did not address to what extent BSC (best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life) was implemented in the FOCUS study.

Subpopulation formed by the company does not concur with research question 3

The FOCUS study included adults with treatment failure to drugs from 2 to 4 different drug classes. In accordance with the G-BA's notes already made for earlier commissions in the therapeutic indication of migraine (A18-71 [erenumab], A19-28 [galcanezumab] [27,28]), from this study, patients in research question 3 with treatment failure or intolerance under ≥ 2 prior therapies with drugs from the drug classes (drugs) named as ACTs in research question 1 are to be regarded as relevant for the present benefit assessment. These are beta-blockers (metoprolol, propranolol), flunarizine, topiramate or amitriptyline; see Section 2.8.1 of the full dossier assessment for more details on the corresponding note by the G-BA.

From the total population of the FOCUS study, the company formed the subpopulation of patients for whom prior use of valproic acid was documented and designated it as mITTc population. The company justified this approach with the fact that, according to the Pharmaceutical Directive (Appendix VI to Section K [29]), valproic acid for the prophylaxis of migraine in adults is only prescribable "if treatment with other drugs approved for this indication has been unsuccessful or is contraindicated".

The mITTc population formed by the company is not an adequate representation of the target population of research question 3. On the one hand, the mITTc population includes a relevant proportion of patients who do not meet the requirement of treatment failure or intolerance to ≥ 2 prior therapies with drugs from the drug classes for research question 1. It can be inferred

from the study documents that about 40% of the patients in the mITTc population received either no or at most one drug from the drug classes (drugs) of research question 1. The remaining 60% of the mITTc population may also include further patients who have received several prior therapies, which do not necessarily comprise at least 2 from the group of the therapies (drug classes) mentioned above, however.

On the other hand, it can be assumed that the total population of the FOCUS study includes further patients not comprised by the mITTc population who are relevant for research question 3 (treatment failure/intolerance under ≥ 2 prior therapies with drugs from the above-mentioned drug classes without valproic acid administration in the prior therapy). However, there was no sufficient documentation on treatment failure, intolerances and contraindications from which the suitability of the patients for research question 3 can be inferred.

Overall, the mITTc population formed by the company is therefore not an adequate representation of the target population of research question 3 described above. It can be assumed, however, that the total population of the FOCUS study comprised relevant patients for research question 3. The company presented no analyses on the patient population of the FOCUS study that is of interest for research question 3. For this reason, overall, no suitable data from the FOCUS study were available for the present benefit assessment.

The data presented by the company for research question 3 were unsuitable to derive an added benefit of fremanezumab in comparison with the ACT for patients.

2.6.1 Results on added benefit (research question 3)

No suitable data were available for the assessment of the added benefit of fremanezumab in comparison with the ACT for research question 3. This resulted in no hint of an added benefit of fremanezumab in comparison with the ACT. An added benefit is therefore not proven.

2.6.2 Probability and extent of added benefit

The company presented no suitable data for the assessment of the added benefit of fremanezumab in comparison with the ACT in adult patients with migraine for whom BSC is the only treatment option. An added benefit of fremanezumab in comparison with the ACT is therefore not proven for these patients.

This deviates from the company’s assessment, which derived an added benefit.

2.6.3 List of included studies (research question 3)

Not applicable as the company presented no relevant data for research question 3 for the benefit assessment.

2.7 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of fremanezumab in comparison with the ACT is summarized in Table 6.

Table 6: Fremanezumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
Adults 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 who are unsuitable for these medications	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), are unsuitable for them or do not tolerate them: 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), are unsuitable for them or do not tolerate them: metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid[c], clostridium botulinum toxin type A[d]	BSC[e]	Added benefit not proven

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.
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 assessment described above deviates from that of the company insofar as the company derived a hint of a considerable added benefit for research question 1 and an indication of considerable added benefit for research question 3. For research question 2, the assessment concurs with that of the company.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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