IQWiG Reports – Commission No. A22-95

Eptinezumab (migraine) –

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

Extract

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Eptinezumab (Migräne) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 November 2022). Please note: This document was translated by an external translator and 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Veronika Bäcker and Sabrina Wolf.

IQWiG thanks the respondents for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondents were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
EMA	European Medicines Agency
EQ-5D	European Quality of Life Questionnaire – 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)
MSQoL	Migraine-Specific Quality of Life
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SPC	Summary of Product Characteristics
VAS	visual analogue scale

I 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 eptinezumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 31 August 2022.

Research question

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

The research questions shown in Table 2 are derived from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of eptinezumab

Research question	Therapeutic indication	ACT[a]
1	Previously untreated as well as previously treated adult patients who have at least 4 migraine days per month and who are candidates for conventional migraine prophylaxis	Metoprolol or propranolol or flunarizine or topiramate or amitriptyline or *Clostridium botulinum* toxin type A[b], taking into account approval and prior therapy
2	Adult patients with at least 4 migraine days per month who do not respond to, are not candidates for, or do not tolerate[c] any of the following drug treatments / drug classes: metoprolol, propranolol, flunarizine, topiramate, amitriptyline, *Clostridium botulinum* toxin type A	Erenumab or **fremanezumab** or galcanezumab

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. Even in chronic migraine, *Clostridium botulinum* toxin type A is not a standard treatment option for all patients in research question 1.
c. In research question 2, treatment with biologic agents in the context of a clinical trial may be an option for patients who previously did not respond to or did not tolerate at least 2 pharmacological therapies (drug classes from research question 1). In cases where patients are not candidates for the drugs from research question 1, this must be documented and justified.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

To simplify presentation and improve readability, the running text of this benefit assessment uses the following designations for the research questions:

- Research question 1: adult patients who are candidates for conventional migraine prophylaxis

- Research question 2: adult patients who are not candidates for conventional migraine prophylaxis

For research question 1 (company's research question), the company followed the G-BA's specification of the ACT. The company analyses research question 2 under its own research questions b1 and b2. For its research question b1, the company followed the ACT specified by the G-BA, choosing fremanezumab from the presented ACT options. For its research question b2, it specified best supportive care (BSC) as the ACT and presented a direct comparison of eptinezumab versus BSC. The company's approach remains without consequence for the present benefit assessment. The benefit assessment is conducted in comparison with the ACT specified by the G-BA.

The assessment is 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 12 weeks were used for the derivation of added benefit.

Research question 1: adult patients who are candidates for conventional migraine prophylaxis

For research question 1, no relevant RCT was found for the comparison of eptinezumab versus the ACT specified by the G-BA. The company did not present any data for assessing the added benefit of eptinezumab versus the ACT. This resulted in no hint of an added benefit of eptinezumab in comparison with the ACT. An added benefit is therefore not proven for research question 1.

Research question 2: adult patients who are not candidates for conventional migraine prophylaxis

Study pool and study design

No relevant RCT was found for the direct comparison of eptinezumab versus the ACT specified by the G-BA. The company presented an adjusted indirect comparison using the common comparator of placebo, with the DELIVER study on the eptinezumab side of the comparison and the FOCUS study on the fremanezumab side.

DELIVER study (with eptinezumab)

The DELIVER study is a double-blind, randomized study comparing eptinezumab versus placebo. The study comprises a 4-week screening phase, a 24-week double-blind, placebo-controlled phase, and a subsequent 48-week phase, in which all patients received eptinezumab.

The study enrolled adult patients with a history of documented migraines of least 12 months (defined in accordance with International Classification of Headache Disorders, 3rd Edition [ICHD-3]). Patients with episodic migraine had to have had an average of ≤ 14 headache days during the screening phase, of which ≥ 4 migraine days. Patients with chronic migraine had to have had an average of ≥ 14 headache days during the screening phase, of which ≥ 8 migraine days.

Enrolled were adults with treatment failure of 2 to 4 of the following preventive medications in the past 10 years: propranolol/metoprolol, flunarizine, amitriptyline, topiramate, candesartan, valproate/divalproex, botulinum toxin A/B. Treatment failure had to have been demonstrated for 2 of the following drugs, ≥ 1 of which due to insufficient effectiveness: propranolol/metoprolol, topiramate, amitriptyline, flunarizine, candesartan.

In the DELIVER study, a total of 892 patients were randomly allocated in a 1:1:1 ratio to treatment with 100 mg eptinezumab (N = 299), 300 mg eptinezumab (N = 294), or placebo (N = 299). Randomization was stratified by number of migraine days per month (≤ 14 / >14) and country. The company presented the results for the comparison of eptinezumab at the 100-mg dosage recommended by the Summary of Product Characteristics (SPC) versus placebo for the subpopulation of patients who previously did not respond to or did not tolerate ≥ 2 drugs (metoprolol/propranolol, amitriptyline, topiramate). The subpopulation comprises 284 patients in the intervention arm and 287 patients in the comparator arm and is relevant for the present research question.

The study allowed the treatment of acute migraine attacks during the study, but only in patients who had already taken that medication prior to the study, and its dosage had to have remained constant for ≥ 12 weeks prior to screening.

The primary outcome of the study was the change in monthly migraine days from baseline to Week12. Secondary outcomes were all-cause mortality, other outcomes of the morbidity and health-related quality of life categories, and adverse events (AEs).

FOCUS study (with fremanezumab)

The FOCUS study was a double-blind, randomized study comparing fremanezumab with placebo. The study has already been described in detail in dossier assessment A19-44 and the associated addendum A19-82. The study comprises a 4-week screening phase, 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 documented chronic or episodic migraine (defined according to ICHD-3) documented for at least 12 months. Patients with episodic migraine had to have had an average of ≥ 6 and ≤ 14 headache days during the screening phase, of which ≥ 4 migraine days. Patients with chronic migraine had to have had an average of ≥ 14 headache days during the screening phase, of which ≥ 8 migraine days.

The study included adults with treatment failure of 2 to 4 of the following drug classes in the prior 10 years: beta blockers (metoprolol, propranolol, atenolol, bisoprolol), anticonvulsants (topiramate), tricyclic antidepressants (amitriptyline), calcium channel blockers (flunarizine), angiotensin-II antagonists (candesartan), *Clostridium botulinum* toxin type A, valproic acid.

In the 12-week double-blind treatment phase, patients with episodic or chronic migraine were randomly allocated in a 1:1:1 ratio to either monthly fremanezumab (N = 283), quarterly fremanezumab (N = 276), or placebo (N = 279).

The quarterly administration of fremanezumab consisted of a 675 mg dose of fremanezumab for all study participants. For the monthly administration, the dose depended on whether the patient had episodic or chronic migraine. In patients with episodic migraine, the fremanezumab dosing regimen (total of 3 doses at 225 mg each) was in compliance with approval. In patients with chronic migraine, the fremanezumab dosing regimen (initial dose of 675 mg, followed by 2 further doses of 225 mg) deviated from the dosage described in the SPC. In the prior benefit assessment procedure of fremanezumab, the different dosing regimens were overall deemed equivalent and analysed jointly.

The study allowed the use of acute medications to treat acute migraine attacks as needed.

The company used the results from a subpopulation of patients who previously failed to respond to or did not tolerate ≥ 2 therapies (drug classes): beta blockers (propranolol or metoprolol), flunarizine, topiramate, or amitriptyline. The subpopulation comprises 388 patients in the intervention arm and 195 patients in the comparator arm and is relevant for the present research question.

Primary outcome of the study was mean change in average monthly migraine days from baseline. Secondary outcomes were all-cause mortality, other outcomes of the morbidity and health-related quality of life categories, and AEs.

Similarity of the studies for the indirect comparison

Overall, the 2 studies DELIVER and FOCUS have a very similar study design, which ultimately differs only in the length of the placebo-controlled phase. Additionally, the studies' patient populations are sufficiently similar. The differences in concomitant treatments available in the DELIVER and FOCUS studies likewise do not call into question the studies' sufficient similarity and hence the permissibility of an adjusted indirect comparison via the common comparator of placebo.

Risk of bias

The risk of bias across outcomes was rated as low for both studies.

In the present situation, no indirect comparison can be conducted for the outcome of symptoms (migraine days per month) because the risk of bias for the result of this outcome is deemed high in the FOCUS study.

There was 1 RCT each on both sides of this adjusted indirect comparison. Hence, the check for homogeneity is not needed. As there is no directly comparative study for the comparison of eptinezumab versus the ACT, it is impossible to check the consistency of results. Therefore, the adjusted indirect comparisons have, at best, low certainty of results. Hence, at most hints, e.g.

of an added benefit, can be derived on the basis of the data available from the adjusted indirect comparison.

