Atogepant
(migraine prophylaxis)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Medical and scientific advice

- Thomas Henze

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 one person.

IQWiG thanks the respondent and the patient organization MigräneLiga e. V. Deutschland for participating and for their support. The respondent and MigräneLiga e. V. Deutschland were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIT-6	6-Item Headache Impact Test
ICHD3	International Classification of Headache Disorders, third edition
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MSQ	Migraine-Specific Quality of Life
NSAID	non-steroidal anti-inflammatory drug
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SOC	System Organ Class
SmPC	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 atogepant. 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 28 February 2025.

Research question

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

The research questions presented in Table 2 were defined in accordance with the ACT specified by the G-BA.

Table 2: Research questions for the benefit assessment of atogepant

Research question	Therapeutic indication	ACT[a]
1	Adults who have at least 4 migraine days per month and who are candidates for conventional migraine prophylaxis	Metoprolol or propranolol or flunarizine (if treatment with beta-receptor blockers is contraindicated or has not been sufficiently effective) or amitriptyline or clostridium botulinum toxin type A (only for chronic migraine[b]) or erenumab
2	Adults who have at least 4 migraine days per month and who do not respond to any of the following drug treatments/drug classes, for whom they are unsuitable, or who do not tolerate them[c]: metoprolol, propranolol, flunarizine, 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 according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**.
b. Even in cases of chronic migraine, clostridium botulinum toxin type A is not a usual treatment option for all patients in research question 1.
c. In research question 2, treatment with biologics may be considered as part of a clinical study if patients have not responded to or have not tolerated at least 2 drug therapies (drug classes from research question 1). In cases where the drugs from research question 1 are not suitable for patients, this must be documented and justified.

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

For easier presentation and better readability, this benefit assessment uses the following wordings for the research questions in the running text:

- 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

The company followed the G-BA's specification of the ACT for both research questions. For research question 2, the company selected the 2 drugs erenumab and fremanezumab as the comparator therapy from the 3 options presented for an indirect comparison.

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 duration of 12 weeks were used to derive the added benefit.

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

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

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

Consistent with the findings of the company, no studies for the direct comparison of atogepant with the ACT were identified for research question 2.

For research question 2, the company therefore presented adjusted indirect comparisons for the assessment of atogepant versus erenumab or fremanezumab via the common comparator placebo. For this purpose, it identified the studies ELEVATE, ADVANCE and PROGRESS on the intervention side, and the studies LIBERTY and FOCUS on the erenumab and fremanezumab side. Primarily relevant for the present assessment were analyses on the indirect comparison of atogepant versus erenumab or fremanezumab using all 5 studies on episodic and/or chronic migraine. Analyses of the indirect comparison of atogepant with erenumab were additionally considered as a sensitivity analysis. These analyses included only those studies in which only patients with episodic migraine were included. The review of the completeness of the study pool did not identify any additional relevant studies for the indirect comparison of atogepant versus erenumab or fremanezumab besides the 5 studies identified by the company.

Study pool and study design

Studies with atogepant (ELEVATE, ADVANCE, PROGRESS)

ELEVATE study

The ELEVATE study is a double-blind RCT comparing atogepant with placebo. Patients with episodic migraine were included in the study. The study consisted of a 4-week screening/baseline phase, a 12-week double-blind, placebo-controlled treatment phase, and a 4-week follow-up phase.

Adult patients aged 18 to 80 years with a history of migraine of at least 12 months were included. Patients had to have 4 to 14 migraine days per month in the 3 months prior to study inclusion and in the screening/baseline phase.

Another inclusion criterion was documented treatment failure of 2 to 4 of the following drugs with different mechanisms of action: beta-blockers (propranolol/metoprolol/atenolol/ bisoprolol/timolol/nadolol), anticonvulsants (topiramate), calcium channel blockers (flunarizine), valproate/divalproex, tricyclic antidepressants (amitriptyline/nortriptyline), venlafaxine/desvenlafaxine, lisinopril, angiotensin II receptor blockers (candesartan), locally approved products (e.g. oxeterone or pizotifen). This included ≥ 1 treatment failure due to insufficient efficacy or tolerability of beta-blockers (propranolol/metoprolol), topiramate, flunarizine or amitriptyline. Patients with medication overuse within 3 months prior to baseline and during the screening/baseline phase were not included.

In the ELEVATE study, a total of 315 patients were randomly allocated in a 1:1 ratio to treatment with 60 mg atogepant (N = 157) or placebo (N = 158).

Treatment with atogepant was administered orally once daily, which was in compliance with the summary of product characteristics (SmPC). The additional treatment of acute migraine attacks with pharmacological or non-pharmacological interventions was possible during the course of the study.

The primary outcome of the study was migraine days/month operationalized as the change from baseline in monthly migraine days across a 12-week period. Secondary outcomes were further outcomes in the categories morbidity and health-related quality, as well as adverse event (AE) outcomes.

The company presented the results of a subpopulation of 126 patients in the intervention arm and 129 patients in the comparator arm who previously did not respond to ≥ 2 of the following drugs with different mechanisms of action, who did not tolerate these, or who had a contraindication: beta-blockers (metoprolol/propranolol), flunarizine, amitriptyline, topiramate or valproic acid. This subpopulation presented by the company was used for this benefit assessment.

ADVANCE study

The ADVANCE study is a 4-arm, double-blind RCT comparing atogepant at 3 different doses and placebo. Patients with episodic migraine were included in the study. The study consisted of a 4-week screening/baseline phase, a 12-week double-blind, placebo-controlled treatment phase, and a 4-week follow-up phase.

As in the ELEVATE study, adult patients aged 18 to 80 years with a history of migraine of at least 12 months were included. Patients had to have 4 to 14 migraine days/month in the 3 months prior to study inclusion.

In contrast to the ELEVATE study, adults with and without prior migraine prevention medication were enrolled. Patients were excluded who had failed > 4 medications for the prophylaxis of migraine, including 2 drugs with different mechanisms of action, out of the following drugs: beta-blockers (propranolol/metoprolol/bisoprolol/atenolol/nadolol/ timolol), anticonvulsants (topiramate), calcium channel blockers (flunarizine), valproate/divalproex, tricyclic antidepressants (amitriptyline/nortriptyline), venlafaxine, lisinopril, angiotensin II receptor blockers (candesartan), locally approved drugs (e.g. oxeterone or pizotifen). In addition, participation in the study was not possible for patients with medication overuse within 3 months before the start of the study or during the screening/baseline phase.

A total of 910 patients were randomly allocated in a ratio of 1:1:1:1 to treatment with atogepant 10 mg (N = 222), atogepant 30 mg (N = 230), atogepant 60 mg (N = 235) or placebo (N = 223).

In compliance with the SPC, atogepant was administered orally once daily at a dose of 60 mg in the relevant study arm. During the course of the study, the patients were allowed to take additional medication to treat acute migraine attacks. Non-pharmacological interventions such as acupuncture or non-invasive neuromodulation devices were not allowed, however.

The primary outcome of the study was migraine days/month operationalized as the change from baseline in monthly migraine days across a 12-week period. Secondary outcomes were further outcomes in the categories morbidity and health-related quality, as well as AE outcomes.

The company presented the results of a subpopulation of 27 patients in the relevant atogepant treatment arm (60 mg) and 18 patients in the placebo arm who previously did not respond to ≥ 2 of the following drugs with different mechanisms of action, who did not tolerate these, or who had a contraindication: beta-blockers (metoprolol/propranolol), flunarizine, topiramate, amitriptyline or valproic acid. This subpopulation presented by the company was used for this benefit assessment.

PROGRESS study

The PROGRESS study is a 3-arm, double-blind RCT with a 4-week screening/baseline phase, a 12-week double-blind, placebo-controlled treatment phase, and a 4-week follow-up phase comparing atogepant in 2 different dosing regimens and placebo. In contrast to the studies ELEVATE and ADVANCE, adult patients with an at least 1-year history of chronic migraine were included. Participation in the study required a history of, on average, 15 headache days/month in the past 3 months in the opinion of the investigator. In addition, 15 or more headache days during the 4-week screening/baseline phase had to be recorded in the electronic diary, of which at least 8 were migraine days.

Adults aged between 18 and 80 years with and without prior migraine prevention medication were allowed to participate in the study. Patients were excluded who had failed > 4 medications for the prophylaxis of migraine, including 2 drugs with different mechanisms of action, out of the following drugs: beta-blockers (propranolol/metoprolol/bisoprolol/ atenolol/nadolol/timolol), anticonvulsants (topiramate), calcium channel blockers (flunarizine/lomerizine/verapamil), valproate/divalproex, tricyclic antidepressants (amitriptyline/nortriptyline), venlafaxine/desvenlafaxine, lisinopril, angiotensin II receptor blockers (candesartan), locally approved drugs (e.g. oxeterone or pizotifen). In contrast to the studies ELEVATE and ADVANCE, concomitant treatment with one migraine prevention medication with proven efficacy was allowed, but the proportion of patients with such concomitant treatment was limited to approximately 15%. In contrast to the studies ELEVATE and ADVANCE, patients with medication overuse could be included in the study.