Results

Mortality

All-cause mortality

No deaths occurred in the 2 studies. This results in no hint of an added benefit of eptinezumab in comparison with fremanezumab for the outcome of all-cause mortality; an added benefit is therefore not proven.

Morbidity

Symptoms (reduction of migraine days per month by ≥ 50%)

For the results on the outcome of symptoms (reduction of migraine days per month by ≥ 50%), the FOCUS study exhibits a high risk of bias. Hence, the certainty of results is insufficient for conducting an adjusted indirect comparison, and the indirect comparison is disregarded in the benefit assessment. The same applies to the operationalizations presented as supplementary information, i.e. reduction of migraine days per month by ≥ 75% and mean change in headache days per month. This results in no hint of an added benefit of eptinezumab in comparison with fremanezumab; an added benefit is therefore not proven.

General impairment from headache (recorded using the Headache Impact Test-6 [HIT-6])

For the outcome of general impairment from headache, recorded using the HIT-6, the adjusted indirect comparison shows no statistically significant difference between eptinezumab and fremanezumab. This results in no hint of an added benefit of eptinezumab in comparison with fremanezumab; an added benefit is therefore not proven.

Health status (European Quality of Life Questionnaire – 5 Dimensions [EQ-5D] visual analogue scale [VAS])

For the outcome of health status (EQ-5D VAS), the adjusted indirect comparison shows no statistically significant difference between eptinezumab and fremanezumab. This results in no hint of an added benefit of eptinezumab in comparison with fremanezumab; an added benefit is therefore not proven.

Health-related quality of life

Migraine-Specific Quality of Life (MSQoL)

For the outcome of health-related quality of life, surveyed with the MSQoL questionnaire, the adjusted indirect comparison showed no statistically significant difference between eptinezumab and fremanezumab for the domains of limitation of role functioning and emotional state. This results in no hint of an added benefit of eptinezumab in comparison with fremanezumab; an added benefit is therefore not proven.

For the domain of prevention of role functioning, the adjusted indirect comparison shows a statistically significant difference in favour of eptinezumab. The standardized mean difference (SMD) was analysed to examine the relevance of the results. However, for the domain of 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. This results in no hint of an added benefit of eptinezumab in comparison with fremanezumab; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs) and discontinuation due to AEs

No statistically significant difference between eptinezumab and fremanezumab was shown in the adjusted indirect comparison for either of the outcomes of SAEs or discontinuation due to AEs. There was no hint of greater or lesser harm from eptinezumab in comparison with fremanezumab for any of these outcomes; greater or lesser harm is therefore not proven for these outcomes.

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

On the basis of the results presented, the probability and extent of added benefit of the drug eptinezumab in comparison with the ACT is assessed as follows:

Research question 1: adult patients who are candidates for conventional migraine prophylaxis

The company did not present any data for assessing the added benefit of eptinezumab in comparison with the ACT in adult patients who are candidates for conventional migraine prophylaxis. An added benefit of eptinezumab versus the ACT is therefore not proven for research question 1.

Research question 2: adult patients who are not candidates for conventional migraine prophylaxis

Overall, based on the adjusted indirect comparison using placebo as the common comparator, there are no relevant favourable nor unfavourable effects of eptinezumab in comparison with 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].

In summary, there is no hint of added benefit of eptinezumab versus fremanezumab for adult patients who have at least 4 migraine days per month and who are not candidates for conventional migraine prophylaxis.

Table 3 summarizes the probability and extent of added benefit of eptinezumab.

Table 3: Eptinezumab – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT**[a]	**Probability and extent of added benefit**
1	Previously untreated as well as previously treated adult patients who have at least 4 migraine days per month and who are candidates for conventional migraine prophylaxis	Metoprolol or propranolol or flunarizine or topiramate or amitriptyline or *Clostridium botulinum* toxin type A[b], taking into account approval and prior therapy	Added benefit not proven
2	Adult patients with at least 4 migraine days per month who do not respond to, are not candidates for, or do not tolerate[c] any of the following drug treatments / drug classes: metoprolol, propranolol, flunarizine, topiramate, amitriptyline, *Clostridium botulinum* toxin type A	Erenumab or **fremanezumab** or galcanezumab	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. Even in chronic migraine, *Clostridium botulinum* toxin type A is not a standard option for all patients in research question 1.
c. In research question 2, treatment with biologic agents may be an option if patients previously did not respond to or did not tolerate at least 2 drug therapies (drug classes from research question 1). In cases where patients are not candidates for the drugs from research question 1, this must be documented and reasoning provided.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

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

I 2 Research question

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

The research questions shown in Table 4 are derived from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of eptinezumab

Research question	Therapeutic indication	ACT[a]
1	Previously untreated as well as previously treated adult patients who have at least 4 migraine days per month and who are candidates for conventional migraine prophylaxis	Metoprolol or propranolol or flunarizine or topiramate or amitriptyline or *Clostridium botulinum* toxin type A[b], taking into account approval and prior therapy
2	Adult patients with at least 4 migraine days per month who do not respond to, are not candidates for, or do not tolerate[c] any of the following drug treatments / drug classes: metoprolol, propranolol, flunarizine, topiramate, amitriptyline, *Clostridium botulinum* toxin type A	Erenumab or **fremanezumab** or galcanezumab

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. Even in chronic migraine, *Clostridium botulinum* toxin type A is not a standard option for all patients in research question 1.
c. In research question 2, treatment with biologic agents may be an option if patients previously did not respond to or did not tolerate at least 2 drug therapies (drug classes from research question 1). In cases where patients are not candidates for the drugs from research question 1, this must be documented and reasoning provided.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

To simplify presentation and improve readability, the running text of this benefit assessment uses the following designations for the research questions:

- Research question 1: adult patients who are candidates for conventional migraine prophylaxis
- Research question 2: adult patients who are not candidates for conventional migraine prophylaxis

For research question 1 (company's research question), the company followed the G-BA's specification of the ACT. The company analyses research question 2 under its own research questions b1 and b2. For its research question b1, the company followed the ACT specified by the G-BA, choosing fremanezumab from the presented ACT options. For its research question b2, it specified BSC as the ACT and presented a direct comparison of eptinezumab versus BSC.

The company's approach remains without consequence for the present benefit assessment. The benefit assessment was conducted in comparison with the ACT specified by the G-BA.

The assessment is 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 12 weeks were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 3 Research question 1: adult patients who are candidates for conventional migraine prophylaxis

I 3.1 Information retrieval and study pool

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 eptinezumab (status: 31 July 2022)
- bibliographical literature search on eptinezumab (last search on 30 June 2022)
- search in trial registries / trial results databases for studies on eptinezumab (last search on 30 June 2022)
- search on the G-BA website for eptinezumab (last search on 4 July 2022)

To check the completeness of the study pool:

- search in trial registries for studies on eptinezumab (last search on 13 September 2022); for search strategies, see I Appendix A of the full dossier assessment

No relevant study was identified from the check. The company likewise did not identify any suitable studies.

I 3.2 Results on added benefit

The company has presented no data for assessing the added benefit of eptinezumab in comparison with the ACT in adult patients who are candidates for conventional migraine prophylaxis. This results in no hint of an added benefit of eptinezumab in comparison with the ACT; an added benefit is therefore not proven for this research question.

I 3.3 Probability and extent of added benefit

The company did not present any data for assessing the added benefit of eptinezumab in comparison with the ACT in adult patients who are candidates for conventional migraine prophylaxis. An added benefit of eptinezumab versus the ACT is therefore not proven for research question 1.

This concurs with the company’s assessment.

I 4 Research question 2: adult patients who are not candidates for conventional migraine prophylaxis

I 4.1 Information retrieval and study pool

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 eptinezumab (status: 31 July 2022)
- bibliographical literature search on eptinezumab (last search on 30 June 2022)
- search in trial registries / trial results databases for studies on eptinezumab (last search on 30 June 2022)
- search on the G-BA website for eptinezumab (last search on 4 July 2022)
- bibliographical literature search on the ACT (last search on 1 July 2022)
- search in trial registries / trial results databases for studies on the ACT (last search on 5 July 2022)
- search on the G-BA website for the ACT (last search on 4 July 2022)

To check the completeness of the study pool:

- search in trial registries for studies on eptinezumab (last search on 13 September 2022); for search strategies, see I Appendix A of the full dossier assessment
- search in trial registries for studies on fremanezumab (last search on 29 September 2022); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, no relevant study with a direct comparison of eptinezumab versus fremanezumab in the present therapeutic indication was identified from the check of completeness of the study pool.

Therefore, the company presents an adjusted indirect comparison according to Bucher [3] for assessing eptinezumab versus fremanezumab using the common comparator of placebo. For the adjusted indirect comparison, the company identifies the DELIVER study on the intervention side and the FOCUS study on the fremanezumab side.

The check of the study pool did not identify any additional relevant study for the adjusted indirect comparison presented by the company.

I 4.1.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, indirect comparison: eptinezumab versus fremanezumab

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Eptinezumab vs. placebo						
18898A (DELIVER[d])	No	Yes	No	Yes [4]	Yes [5,6]	Yes [7]
Fremanezumab vs. placebo						
TEV48125-CNS-30068 (FOCUS[d])	No	No	Yes	No	Yes [8,9]	Yes [10-18]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool concurs with that of the company. The FOCUS study has already been presented and assessed for a previous benefit assessment of fremanezumab [17,18].

Figure 1 shows a schematic representation of the indirect comparison.

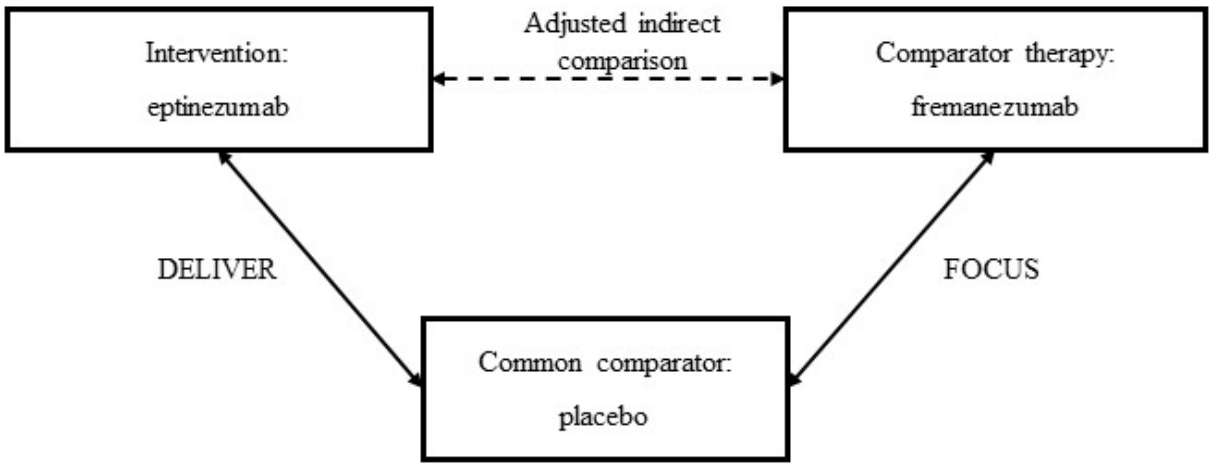

Figure 1: Study pool for the adjusted indirect comparison between eptinezumab and fremanezumab using placebo as common comparator

I 4.1.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, indirect comparison: eptinezumab versus fremanezumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Eptinezumab vs. placebo						
DELIVER	RCT, double-blind, parallel-group	Adults (18–75 years) with a history of chronic[b] or episodic[b] migraines, ≥ 4 migraine days per month within the past 3 months prior to screening, and treatment failure of 2–4 migraine prophylactic drugs[c] in the past 10 years	Eptinezumab 100 mg (N = 299) Eptinezumab 300 mg (N = 294)[d] Placebo (N = 299) Relevant subpopulation thereof[e]: Eptinezumab 100 mg (N = 284) Placebo (n = 287)	Screening: 28–30 days Treatment: 24 weeks[f] Observation: 12 weeks after the last dose of the study medication	A total of 96 centres in: Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Georgia, Germany, Hungary, Italy, Poland, Russia, Slovakia, Spain, Sweden, United Kingdom, United States 06/2020–10/2021	Primary: change in monthly migraine days from baseline (Week 12) Secondary: all-cause mortality, morbidity, health-related quality of life, AEs
Fremanezumab vs. placebo						
FOCUS	RCT, double-blind, parallel-group	Adults (18–70 years) with a history of chronic[b] or episodic[b] migraines, ≥ 4 migraine days per month, and treatment failure of 2–4 migraine prophylactic drugs[c] in the past 10 years	Fremanezumab, 225 mg monthly (N = 283) Fremanezumab, 675 mg quarterly (N = 276) Placebo (N = 279) Relevant subpopulation thereof[e]: Fremanezumab monthly/quarterly (n = 388) Placebo (n = 195)	Screening/run-in phase: within 28 days Treatment: 12 weeks[i] Observation: 6 months after the last dose of the study medication	98 centres in: Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, United States, United Kingdom 11/2017–10/2018	Primary: mean change in monthly average number of migraine days from baseline Secondary: all-cause mortality, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, indirect comparison: eptinezumab versus fremanezumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Chronic migraine was defined as > 14 headache days per month, of which ≥ 8 migraine days; episodic migraine was defined as ≤ 14 headache days per month (in the FOCUS study as ≥ 6 to ≤ 14 headache days per month), of which ≥ 4 migraine days.
c. Defined as documented treatment failure to 2–4 of the following prior therapies: metoprolol/propranolol, topiramate, amitriptyline, flunarizine, candesartan, valproate/divalproex, *Clostridium botulinum* toxin type A/B. Treatment failure had to have been demonstrated to 2 of the following prior therapies, ≥ 1 of which due to insufficient effectiveness: propranolol/metoprolol, topiramate, amitriptyline, flunarizine, candesartan.
d. This arm is irrelevant for the assessment and is not presented in the following tables.
e. Definition of the relevant subpopulation: patients who did not respond to ≥ 2 of the following conventional migraine prophylactics, were intolerant to them, or were contraindicated for them: metoprolol/propranolol, topiramate, amitriptyline, flunarizine, *Clostridium botulinum* toxin A.
f. Following the placebo-controlled, double-blind treatment phase, all participants in the eptinezumab arms entered a 48-week extension phase, where they received further treatment with 100 mg or 300 mg eptinezumab every 12 weeks until Week 60 according to their original group allocation. Patients in the placebo arm were allocated in a 1:1 ratio to treatment with 100 mg or 300 mg eptinezumab.
g. Defined as documented treatment failure to 24 of the following prior therapies (drug classes): beta blockers (metoprolol, propranolol, atenolol, bisoprolol), anticonvulsants (topiramate), tricyclic antidepressants (amitriptyline), calcium channel blockers (flunarizine),angiotensin-II antagonists (candesartan), *Clostridium botulinum* toxin type A, or valproic acid (see study description for a definition of treatment failure).
h. In the study arm with monthly fremanezumab dosing, patients with chronic migraine received an initial dose of 675 mg. This departs from the specifications in the SPC (also see A19-44 [17]).
i. Following the placebo-controlled treatment phase, all patients received further monthly treatment with 225 mg fremanezumab for a total of 3 doses in an open-label extension phase.

AE: adverse event; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the interventions – RCT, indirect comparison: eptinezumab versus fremanezumab (multipage table)

Study	Intervention/comparator therapy	Common comparator
Eptinezumab vs. placebo		
DELIVER	Eptinezumab 100 mg every 12 weeks, i.v.	Placebo, every 12 weeks, i.v.
	Required prior treatment ▪ 2–4 failed migraine prophylactic medications in the prior 10 years with the following drugs[a]: ▫ propranolol/metoprolol ▫ topiramate ▫ amitriptyline ▫ flunarizine ▫ candesartan ▫ valproate/divalproex[b] ▫ *Clostridium botulinum* toxin type A/B (documented administration for chronic migraine)[b] ▪ triptans in prior history or at study enrolment **Prohibited prior and concomitant treatment** ▪ CGRP antibodies < 24 weeks prior to screening (for acute treatment, < 4 weeks prior to screening) and during the study ▪ NSAIDs as migraine prophylaxis[c] ▪ Procedures for CNS and migraine treatment (neuromodulation, neurostimulation) or therapeutic injections (trigger point therapy, extracranial nerve blockade, or facet joint injection) < 8 weeks prior to screening and during the study ▪ *Clostridium botulinum* toxin type A injections in the head-neck area ≤ 16 weeks prior to screening and during the study ▪ MAO inhibitors, ketamine, methysergide, methylergonovine, or nimesulide < 12 weeks prior to screening and during the study **Permitted concomitant treatment** ▪ Acute migraine treatment (prescription or nonprescription) allowed if started prior to the study and taken at a constant dosage for ≥ 12 weeks prior to screening ▪ Other drugs in the same drug classes which are not found in the "required prior treatment" list are allowed for other therapeutic indications. ▪ Nonpharmacological interventions (including cognitive behavioural therapy) if taken at a constant dose and started ≥ 12 weeks prior to screening ▪ Barbiturates and prescription-only opiates (e.g. tramadol or tapentadol) < 4 days/month at constant dose for at least 12 weeks prior to screening	
Fremanezumab vs. placebo		
FOCUS	Fremanezumab, monthly: ▪ Starting dose ▫ in chronic migraine: 675 mg, s.c. ▫ in episodic migraine: 225 mg, s.c. ▪ Followed by 225 mg s.c. every 4 weeks (for a total of 2 further doses) or Fremanezumab, quarterly: ▪ in episodic and chronic migraine: single dose of 675 mg s.c. ▪ followed by placebo doses every 4 weeks (for a total of 2 doses)	Placebo every 4 weeks (total of 3 doses)