A total of 778 patients were randomly allocated in a ratio of 1:1:1 to treatment with atogepant 30 mg twice daily (N = 257), atogepant 60 mg once daily (N = 262) or placebo twice daily (N = 259).

In compliance with the SPC, atogepant was administered orally once daily at a dose of 60 mg in the relevant study arm. During the course of the study, participants were allowed to take acute migraine medications.

The primary outcome of the study was migraine days/month operationalized as the change from baseline in monthly migraine days across a 12-week period. Secondary outcomes were further outcomes in the categories morbidity and health-related quality, as well as AE outcomes.

The company presented the results of a subpopulation of 64 patients in the relevant atogepant treatment arm and 56 patients in the comparator arm who previously did not respond to ≥ 2 of the following drugs with different mechanisms of action, who did not tolerate these, or who had a contraindication: beta-blockers (metoprolol/propranolol),

flunarizine, topiramate, amitriptyline, clostridium botulinum toxin type A or valproic acid. This subpopulation presented by the company was used for this benefit assessment.

LIBERTY study (study with erenumab)

The LIBERTY study is a randomized, double-blind study comparing erenumab with placebo over 12 weeks. Patients with episodic migraine were included in the study. The study was already described in detail in dossier assessment A18-71.

The LIBERTY study included adult patients aged 18 to 65 years with a documented history of migraine for at least 12 months. In addition, the patients had to have a history of 4 to 14 migraine days/month on average across the past 3 months and failed 2 to 4 prior migraine prophylaxis treatments. Treatment failure or unsuitability of valproic acid was another prerequisite for inclusion in the study. Patients with medication overuse within 1 months before the start of the study and during the screening/baseline phase were not included.

A total of 246 patients were randomly allocated in a 1:1 ratio to treatment with erenumab (N = 121) or placebo (N = 125).

The study staff administered 140 mg erenumab or placebo subcutaneously every 4 weeks at scheduled visits. In addition, acute treatment of migraine attacks with pharmacological or non-pharmacological interventions was permitted during the study.

The primary outcome of the study was migraine days/month, operationalized as a ≥ 50% reduction in migraine days/month in Week 12. Relevant secondary outcomes were further outcomes in the category morbidity and AE outcomes.

The company presented the results of a subpopulation of 88 patients in the intervention arm and 105 patients in the comparator arm who previously did not respond to ≥ 2 of the following drugs with different mechanisms of action or did not tolerate them: beta-blockers (propranolol/metoprolol), flunarizine, topiramate or amitriptyline. The subpopulation also included those patients who responded inadequately to only one of these drugs and had a contraindication to another drug with a different mechanism of action. In addition, the company only included in the subpopulation those patients with a prior treatment with valproic acid for whom valproic acid was the last treatment regimen prior to study inclusion. This subpopulation presented by the company was used for this benefit assessment.

FOCUS study (study with fremanezumab)

The FOCUS study is a 3-arm, double-blind, randomized study comparing 2 different doses of fremanezumab with placebo. The study was already described in detail in dossier assessment A19-44 and its addendum A19-82. Patients with chronic or episodic migraine were included in the study. The study consisted of a 4-week screening/baseline phase, a 12-week double-blind,

placebo-controlled treatment phase, and a subsequent 12-week open-label phase, in which all patients received fremanezumab.

The study included adult patients aged 18 to 70 years with a documented history of chronic or episodic migraine for at least 12 months. Patients with episodic migraine had to have an average of ≥ 6 and ≤ 14 headache days during the screening/baseline phase, of which ≥ 4 were migraine days. Patients with chronic migraine had to have an average of > 14 headache days during the screening/baseline phase, of which ≥ 8 were migraine days. Patients with preventive migraine treatment in the screening/baseline phase were not included in the study.

Adults with treatment failure of 2 to 4 of the following drugs with different mechanisms of action in the past 10 years were included: 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.

In the 12-week double-blind treatment phase, a total of 838 patients with episodic or chronic migraine were randomly assigned in a ratio of 1:1:1 to receive either monthly fremanezumab (N = 283), quarterly fremanezumab (N = 276) or placebo (N = 279).

In this benefit assessment, monthly and quarterly fremanezumab administration was considered equivalent and considered jointly. The monthly dosing regimen differed depending on whether the patients had episodic or chronic migraine and only partially concurred with the recommendations of the SmPC (initially higher dosage for chronic migraine). According to the European Medicines Agency (EMA) the 2 dosing regimens (with and without an initially increased dose in patients with chronic migraine) are considered to be comparable in the present therapeutic indication. Patients in the study were allowed to use additional acute medication to treat acute migraine attacks, as needed. It is assumed that the use of non-drug interventions was possible in principle.