Table 7: Characteristics of the interventions – RCT, indirect comparison: eptinezumab versus fremanezumab (multipage table)

Study	Intervention/comparator therapy	Common comparator
	Required prior treatment ▪ 2–4 failed medications for migraine prophylaxis in the prior 10 years with the following drugs: ▫ propranolol, metoprolol, atenolol, and bisoprolol ▫ topiramate ▫ amitriptyline ▫ flunarizine ▫ candesartan ▫ *Clostridium botulinum* toxin type A[d] ▫ valproic acid **Prohibited prior treatment** ▪ Procedure or intervention against migraine (e.g. planned nerve block and transcranial magnetic stimulation) within 2 months prior to screening ▪ *Clostridium botulinum* toxin type A injections in the head-neck area within 3 months prior to screening ▪ Opiates or barbiturate-containing analgesics ≥ 4 days within the screening phase ▪ Ergotamines or triptanes as migraine prophylaxis ▪ NSAIDs as migraine prophylaxis[c] ▪ CGRP antibodies **Permitted concomitant treatment[e]** ▪ Pharmacological interventions for the acute treatment of a migraine attack ▪ Other drugs in the same drug classes which are not found in the "required prior treatment" list are allowed for other therapeutic indications. ▪ Other prescription drugs must have been administered at a constant dose for at least 2 months at the time of the screening and remain unchanged throughout the double-blind treatment phase. ▪ Nonprescription drugs or dietary supplements **Nonpermitted concomitant treatment** ▪ Initiation of migraine prophylaxis (see "Required prior treatment") during the screening / run-in phase[f] as well as for the duration of the study[g]	

a. The listed migraine prophylactic drugs were disallowed < 1 week before screening and during the study.
b. Valproate/divalproex or botulinum toxin A/B were not allowed to be the last therapy prior to study start.
c. Low-dose aspirin for the prevention of cardiovascular diseases was allowed.
d. If *Clostridium botulinum* toxin type A was used as the prior prophylactic medication, at least 2 injections had to have been administered, and 3 months had to have passed since the last injection prior to screening.
e. Information on allowed nonpharmacological concomitant treatments is not available in the study documents, but they were not explicitly ruled out (see [18]).
f. At the time of screening, at least 5 half-lives of the prior pharmacological migraine prophylaxis must have passed.
g. Likewise disallowed for the treatment of therapeutic indications other than migraine (except as a topical application or in the form of eye drops).

CGRP: calcitonin-gene related peptide; CNS: central nervous system; i.v.: intravenous; MAO: monoaminooxidase; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial; s. c.: subcutaneous

DELIVER study (with eptinezumab)

The DELIVER study is a double-blind, randomized study comparing eptinezumab versus placebo. Patients with chronic or episodic migraine were included in the study. The study

comprised a 4-week screening phase, a 24-week double-blind, placebo-controlled phase, and a subsequent 48-week phase in which all patients received either 100 mg or 300 mg eptinezumab.

The study enrolled adult patients who had exhibited at least 12 months of documented chronic or episodic migraine (defined in accordance with ICHD-3 [19]). Patients with episodic migraine had to have had an average of ≤ 14 headache days during the screening phase, of which ≥ 4 migraine days. Patients with chronic migraine had to have had an average of ≥ 14 headache days during the screening phase, of which ≥ 8 migraine days.

The extent to which the inclusion criterion of headache or migraine days per month had been met was checked based on the patients' entries into an electronic migraine diary during the 4-week screening phase. This check simultaneously determined patients' compliance in terms of filling out the diary. For transitioning to the randomized treatment phase, compliance in the screening phase had to be at least 24 of 28 days (≥ 85%).

Enrolled were adults with treatment failure of 2 to 4 of the following preventive medications in the past 10 years: propranolol/metoprolol, flunarizine, amitriptyline, topiramate, candesartan, valproate/divalproex, botulinum toxin A/B. Treatment failure had to have been demonstrated for 2 of the following drugs, ≥ 1 of which due to insufficient effectiveness: propranolol/metoprolol, topiramate, amitriptyline, flunarizine, candesartan. Treatment failure was defined as no clinically meaningful improvement after at least 3 months of migraine prophylaxis taken at a constant dose, treatment discontinuation due to adverse events (AEs), or treatment being contraindicated or unsuitable for the patient's migraine prophylaxis.

In the DELIVER study, a total of 892 patients were randomly allocated in a 1:1:1 ratio to treatment with 100 mg eptinezumab (N = 299), 300 mg eptinezumab (N = 294), or placebo (N = 299). Randomization was stratified by number of migraine days per month (≤14 / >14) and country.

According to the SPC [20], the recommended dosage is eptinezumab 100 mg every 12 weeks, with some patients potentially benefiting from 300 mg eptinezumab. Within 12 weeks after treatment start, it should be checked whether dose escalation is needed [20]. In the DELIVER study, patients without prior dose escalation were randomized directly to 300 mg eptinezumab, without prior dose escalation; therefore, this treatment arm is irrelevant for the benefit assessment and is disregarded hereinbelow.

The study allowed the treatment of acute migraine attacks during the study, but only in patients who had already taken that medication prior to the study, and its dosage had to have remained constant for ≥ 12 weeks prior to screening.

The company has presented the results for the subpopulation of patients who previously did not respond to or did not tolerate ≥ 2 drugs (metoprolol/propranolol, flunarizine, amitriptyline, topiramate). The subpopulation comprises 284 patients in the intervention arm and 287 in the

comparator arm. This subpopulation presented by the company is relevant for the present research question and is used for the benefit assessment.

Primary outcome of the study was the change in monthly migraine days from baseline to Week 12. Secondary outcomes were all-cause mortality, other outcomes of the morbidity and health-related quality of life categories, and AEs.

FOCUS study (with fremanezumab)

The FOCUS study was a double-blind, randomized study comparing fremanezumab with placebo. The study has already been described in detail in dossier assessment A19-44 and the associated addendum A19-82. Patients with chronic or episodic migraine were included in the study. The study comprises a 4-week screening phase, a 12-week double-blind, placebo-controlled phase, and a subsequent 12-week open-label phase, in which all patients received fremanezumab.

The study enrolled a total of 838 adult patients with at least 12 months of documented chronic or episodic migraine (defined according to ICHD-3 [19]). Patients with episodic migraine had to have had an average of ≥ 6 and ≤ 14 headache days during the screening phase, of which ≥ 4 migraine days. Patients with chronic migraine had to have had an average of ≥ 14 headache days during the screening phase, of which ≥ 8 migraine days. Patients with headache during ≥ 80% of their waking phase and without headache on < 4 days/month were excluded from the study. The study likewise excluded patients with migraine prophylaxis in the screening phase and those taking opioids or barbiturates for migraine treatment on > 4 days.

The extent to which the inclusion criterion of headache or migraine days per month had been met was checked based on the patients' entries into an electronic migraine diary during the 4-week screening phase. This check simultaneously determined patients' compliance in terms of filling out the diary. For transitioning into the randomized treatment phase, compliance in the screening phase had to be ≥ 85%.

The study enrolled adults with treatment failure to 2 to 4 of the following drug classes in the prior 10 years: beta blockers (metoprolol, propranolol, atenolol, bisoprolol), anticonvulsants (topiramate), tricyclic antidepressants (amitriptyline), calcium channel blocker (flunarizine), angiotensin-II antagonists (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 administered at a constant dose, treatment discontinuation because of AEs, or treatment being contraindicated or unsuitable for the patient's preventive treatment of migraine.

In the 12-week double-blind treatment phase, patients with episodic or chronic migraine were randomly allocated in a 1:1:1 ratio to monthly fremanezumab (N = 283), quarterly fremanezumab (N = 276), or placebo (N = 279).

The quarterly dosing regimen of fremanezumab consisted of a 675 mg dose of fremanezumab for all study participants. The monthly regimen depended on whether patients had episodic or chronic migraine. The fremanezumab regimen in patients with episodic migraine (total of 3 doses at 225 mg each) was in compliance with the approval. The fremanezumab dosing regimen used in patients with chronic migraine (initial administration of 675 mg, followed by 2 further 225 mg doses) deviated from the dosage described in the SPC [21]. The SPC provides for either a monthly fremanezumab dose of 225 mg or a quarterly fremanezumab dose of 675 mg for all patients, regardless of whether they have episodic or chronic migraine [21]. According to the European Medicines Agency (EMA), the 2 dosing regimens (with and without an initial dose of 675 mg in patients with chronic migraine) are comparable in the present therapeutic indication; therefore, the dosing regimen is deemed adequate in the present therapeutic indication [17]. The monthly and quarterly fremanezumab regimens were deemed equivalent and analysed jointly.

The study allowed the use of acute medications to treat acute migraine attacks as needed.

The company used the results from a subpopulation of patients who previously failed to respond to or did not tolerate ≥ 2 therapies (drug classes): beta blockers (propranolol or metoprolol), flunarizine, topiramate, or amitriptyline. The subpopulation comprises 388 patients in the intervention arm and 195 in the comparator arm. This subpopulation presented by the company is relevant for the present research question and is used for the benefit assessment.

Primary outcome of the study was mean change in average monthly migraine days from baseline. Secondary outcomes were all-cause mortality, other outcomes of the morbidity and health-related quality of life categories, and AEs.

Table 8 shows the characteristics of the patients in the studies included.

Table 8: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: eptinezumab versus fremanezumab (multipage table)

Study	DELIVER		FOCUS	
Characteristic Category	Eptinezumab 100 mg	Placebo	Fremanezumab	Placebo
	N[a] = 284	N[a] = 287	N[a] = 388	N[a] = 195
Age [years], mean (SD)	44 (11)	44 (11)	45 (11)	46 (11)
Sex [f/m], %	93/7	89/11	85/15	87/13
Ancestry, n (%)				
White	276 (97)	279 (97)	361 (93)	182 (93)
Other	0 (0)	2 (< 1)	8 (2)[b]	3 (2)[b]
Not reported	8 (3)	6 (2)	19 (5)	10 (5)
Region, n (%)				
Europe	283 (> 99)	285 (> 99)	ND[c]	ND[c]
United States	1 (< 1)	2 (< 1)	ND[c]	ND[c]
Disease duration: time since migraine diagnosis [years], mean (SD)	18.4 (11.7)	17.8 (11.6)	23.4 (13.1)	22.9 (13.1)
Migraine type, n (%)				
EM	169 (60)	167 (58)	149 (38)	76 (39)
CM	115 (40)	120 (42)	239 (62)	119 (61)
Number of migraine days [days/month], mean (SD)	13.8 (5.7)	13.9 (5.8)	14.3 (5.4)	14.2 (5.9)
Percentage of migraine attacks with severe pain intensity [%], mean (SD)	47.1 (29.8)	40.4 (29.9)	ND	ND
Number of headache days [days/months], mean (SD)[d]	14.5 (5.7)	14.5 (5.9)	14.2 (5.8)	14.2 (6.1)
Failed migraine prevention drugs[e], n (%)				
2	207 (73)	204 (71)	296 (76)	143 (73)
3	67 (24)	69 (24)	83 (21)	49 (25)
4	10 (4)	14 (5)	9 (2)	3 (2)
Type of treatment failure				
contraindication	1 (< 1)	1 (< 1)	ND	ND
insufficient effectiveness	284 (100)	286 (> 99)	ND	ND
tolerability-related	154 (54)	150 (52)	ND	ND
Number of days on which migraine-specific acute medication was taken [days/month], mean (SD)	11.2 (5.5)	11.2 (6.0)	9 (6.4)	9.2 (6.7)
Any nonpharmacological prophylaxis of migraine, n (%)	ND	ND	ND	ND
Treatment discontinuation, n (%)[f]	ND	ND	ND	ND
Study discontinuation, n (%)[f]	ND	ND	ND	ND

Table 8: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: eptinezumab versus fremanezumab (multipage table)

Study	DELIVER		FOCUS	
Characteristic Category	Eptinezumab 100 mg	Placebo	Fremanezumab	Placebo
	N[a] = 284	N[a] = 287	N[a] = 388	N[a] = 195

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation; combination of the categories of Black, Asian, and Other.
c. Information regarding region for the total population n/N (%), FOCUS study:
Europe: 479/559 (86) vs. 239/279 (86), USA: 80/559 (14) vs. 40/279 (14) (see [22]).
d. Discrepant information provided within Module 4 A for the DELIVER study; the following information is also found: mean (SD) 14.5 (5.9) versus 14.4 (5.5).
e. Insufficient response or intolerance to a prophylactic therapy with the following drugs: propranolol/metoprolol, topiramate, flunarizine, amitriptyline.
f. Information on discontinuations in the total population n/N (%), although the study documents do not show whether they were treatment or study discontinuations.
DELIVER study: 11/299 (4) vs. 5/299 (2); FOCUS study: 15/559 (3) vs. 13/279 (5).

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

The characteristics of the relevant subpopulations are largely balanced between the arms of the individual studies. In both studies, the mean patient age was about 45 years, and most participants were of White ancestry. On average, the study populations had about 14 migraine days per month. Differences between the studies were found in the percentage of patients with chronic migraine, which was about 40% in the DELIVER study and about 60% in the FOCUS study. On average, patients had been suffering from the disease for about 18 years in the DELIVER study and for about 23 years in the FOCUS study. In both studies, > 70% of patients had received 2 migraine prophylactics prior to study inclusion.

No information was available on study or treatment discontinuations for the relevant subpopulations of both studies. The percentage of discontinuations was very low in the total populations. However, the study documents do not show whether they were study or treatment discontinuations.

I 4.1.3 Similarity of the studies for the indirect comparison

Study design

The DELIVER and FOCUS studies are multicentre, double-blind RCTs which each enrolled adult patients with chronic or episodic migraine with ≥ 4 migraine days per month. The study designs differed in the duration of the placebo-controlled phase, which equalled 24 weeks in the DELIVER study and 12 weeks in the FOCUS study. However, outcomes in the morbidity and health-related quality of life categories were also surveyed after 12 weeks; therefore, results of both studies in this category are available for a similar time period. In the DELIVER study, side effects outcomes are available only for the entire 24-week placebo-controlled phase. Due

to the comparatively low number of events, this remains without consequence for the indirect comparison in the present situation.

The periods during which the studies were conducted differ slightly. While the DELIVER study started in June 2020 and its placebo-controlled phase ended in October 2021, the FOCUS study started earlier, in November 2017, and its placebo-controlled phase ended in October 2018.

Similarity of the patient population

Information on patient characteristics and prior therapies is found in Section I 4.1.2.

The participants' demographic and clinical characteristics are sufficiently comparable between the DELIVER and FOCUS studies. The studies did not meaningfully differ in the number of prior failed pharmacological migraine therapies because the study populations were comparably limited to the relevant subpopulation on the basis of prior pharmacological therapies.

Similarity of the common comparator

In the present indirect comparison, the common comparator is placebo. Both studies allowed the use of acute medication for the treatment of migraine attacks. The DELIVER study, however, requires that pharmacological interventions for the acute treatment of a migraine attack have been administered at a constant dose ≥ 12 weeks prior to screening (i.e. no first-time use).

The DELIVER study additionally allows the use of nonpharmacological interventions (including cognitive behavioural therapy) if they continued unchanged for ≥ 12 weeks prior to screening. According to the information provided in Module 4 A, further measures such as acupuncture or endurance sports were likewise allowed. Nonpharmacological interventions disallowed during the study and ≥ 8 weeks prior to the study include devices for the stimulation of the central nervous system such as neuromodulation and neurostimulation or injection therapy. For the FOCUS study, no information is available on the use of nonpharmacological measures, or these measures were not documented. Since the FOCUS study did not explicitly exclude nonpharmacological measures, fremanezumab was assessed [18] under the general assumption that their use was allowed.

The differences between the DELIVER and FOCUS studies in the allowed concomitant treatment are not reflected by the clinical characteristics in the DELIVER and FOCUS studies' placebo arms – neither in the number of monthly migraine days nor in the monthly use of migraine-specific acute medications.

Summary of the studies' similarity

Similarity is a key requirement for the consideration of studies in the adjusted indirect comparison. The DELIVER and FOCUS studies have a very similar study design, which ultimately differs only in the duration of the placebo-controlled phase. Additionally, the studies'

patient populations are sufficiently similar. The described differences between the DELIVER and FOCUS studies regarding their allowed concomitant treatments likewise do not call into question sufficient similarity and hence the permissibility of an adjusted indirect comparison using the common comparator of placebo.

I 4.1.4 Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, indirect comparison: eptinezumab versus fremanezumab

Comparison Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of additional aspects	Risk of bias at study level
			Patients	Treatment providers			
Eptinezumab vs. placebo							
DELIVER	Yes	Yes	Yes	Yes	Yes	Yes	Low
Fremanezumab vs. placebo							
FOCUS	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for both studies.