The primary outcome of the study was migraine days/month operationalized as the change from baseline in the monthly average number of migraine days. Secondary outcomes were further outcomes in the categories morbidity and health-related quality, as well as AEs.

The company used the results of a subpopulation of 388 patients in the intervention arm and 195 patients in the comparator arm who previously did not respond to ≥ 2 treatments (drug classes) or did not tolerate them: beta-blockers (propranolol or metoprolol), flunarizine, topiramate or amitriptyline. This subpopulation presented by the company was used for this benefit assessment.

Similarity of the studies for the indirect comparison

The 5 studies ELEVATE, ADVANCE, PROGRESS, LIBERTY and FOCUS had a similar study design. The patient populations of the presented studies showed differences, which mainly resulted from the difference in the underlying disease characteristic migraine type (episodic or chronic migraine) and their associated features. Overall, however, these differences did not call into question an adequate similarity of the studies and thus the possibility of conducting an indirect comparison via the common comparator placebo, taking into account all 5 studies.

To address the uncertainty caused by the differences described above, in addition to the analyses of the indirect comparison across all 5 studies, this benefit assessment considered analyses of the indirect comparison that only included studies exclusively with patients with episodic migraine (ELEVATE and ADVANCE on the intervention side and LIBERTY on the comparator side).

Analyses presented by the company

The company conducted a separate indirect comparison for each of the 2 ACT options it had selected and used these analyses as the main analyses for its assessment. For the adjusted indirect comparison of atogepant with erenumab, the company only considered the ELEVATE study on the intervention side. For the adjusted indirect comparison of atogepant with fremanezumab, the company argued that due to the inclusion of patients with different migraine types (episodic and chronic migraine) in the FOCUS study on the comparator side, an approximation of the similarity of the studies on both sides of the indirect comparison was possible if, in addition to the relevant subpopulation of the ELEVATE study on the intervention side, the relevant subpopulations of the ADVANCE and PROGRESS studies were also taken into account.

The company refrained from joint consideration of the studies on the 2 comparators erenumab and fremanezumab selected on the comparator side in a joint indirect comparison, as it considered the similarity of the studies to be insufficient, particularly with regard to the proportion of patients with chronic migraine. For this reason, the company presented an indirect comparison considering all 5 studies on the intervention and comparator side only as supplementary information in Appendix 4-G to Module 4 A of the dossier. However, in view of the fact that the company summarized studies on the different types of migraine in its indirect comparison versus fremanezumab on the intervention side, it remained unclear why it did not also provide such a summary on the comparator side.

Methods for conducting the indirect comparison

The company described that Bucher's methodological approach was used to conduct the adjusted indirect comparisons. For a meta-analytical summary of study results on the intervention or comparator side, the company chose a fixed-effect model using the inverse

variance method. The company justified the choice of the fixed-effect model on the atogepant side with a sufficient similarity of the 3 studies ELEVATE, ADVANCE and PROGRESS.

Even if the overall similarity of the studies presented for the indirect comparison was not called into question, the relevant subpopulations used nevertheless showed differences with regard to the underlying disease characteristic migraine type (episodic or chronic migraine) and other associated disease characteristics. Therefore, a method that takes random effects into account would be adequate for carrying out the indirect comparison.

Risk of bias

The risk of bias across outcomes was rated as low for all 5 studies.

The risk of bias of the results for the symptom outcome (migraine days/month) was assessed as high for each of the studies ELEVATE, ADVANCE, LIBERTY and FOCUS, as there was insufficient information on the frequency or distribution of missing values in the electronic diary. The high proportion of patients not taken into account and the unknown proportion of values imputed by non-responder imputation in the analyses for this outcome were a further aspect of bias for the results of the studies ADVANCE and LIBERTY.

For the outcome health status (EQ-5D visual analogue scale [VAS]), the risk of bias of the results from the studies ELEVATE and PROGRESS was rated as high. The risk of bias for the other studies was assessed as low.

The risk of bias of the results of the other outcomes was assessed as low in each case.