Transferability of the study results to the German health care context

The company assumes good transferability of the results of the DELIVER and the FOCUS studies to the German healthcare context and justifies this assumption by citing, e.g. the studies being conducted largely in European study centres where the standard of care for migraine patients is deemed similarly high. Additionally, from the studies for the early benefit assessment, a subpopulation was used consisting of patients who had treatment failure with or were not candidates for ≥ 2 prior therapies with the drugs propranolol/metoprolol, amitriptyline, topiramate, and flunarazine, i.e. therapies specified by the G-BA as "conventional" migraine prophylactics in Germany.

Further, the company derives ready transferability to the demographic structure of the German population from the fact that the majority of migraine patients were female and developed the disease in middle age. In the company's view, this is also reflected by the characteristics of the included patients, who were predominantly white, female, and, on average, in their mid-40s.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4.2 Results on added benefit

I 4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - symptoms, measured by migraine days per month
  - general headache-related disability, recorded using the HIT-6
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - health-related quality of life, surveyed with the Migraine-Specific Quality of Life questionnaire (MSQoL)
- Side effects
  - SAEs
  - discontinuation due to AEs
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that taken by the company, which used further outcomes in the dossier (Module 4A).

Table 10 shows whether the included studies provided data on the respective outcome (yes/no) and whether an indirect comparison is possible based on the available data (yes/no).

Table 10: Matrix of outcomes – RCT, indirect comparison: eptinezumab versus fremanezumab

Comparison Study	Outcomes							
	All-cause mortality	Symptoms (migraine days per month; as supplementary information: headache days per month)	General headache-related disability (HIT-6)	Health status (EQ-5D VAS)	Health-related quality of life (MSQoL)	SAEs	Discontinuation due to AEs	Specific AEs
Eptinezumab vs. placebo								
DELIVER	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[a]
Fremanezumab vs. placebo								
FOCUS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[b]
Indirect comparison possible	Yes	No[c]	Yes	Yes	Yes	Yes	Yes	No

a. No specific AEs identified based on the AEs occurring in the relevant study.
b. No complete analyses available on AEs. It is impossible to select specific AEs based on complete data because data are available only on the SOC level and not on the PT level.
c. Certainty of results insufficient for performing an adjusted indirect comparison (see Table 11 and Section I 4.2.2).

AE: adverse event; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HIT-6: Headache Impact Test-6; MSQoL: Migraine-Specific Quality of Life; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Symptoms – migraine days per month

In the following benefit assessment, the outcome of symptoms was assessed on the basis of migraine days per month. In both studies, data were recorded daily by patients in their electronic patient diary.

Both studies defined migraine days per month based on the ICHD-3 criteria [19]. Hence, the 2 operationalizations are assumed to be sufficiently similar. Against the background of patients' symptom burden, reduction by ≥ 50% represents an appropriate response criterion, regardless of whether the migraine is episodic or chronic. Therefore, reduction of migraine days per month by ≥ 50% is used for the derivation of added benefit. The analyses of reduction by ≥ 75% are presented as supplementary information. However, the indirect comparison for this outcome is disregarded in the benefit assessment because the results for the outcome of symptoms (migraine days per month) in the FOCUS study do not exhibit the certainty of results required for performing an adjusted indirect comparison (see Table 11 and Section I 4.2.2).

The benefit assessment disregarded headache days per month because migraine days per month reflect the patients' burden of disease more accurately than the less specific number of days with headache of any type. Migraine days per month already reflect the parameter of interest in the present therapeutic indication, i.e. migraine or probable migraine according to the ICHD-3 classification.

I 4.2.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, indirect comparison: eptinezumab versus fremanezumab

Comparison Study	Study level	Outcomes							
		All-cause mortality	Symptoms (migraine days per month; as supplementary information: headache days per month)	General headache-related disability (HIT-6)	Health status (EQ-5D VAS)	Health-related quality of life (MSQoL)	SAEs	Discontinuation due to AEs	Specific AEs
Eptinezumab vs. placebo									
DELIVER	L	L	L	L	L	L	L	L	–[a]
Fremanezumab vs. placebo									
FOCUS	L	L	H[b]	L	L	L	L	L	–[c]

a. No specific AEs were identified based on the AEs occurring in the study.
b. No information available on the frequency or distribution of missing values in the electronic diary.
c. No usable analyses available on AEs. It is impossible to select specific AEs based on complete data because data are available only on the SOC level and not on the PT level.

AE: adverse event; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; H: high; HIT-6: Headache Impact Test 6; L: low; MSQoL: Migraine-Specific Quality of Life; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias is deemed low for the results on the outcomes of both studies, except for 1 outcome in the FOCUS study: Like in the prior benefit assessment A19-82 [18], the risk of bias for the result regarding the outcome of symptoms (migraine days per month) is deemed high for the FOCUS study because no information is available on the frequency or distribution of missing values in the electronic diary.

I 4.2.3 Results

Table 12 to Table 14 summarize the results on the comparison of eptinezumab with fremanezumab in patients with ≥ 4 migraine days per month who had not responded to ≥ 2 prior therapies with propranolol/metoprolol or flunarizine or topiramate or amitriptyline or who did not tolerate these therapies. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

For the DELIVER study, tables on common AEs and common SAEs are presented in I Appendix B of the full dossier assessment. For the FOCUS study, the table on common AEs on the SOC level is likewise presented in I Appendix B of the full dossier assessment. No information is available on Preferred Terms (PTs) for the FOCUS study (see A19-82 [18]).

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, indirect comparison: eptinezumab versus fremanezumab (multipage table)

Outcome category Outcome Comparison Study	Eptinezumab or fremanezumab N	 Patients with event n (%)	Placebo N	 Patients with event n (%)	Between-group difference RR [95% CI]; p-value
Mortality					
All-cause mortality					
Eptinezumab vs. placebo					
DELIVER (until Week 24)	284	0 (0)	287	0 (0)	–
Fremanezumab vs. placebo					
FOCUS (until Week 12)	388	0 (0)	195	0 (0)	–
Indirect comparison using common comparators[a]: eptinezumab vs. fremanezumab					–
Morbidity					
Symptoms: migraine days per month					
Reduction by ≥ 50%					
Eptinezumab vs. placebo					
DELIVER (until Week 12)	284	123 (43.3)	287	38 (13.2)	3.27 [2.36; 4.53]; < 0.001[b]
Fremanezumab vs. placebo					
FOCUS (until Week 12)	388	144 (37.1[c])	195	19 (9.7[c])	3.82 [2.44; 5.97]; < 0.001[d]
Indirect comparison via common comparators[a]: eptinezumab vs. fremanezumab					–[e]
Reduction by ≥ 75% (supplementary information)					
Eptinezumab vs. placebo					
DELIVER (Weeks 1–12)	284	47 (16.5)	287	6 (2.1)	7.90 [3.44; 18.1]; < 0.001[b]
Fremanezumab vs. placebo					
FOCUS (Weeks 1–12)	388	46 (11.9[c])	195	5 (2.6[c])	4.64 [1.87; 11.48]; < 0.001[d]
Indirect comparison via common comparators[a]: eptinezumab vs. fremanezumab					–[e]
Side effects					
AEs (supplementary information)					
Eptinezumab vs. placebo					
DELIVER (until Week 24)	284	115 (40.5)	287	112 (39.0)	–
Fremanezumab vs. placebo					
FOCUS (until Week 12)	388	208 (53.6)	195	101 (51.8[c])	–

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, indirect comparison: eptinezumab versus fremanezumab (multipage table)