Results

In the given data situation, a method that takes random effects into account would be adequate for carrying out the indirect comparison, as described above. This is due to the fact that the 3 studies ELEVATE, ADVANCE and PROGRESS on the intervention side showed differences with regard to the underlying disease characteristic migraine type (episodic or chronic migraine) and other associated disease features. In its indirect comparison, the company chose a fixed-effect model for the meta-analytical summary of the 3 studies on the atogepant side. However, since analyses presented by the company for the indirect comparison did not show a statistically significant and relevant effect for any of the outcomes even when using such a model (to determine relevance via the standardized mean difference (SMD), the associated confidence interval must be completely outside the irrelevance range [–0.2; 0.2]), the company’s approach in the given data situation was of no consequence for the conclusion of the benefit assessment.

The company presented an analysis of the indirect comparison, taking into account all studies on the intervention side, exclusively for the outcomes of general impact of headache

(recorded using the 6-Item Headache Impact Test [HIT-6]), health status (EQ-5D VAS), health-related quality of life (recorded using the Migraine-Specific Quality of Life questionnaire MSQ) and discontinuation due to AEs. It could be deduced from the results for these outcomes that even when conducting an indirect comparison with a method that took random effects into account, no statistically significant and relevant effect could be expected.

Even in the sensitivity analyses, which only included studies in patients with episodic migraine, the indirect comparison did not show a statistically significant and relevant effect for any of the outcomes.

Overall, there is no hint of an added benefit of atogepant versus the ACT for any of the outcomes in patients who have at least 4 migraine days per month and who are not candidates for conventional migraine prophylaxis; an added benefit is therefore not proven.

Results on added benefit

In summary, there is no hint of an added benefit of atogepant versus the ACT for patients who have at least 4 migraine days per month and who are not candidates for conventional migraine prophylaxis. An added benefit of atogepant in comparison with the ACT is therefore not proven for research question 2.

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

Table 3 presents a summary of the probability and extent of the added benefit of atogepant.

[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: Atogepant – probability and extent of the added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults who have at least 4 migraine days per month and who are candidates for conventional migraine prophylaxis	Metoprolol or propranolol or flunarizine (if treatment with beta-receptor blockers is contraindicated or has not been sufficiently effective) or amitriptyline or clostridium botulinum toxin type A (only for chronic migraine[b]) or erenumab	Added benefit not proven
2	Adults who have at least 4 migraine days per month and who do not respond to any of the following drug treatments/drug classes, for whom they are unsuitable, or who do not tolerate them[c]: metoprolol, propranolol, flunarizine, 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 according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**.
b. Even in cases of chronic migraine, clostridium botulinum toxin type A is not a usual treatment option for all patients in research question 1.
c. In research question 2, treatment with biologics may be considered as part of a clinical study if patients have not responded to or have not tolerated at least 2 drug therapies (drug classes from research question 1). In cases where the drugs from research question 1 are not suitable for patients, this must be documented and justified.

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 2 Research question

The aim of this report is to assess the added benefit of atogepant in comparison with the ACT for prophylaxis of migraine in adult patients who have at least 4 migraine days per month.

The research questions presented in Table 4 were defined in accordance with the ACT specified by the G-BA.

Table 4: Research questions for the benefit assessment of atogepant

Research question	Therapeutic indication	ACT[a]
1	Adults who have at least 4 migraine days per month and who are candidates for conventional migraine prophylaxis	Metoprolol or propranolol or flunarizine (if treatment with beta-receptor blockers is contraindicated or has not been sufficiently effective) or amitriptyline or clostridium botulinum toxin type A (only for chronic migraine[b]) or erenumab
2	Adults who have at least 4 migraine days per month and who do not respond to any of the following drug treatments/drug classes, for whom they are unsuitable, or who do not tolerate them[c]: metoprolol, propranolol, flunarizine, 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 according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**.
b. Even in cases of chronic migraine, clostridium botulinum toxin type A is not a usual treatment option for all patients in research question 1.
c. In research question 2, treatment with biologics may be considered as part of a clinical study if patients have not responded to or have not tolerated at least 2 drug therapies (drug classes from research question 1). In cases where the drugs from research question 1 are not suitable for patients, this must be documented and justified.

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

For easier presentation and better readability, this benefit assessment uses the following wordings for the research questions in the running text:

- 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

The company followed the G-BA's specification of the ACT for both research questions. For research question 2, the company considered all options of the ACT for a direct comparison. For an indirect comparison, however, the company selected the 2 drugs erenumab and

fremanezumab as the comparator therapy from the 3 options presented. It described that galcanezumab was not considered as a comparator due to the smaller evidence base and the associated uncertainty. In particular, the company referred to the small subpopulations of the pivotal studies used for the benefit assessment of galcanezumab, to the availability of data on individual outcomes, and to the fact that patients who showed a lack of response to at least 3 drug classes of prophylactic migraine treatments were excluded from the studies on galcanezumab. Referencing § 6, Section 2a of the Regulation for Early Benefit Assessment of New Pharmaceuticals [3], it additionally stated that it was possible to prove the added benefit versus each of the 3 specified options of the ACT.