Outcome category Outcome Comparison Study	Eptinezumab or fremanezumab N	 Patients with event n (%)	Placebo N	 Patients with event n (%)	Between-group difference RR [95% CI]; p-value
SAEs					
Eptinezumab vs. placebo					
DELIVER (until Week 24)	284	4 (1.4)	287	4 (1.4)	1.0 [0.3; 4.0]; 0.987[f]
Fremanezumab vs. placebo					
FOCUS (until Week 12)	388	4 (1.0[c])	195	3 (1.5[c])	0.67 [0.15; 2.96]; 0.625[g]
Indirect comparison via common comparators[a]:					
Eptinezumab vs. fremanezumab					1.49 [0.21; 10.76]; 0.691
Discontinuation due to AEs					
Eptinezumab vs. placebo					
DELIVER (until Week 24)	284	0 (0)	287	0 (0)	1.01 [0.06; 16.1]; 0.994[f]
Fremanezumab vs. placebo					
FOCUS (until Week 12)	388	3 (0.8)	195	2 (1.0[c])	0.75 [0.13; 4.47]; 0.829[g]
Indirect comparison via common comparators[a]:					
eptinezumab vs. fremanezumab					1.35 [0.05; 35.87]; 0.858

a. Indirect comparison according to Bucher [3].
b. RR and CI: log-binomial model; adjusted for monthly migraine days at study start (≤ 14 days / > 14 days); p-value: logistical model; adjusted for monthly migraine days at study start (≤ 14 days / > 14 days) as well as baseline. The mean percent change in monthly migraine days was calculated using three 4-week intervals. Replaced depending on the number of missing diary entries (< 14 days / ≥ 14 days) and the reason for discontinuation, if applicable; in the three 4-week intervals, both treatment groups had diary entries on ≥ 21 days for > 90% of patients.
c. Institute's calculation.
d. RR, CI, and p-value (unconditional exact test, CSZ method according to [23]: unadjusted; patients with missing baseline score were rated as nonresponders. In patients with diary entries on ≥ 10 days/month, the available data were extrapolated to 28 days; in patients with diary entries on < 10 days/month, the missing values were carried forward using the LOCF method. The extent of replacements performed is unclear.
e. No indirect comparison was used for the benefit assessment because the certainty of results was insufficient for performing an adjusted indirect comparison (see Section I 4.2.2).
f. RR and CI: log-binomial model; p-value: CMH test; each adjusted based on monthly headache days at baseline (≤ 14 days / > 14 days). In case of a zero cell, a correction value of 0.5 was added to each cell entry in the corresponding 2x2 table; for calculating RR and performing the test, the correction was performed per stratum, i.e. only strata with zero cells were adjusted.
g. RR, CI, and p-value (unconditional exact test, CSZ method according to [23]); unadjusted.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; LOCF: last observation carried forward; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Table 13: Results (morbidity, presented as supplementary information, continuous) – RCT, indirect comparison: eptinezumab versus fremanezumab

Outcome category Outcome Comparison Study	Eptinezumab or fremanezumab			Placebo			Between-group difference
	N[a]	Values at baseline mean (SD)	Mean change over the course of the study until Week 12 mean (SE or SD)[b]	N[a]	Values at baseline mean (SD)	Mean change over the course of the study until Week12 mean (SE or SD)[b]	MD [95% CI]; p-value
Morbidity							
Symptoms: headache days per month, any severity (presented as supplementary information)							
Eptinezumab vs. placebo							
DELIVER	284	14.5 (5.7)	-4.6 (0.4)[c]	287	14.5 (5.9)	-2.0 (0.4)[c]	-2.7 [-3.4; -1.9]; < 0.001[c]
Fremanezumab vs. placebo							
FOCUS	388	14.2 (5.8)	-4.7 (4.6)	195	14.2 (6.1)	-1.3 (4.2)	-3.47 [-4.32; -2.62]; < 0.001[d]
Indirect comparison using common comparators: eptinezumab vs. fremanezumab							–[e]

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. Information was provided on the SE for the DELIVER study and on the SD for the FOCUS study.
c. Mean and SE (mean change per treatment group) as well as MD, CI, and p-value (group comparison): MMRM. Replaced depending on the number of missing diary entries (< 14 days / ≥ 14 days) and the reason for discontinuation, if applicable; in the three 4-week intervals, both treatment groups had diary entries on ≥ 21 days for > 90% of patients. The effect represents the difference in mean changes (compared to study start) between the treatment groups in the first 12 months of the study.
d. MD, CI, and p-value (between-group comparison); according to study documents: MMRM. Patients with missing baseline value were excluded from the analysis. In patients with diary entries on ≥ 10 days/month, the available data were extrapolated to 28 days; in patients with diary entries on < 10 days per month, the missing values were carried forward using the LOCF method. The extent of replacements performed is unclear. The effect represents the difference in mean changes (compared to study start) between the treatment groups in the 12 months of the study.
e. No indirect comparison was used for the benefit assessment because the certainty of results was insufficient for performing an adjusted indirect comparison (see Section I 4.2.2).

CI: confidence interval; LOCF: last observation carried forward; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison: eptinezumab versus fremanezumab (multipage table)

Outcome category	Eptinezumab or fremanezumab			Placebo			Between-group difference
Outcome Compar-ison Study	N[a]	Values at baseline mean (SD)	Change at Week 12 mean[b] (SE or SD)b	N[a]	Values at baseline mean (SD)	Change by Week 12 mean (SE and SD)[b]	MD [95% CI]; p-value
Morbidity							
General headache-related disability (HIT-6)[c]							
Eptinezumab vs. placebo							
DELIVER	ND[d]	66.6 (4.7)	-7.1 (0.7)[e]	ND[d]	66.3 (4.4)	-3.2 (0.6)[e]	-3.8 [-5.1; -2.6]; < 0.001[e]
Fremanezumab vs. placebo							
FOCUS	388	64.2 (4.4)	-6.4 (7.2)	195	64.0 (5.2)	-3.0 (6.2)	-3.37 [-4.45; -2.30]; < 0.001[f]
Indirect comparison using common comparators[g]:							
eptinezumab vs. fremanezumab							-0.43 [-2.08; 1.22]; 0.609
Health status (EQ-5D VAS)[h]							
Eptinezumab vs. placebo							
DELIVER	ND[d]	76.0 (19.0)	2.3 (1.5)[e]	ND[d]	73.9 (20.6)	-2.9 (1.5)[e]	5.2 [2.20; 8.29]; < 0.001[e]
Fremanezumab vs. placebo							
FOCUS	388	69.6 (21.2)	6.3 (20.1)	195	70.1 (20.1)	1.7 (17.6)	4.22 [1.28; 7.17]; 0.005[i]
Indirect comparison using common comparators[g]:							
eptinezumab vs. fremanezumab							0.98 [-3.26; 5.22]; 0.650
Health-related quality of life							
MSQoL[h]							
Limitation of role functioning							
Eptinezumab vs. placebo							
DELIVER	ND[d]	35.7 (17.6)	25.3 (1.9)[e]	ND[d]	35.0 (17.0)	14.0 (1.8)[e]	11.3 [7.87; 14.8]; < 0.001[e]
Fremanezumab vs. placebo							
FOCUS	388	47.6 (17.4)	18.3 (20.4)	195	47.6 (19.0)	9.7 (17.2)	9.06 [5.77; 12.35]; < 0.001[f]
Indirect comparison using common comparators[g]:							
eptinezumab vs. fremanezumab							2.24 [-2.54; 7.02]; 0.358

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison: eptinezumab versus fremanezumab (multipage table)

Outcome category	Eptinezumab or fremanezumab			Placebo			Between-group difference
Outcome Compar-ison Study	N[a]	Values at baseline mean (SD)	Change at Week 12 mean[b] (SE or SD)b	N[a]	Values at baseline mean (SD)	Change by Week 12 mean (SE and SD)[b]	MD [95% CI]; p-value
Prevention of role functioning							
Eptinezumab vs. placebo							
DELIVER	ND[d]	50.2 (21.6)	23.1 (1.7)[e]	ND[d]	50.4 (22.0)	11.8 (1.7)[e]	11.3 [8.01; 14.5]; < 0.001[e]
Fremanezumab vs. placebo							
FOCUS	388	63.2 (20.4)	14.5 (18.5)	195	64.2 (21.0)	8.6 (17.4)	5.81 [2.82; 8.80]; < 0.001[f]
Indirect comparison using common comparators[g]:							
eptinezumab vs. fremanezumab							5.49 [1.08; 9.9]; 0.015 SMD: 0.2 [0.04; 0.35]
Emotional state							
Eptinezumab vs. placebo							
DELIVER	ND[d]	50.1 (24.5)	21.2 (2.0)[e]	ND[d]	48.6 (26.7)	9.9 (1.9)[e]	11.3 [7.63; 15.0]; < 0.001[e]
Fremanezumab vs. placebo							
FOCUS	388	60.6 (23.9)	16.6 (22.6)	195	60.6 (25.3)	8.1 (21.9)	9.14 [5.52; 12.77]; < 0.001[f]
Indirect comparison using common comparators[g]:							
eptinezumab vs. fremanezumab							2.16 [-3.01; 7.33]; 0.413

a Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. Information was provided on the SE for the DELIVER study and on the SD for the FOCUS study.
c. Lower values indicate lower general headache-related disability (scale range of 36 to 78); in the direct comparison, a negative between-group difference indicates an advantage for eptinezumab or fremanezumab. In the direct comparison, negative effects indicate an advantage for eptinezumab.
d. It is unclear how many patients were included in the analysis; information is available only on the number of patients with a survey at various time points. According to this information, however, more than 90% of patients of both treatment groups must have been included.
e. Mean and SE (mean change per treatment group) as well as MD, CI, and p-value (between-group comparison): MMRM. Effect represents the difference in changes (compared to baseline) between the treatment groups at Week 12.
f. MD, CI, and p-value (between-group comparison); according to study documents: MMRM. Effect represents the difference in changes (compared to baseline) between the treatment groups at Week 12.
g. Indirect comparison according to Bucher [3]. Higher values indicate better health status (scale range of 0 to 100) or better health-related quality of life (scale range for limitations in role functioning 7 to 42, prevention of role functioning 4 to 24, emotional functioning 3 to 18); in the direct comparison, a positive between-group difference indicates an advantage for eptinezumab or fremanezumab. In the indirect comparison, positive effects indicate an advantage for eptinezumab.
i. MD, CI, and p-value (between-group comparison); according to study documents: ANCOVA. Effect represents the difference in changes (compared to baseline) between the treatment groups at Week 12.