Irrespective of the possibility of selecting individual therapies from the ACT options specified by the G-BA, the justification presented by the company for selecting only 2 of the 3 specified options was not comprehensible. The pivotal studies on galcanezumab provided results for a subpopulation that comprised a total of 218 patients across all studies (for details, see the benefit assessment procedure for galcanezumab [4,5]). In addition, the subpopulation considered by the company from the study on erenumab was of a similar size. Furthermore, the subpopulations considered by the company for the comparators erenumab and fremanezumab mainly included patients with 2 to 3 failed migraine prophylaxis medications. Against this background, it remained unclear why the company did not also consider the results of the studies on galcanezumab for the available outcomes in the assessment.

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 duration of 12 weeks were used to derive the 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 for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- study list on atogepant (status: 16 December 2024)
- bibliographical literature search on atogepant (last search on 16 December 2024)
- search of trial registries/trial results databases for studies on atogepant (last search on 17 December 2024)

To check the completeness of the study pool:

- search of trial registries for studies on atogepant (last search on 21 March 2025); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, this review did not identify any relevant studies for research question 1.

I 3.2 Results on added benefit

The company presented no data for the assessment of the added benefit of atogepant in comparison with the ACT for adult patients who are candidates for conventional migraine prophylaxis. There is no hint of an added benefit of atogepant 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 presented no data for the assessment of the added benefit of atogepant in comparison with the ACT in adult patients who have at least 4 migraine days per month and who are candidates for conventional migraine prophylaxis. An added benefit of atogepant in comparison with 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 for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- study lists on atogepant (status: 16 December 2024)
- bibliographical literature search on atogepant (last search on 16 December 2024)
- search of trial registries/trial results databases for studies on atogepant (last search on 17 December 2024)
- search on the G-BA website for atogepant (last search on 17 December 2024)
- bibliographical literature search on erenumab and fremanezumab (last search on 16 December 2024)
- search of trial registries/trial results databases for studies on erenumab and fremanezumab (last search on 17 December 2024)
- search on the G-BA website for erenumab and fremanezumab (last search on 17 December 2024)

To check the completeness of the study pool:

- search of trial registries for studies on atogepant (last search on 21 March 2025); for search strategies, see I Appendix A of the full dossier assessment
- search of trial registries for studies on erenumab and fremanezumab (last search on 21 March 2025); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, this review did not identify any studies of direct comparison of atogepant versus the ACT for the given research question.

The company therefore presented adjusted indirect comparisons [6] via the common comparator placebo for research question 2. From the 3 ACT options, it considered the 2 options erenumab and fremanezumab for the assessment (see Chapter I 2). On the intervention side, it identified the studies ELEVATE, ADVANCE and PROGRESS, and on the erenumab and fremanezumab side the studies LIBERTY and FOCUS. In Module 4 A of the dossier, the company presented various indirect comparisons using subsets of these studies, as well as an indirect comparison using all 5 studies, which it either used for its assessment or presented as supplementary information in Appendix 4-G to Module 4 A of the dossier (for a detailed explanation of the company's approach, see Section I 4.1.3).

Primarily relevant for the present assessment were analyses on the indirect comparison of atogepant versus erenumab or fremanezumab using all 5 studies. As supplementary information, analyses on the indirect comparison of atogepant with erenumab were considered as a sensitivity analysis (for an explanation of the approach in this benefit assessment, see Section I 4.1.3).

The review of the completeness of the study pool did not identify any additional relevant studies for the indirect comparison of atogepant versus erenumab or fremanezumab besides the 5 studies identified 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: atogepant vs. erenumab or fremanezumab

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Atogepant vs. placebo						
3101-304-002 (ELEVATE[d])	No	Yes	No	Yes [7,8]	Yes [9,10] }	Yes [11]
3101-301-002 (ADVANCE[d])	Yes	Yes	No	Yes [12,13]	Yes [14]	Yes [15,16]
3101-303-002 (PROGRESS[d])	Yes	Yes	No	Yes [17,18]	Yes [19,20]	Yes [21]
Erenumab vs. placebo						
CAMG334A2301 (LIBERTY[d])	No	No	Yes	No	Yes [22,23]	Yes [24-29]
Fremanezumab vs. placebo						
TEV48125-CNS-30068 (FOCUS[d])	No	No	Yes	No	Yes [30,31]	Yes [32-40]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on 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; RCT: randomized controlled trial

The study pool was consistent with that selected by the company. On the intervention side, it included the studies ELEVATE, ADVANCE and PROGRESS. On the comparator side, the study pool included the studies LIBERTY and FOCUS. The LIBERTY study had already been submitted and assessed for a previous benefit assessment of erenumab [24]. The FOCUS study had also

already been submitted and assessed for a previous benefit assessment of fremanezumab [32].

Figure 1 is a schematic representation of the study pool.

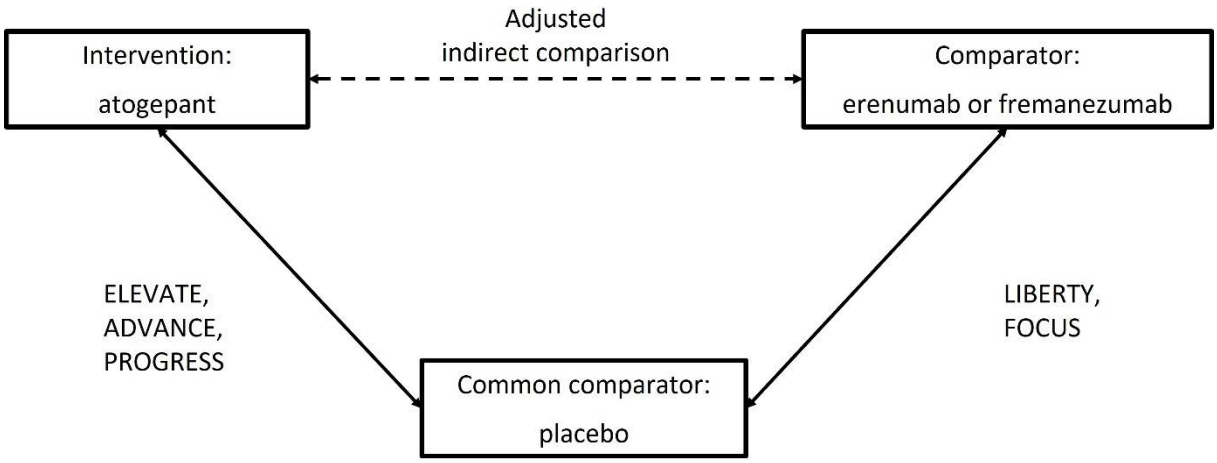

Figure 1: Study pool for the adjusted indirect comparison between atogepant and erenumab or fremanezumab via the common comparator placebo

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: atogepant vs. erenumab or fremanezumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Atogepant vs. placebo						
ELEVATE	RCT, double-blind, parallel	Adults (18–80 years) with episodic migraine (4–14 migraine days/months) and treatment failure[b] of 2–4 migraine prophylaxis medications	atogepant 60 mg QD (N = 157) placebo (N = 158) Relevant subpopulation thereof[c]: atogepant 60 mg QD (n = 126) placebo (n = 129)	Screening[d]: 4 weeks Treatment: 12 weeks Follow-up: up to 4 weeks after the last dose of study intervention	73 centres in Canada, Czech Republic, Denmark, France, Germany, Hungary, Italy, Netherlands, Poland, Russia, Spain, United Kingdom and United States 3/2021–8/2022	Primary: change from baseline in number of monthly migraine days across 12 weeks Secondary: morbidity, health-related quality of life, AEs
ADVANCE	RCT, double-blind, parallel	Adults (18–80 years) with episodic migraine (4–14 migraine days/month)	▪ atogepant ▫ 10 mg QD (N = 222)[e] ▫ 30 mg QD (N = 230)[e] ▫ 60 mg QD (N = 235) ▪ placebo QD (N = 223) Relevant subpopulation thereof[c]: ▪ atogepant ▫ 60 mg QD (n = 27) ▪ placebo QD (n = 18)	Screening[d]: 4 weeks Treatment: 12 weeks Follow-up: up to 4 weeks after the last dose of study intervention	128 centres in United States 12/2018–6/2020	Primary: change from baseline in number of monthly migraine days across 12 weeks Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Atogepant vs. placebo						
PROGRESS	RCT, double-blind, parallel	Adults (18–80 years) with at least a 1-year history of chronic migraine[f, g]	▪ atogepant ▫ 30 mg BID (N = 257)[e] ▫ 60 mg QD (N = 262) ▪ placebo BID (N = 259) Relevant subpopulation thereof[c]: ▪ atogepant ▫ 60 mg QD (N = 64) ▪ placebo BID (N = 56)	Screening[d]: 4 weeks Treatment: 12 weeks Follow-up: up to 4 weeks after the last dose of study intervention	142 centres in Canada, China, Czech Republic, Denmark, France, Germany, Italy, Japan, Poland, Russia, South Korea, Spain, Sweden, Taiwan, United Kingdom, United States 3/2019–1/2022	Primary: change from baseline in number of monthly migraine days across 12 weeks Secondary: morbidity, health-related quality of life, AEs
Erenumab vs. placebo						
LIBERTY	RCT, double-blind, parallel	Adults (18–65 years) with episodic migraine (4–14 migraine days/months) and treatment failure of 2–4 migraine prophylaxis medications[h]	erenumab (N = 121) placebo (N = 125) Relevant subpopulation thereof[c]: erenumab (n = 88) placebo (n = 105)	Screening[d]: up to 6 weeks Treatment: 12 weeks[i] Follow-up: up to 16 weeks after the last dose of study intervention in the double-blind phase[i]	59 centres in Australia, Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, United Kingdom 3/2017–10/2017[j]	Primary: ≥ 50% reduction in monthly migraine days in Month 3 Secondary: morbidity, AEs