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison: eptinezumab versus fremanezumab (multipage table)

Outcome category	Eptinezumab or fremanezumab			Placebo			Between-group difference
Outcome Compar-ison Study	N[a]	Values at baseline mean (SD)	Change at Week 12 mean[b] (SE or SD)b	N[a]	Values at baseline mean (SD)	Change by Week 12 mean (SE and SD)[b]	MD [95% CI]; p-value

ANCOVA: analysis of covariance; CI: confidence interval; HIT-6: Headache Impact Test-6; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; LOCF: last observation carried forward; MD: mean difference; MMRM: mixed-effects model repeated measures; MSQoL: Migraine-Specific Quality of Life; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; VAS: visual analogue scale

There was 1 RCT each on both sides of this adjusted indirect comparison. Hence, homogeneity was not checked. As there is no directly comparative study for the comparison of eptinezumab versus the ACT, it is impossible to check the consistency of results. Therefore, the adjusted indirect comparisons had at most a low certainty of results. Hence, on the basis of the available data, at most hints, e.g. of an added benefit, could be derived from the adjusted indirect comparison.

Additionally, the risk of bias is high for the result regarding the outcome of symptoms (migraine days / month) in the FOCUS study. Hence, the certainty of results is insufficient for conducting an adjusted indirect comparison, and the indirect comparison is disregarded in the benefit assessment.

Mortality

All-cause mortality

No deaths occurred in the 2 studies. This results in no hint of an added benefit of eptinezumab in comparison with fremanezumab for the outcome of all-cause mortality; an added benefit is therefore not proven.

Morbidity

Symptoms (reduction of migraine days per month by ≥ 50%)

For the result regarding the outcome of symptoms (reduction in migraine days per month by ≥ 50%), the FOCUS study exhibits a high risk of bias (see Section I 4.2.2). Hence, the certainty of results is insufficient for conducting an adjusted indirect comparison, and the indirect comparison is disregarded in the benefit assessment. The same applies to the operationalizations presented as supplementary information, i.e. reduction of migraine days per month by ≥ 75% and mean change in headache days per month. This results in no hint of an added benefit of eptinezumab in comparison with fremanezumab; an added benefit is therefore not proven.

General headache-related disability (HIT-6)

For the outcome of general headache-related disability (HIT-6), the adjusted indirect comparison shows no statistically significant difference between eptinezumab and fremanezumab. This results in no hint of an added benefit of eptinezumab in comparison with fremanezumab; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

For the outcome of health status (EQ-5D VAS), the adjusted indirect comparison shows no statistically significant difference between eptinezumab and fremanezumab. This results in no hint of an added benefit of eptinezumab in comparison with fremanezumab; an added benefit is therefore not proven.

Health-related quality of life

MSQoL

For the outcome of health-related quality of life, surveyed with the MSQoL, the adjusted indirect comparison shows no statistically significant difference between eptinezumab and fremanezumab for the domains of limitation of role functioning and emotional state. This results in no hint of an added benefit of eptinezumab in comparison with fremanezumab; an added benefit is therefore not proven.

For the domain of prevention of role functioning, the adjusted indirect comparison shows a statistically significant difference in favour of eptinezumab. The SMD was analysed to examine the relevance of the results. However, for the domain of 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. This results in no hint of an added benefit of eptinezumab in comparison with fremanezumab; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

No statistically significant difference between eptinezumab and fremanezumab was shown in the adjusted indirect comparison for either of the outcomes of SAEs or discontinuation due to AEs. There was no hint of greater or lesser harm from eptinezumab in comparison with fremanezumab for any of these outcomes; greater or lesser harm is therefore not proven for these outcomes.

I 4.2.4 Subgroups and other effect modifiers

No subgroup analyses for the indirect comparison are available for the present benefit assessment of eptinezumab. Thus, no conclusions on potential effect modifications are possible for the comparison of eptinezumab versus fremanezumab.

I 4.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 4.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section I 4.2 (see Table 15).

Table 15: Extent of added benefit at outcome level: eptinezumab versus fremanezumab (multipage table)

Outcome category **Outcome**	**Eptinezumab vs. fremanezumab** **Proportion of events (%) or mean** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser/added benefit not proven
Morbidity		
Symptoms, migraine days per month; reduction by ≥ 50%	No usable data[c]	Lesser/added benefit not proven
General headache-related disability (HIT-6)	-7.1 vs. -6.4 MD: -0.43 [-2.08; 1.22] p = 0.609	Lesser/added benefit not proven
Health status (EQ-5D VAS)	2.3 vs. 6.3 MD: 0.98 [-3.26; 5.22] p = 0.650	Lesser/added benefit not proven
Health-related quality of life		
MSQoL		
Limitation of role functioning	25.3 vs. 18.3 MD: 2.24 [-2.54; 7.02] p = 0.358	Lesser/added benefit not proven
Prevention of role functioning	23.1 vs. 14.5 MD: 5.49 [1.08; 9.9] p = 0.015 SMD[d]: 0.2 [0.04; 0.35]	Lesser/added benefit not proven
Emotional state	21.2 vs. 16.6 MD: 2.16 [-3.01; 7.33] p = 0.413	Lesser/added benefit not proven
Side effects		
SAEs	1.4% vs. 1.0% RR: 1.49 [0.21; 10.76] p = 0.691	Greater/lesser harm not proven
Discontinuation due to AEs	0% vs. 0.8% RR: 1.35 [0.05; 35.87] p = 0.858	Greater/lesser harm not proven

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category and the scale level of the outcome, effect size is estimated with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L).
c. Effect estimate from the indirect comparison not presented due to insufficient certainty of results (see Section I 4.2.2).
d. If the CI for the SMD 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.

Table 15: Extent of added benefit at outcome level: eptinezumab versus fremanezumab (multipage table)

Outcome category **Outcome**	**Eptinezumab vs. fremanezumab** **Proportion of events (%) or mean** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
AE: adverse event; CI: confidence interval; CI_L: lower limit of CI; CI_u: upper limit of CI; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; MD: mean difference; MSQoL: Migraine-Specific Quality of Life; RR: relative risk; SMD: standardized mean difference; SAE: serious adverse event; VAS: visual analogue scale		

I 4.3.2 Overall conclusion on added benefit

Table 16 summarizes the results included in the overall conclusion on the extent of added benefit.

Table 16: Favourable and unfavourable effects from the assessment of eptinezumab versus fremanezumab

Favourable effects	**Unfavourable effects**
–	–
For the outcome of symptoms (migraine days per month; reduction by ≥ 50%), no usable data are available for the indirect comparison.	

Overall, based on the adjusted indirect comparison using placebo as the common comparator, there are no relevant favourable nor unfavourable effects of eptinezumab in comparison with fremanezumab.

In summary, there is no hint of added benefit of eptinezumab versus fremanezumab for adult patients who have at least 4 migraine days per month and who are not candidates for conventional migraine prophylaxis.

This assessment deviates from that by the company, which derived a hint of a non-quantifiable added benefit for eptinezumab versus the ACT of fremanezumab.

I 5 Probability and extent of added benefit – summary

Table 17 summarizes the results of the assessment of the added benefit of eptinezumab in comparison with the ACT.

Table 17: Eptinezumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Previously untreated as well as previously treated adult patients who have at least 4 migraine days per month and who are candidates for conventional migraine prophylaxis	Metoprolol or propranolol or flunarizine or topiramate or amitriptyline or *Clostridium botulinum* toxin type A[b], taking into account approval and prior therapy	Added benefit not proven
2	Adult patients with at least 4 migraine days per month who do not respond to any of the following drug treatments/classes, for whom they are unsuitable, or who do not tolerate them[c]: metoprolol, propranolol, flunarizine, topiramate, amitriptyline, *Clostridium botulinum* toxin type A	Erenumab or **fremanezumab** or galcanezumab	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. Even in chronic migraine, *Clostridium botulinum* toxin type A is not a standard option for all patients in research question 1.
c. In research question 2, treatment with biologic agents may be an option if patients previously did not respond to or did not tolerate at least 2 drug therapies (drug classes from research question 1). In cases where patients are not candidates for the drugs from research question 1, this must be documented and reasoning provided.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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