Table 6: Characteristics of the studies included – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Fremanezumab vs. placebo						
FOCUS	RCT, double-blind, parallel	Adults (18–70 years) with chronic[k, l] or episodic migraine[k] and treatment failure of 2–4 preventive migraine medications[m] within the past 10 years[n]	▪ fremanezumab, monthly ▫ 225 mg (N = 283)[o] ▪ fremanezumab, quarterly ▫ 675 mg (N = 276) ▪ placebo (N = 279) Relevant subpopulation thereof[c]: ▪ fremanezumab, monthly/quarterly (n = 388) ▪ placebo (n = 195)	Screening[d]: 28 days Treatment: 12 weeks[p] Follow-up: up to 6 months after the last dose of study intervention[p]	98 centres in Belgium, Czech Republic, Denmark, Germany, Finland, France, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, United Kingdom, United States 11/2017–10/2018	Primary: change from baseline in the monthly average number of migraine days during the 12-week period after the first dose Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.

b. Defined as documented treatment failure of 2–4 of the following drugs with different mechanisms of action: beta-blockers (propranolol/metoprolol/atenolol/bisoprolol/timolol/nadolol), anticonvulsants (topiramate), calcium channel blockers (flunarizine), valproate/divalproex, tricyclic antidepressants (amitriptyline/nortriptyline), venlafaxine/desvenlafaxine, lisinopril, angiotensin II receptor blockers (candesartan), locally approved products (e.g. oxeterone or pizotifen). This included ≥ 1 treatment failure due to insufficient efficacy or tolerability of beta-blockers (propranolol/metoprolol), topiramate, flunarizine or amitriptyline.

c. The relevant subpopulations of the studies were formed as follows:

- ELEVATE, ADVANCE and PROGRESS: patients who did not respond to, did not tolerate, or had contraindications to at least 2 of the following drugs with different mechanisms of action: beta-blockers (metoprolol or propranolol), flunarizine, topiramate, amitriptyline or valproic acid, and clostridium botulinum toxin for chronic migraine only.
- LIBERTY: patients who had an inadequate response to or did not tolerate at least 2 of the following drugs with different mechanisms of action (beta-blockers [metoprolol or propranolol], topiramate, flunarizine, amitriptyline), or who had an inadequate response to or did not tolerate 1 of the above drugs and were unsuitable for another drug for medical reasons, and who, in the case of treatment with valproic acid, received this as the last treatment option before baseline
- FOCUS: patients who did not respond to or did not tolerate at least 2 of the following drugs with different mechanisms of action: beta-blockers (propranolol or metoprolol), flunarizine, topiramate or amitriptyline.

d. In the studies, the eligibility of the patients for randomization was reviewed in the 4 weeks before randomization by reviewing the recorded migraine or headache frequency and the compliance in completing the electronic migraine diary (for details see the following text). This phase is referred to as the screening/baseline phase for all studies in this assessment.

Table 6: Characteristics of the studies included – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

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

e. The arm is irrelevant for the assessment and is disregarded in the following tables.
f. Defined as: 1) history of, on average, ≥ 15 headache days per month in the 3 months prior to Visit 1 in the opinion of the investigator, and 2) ≥ 15 headache days during the 4-week screening/baseline period per the electronic diary, and 3) ≥ 8 migraine days during the 4-week screening/baseline period per the electronic diary.
g. Patients with medication overuse (defined as use of triptans or ergotamines on ≥ 10 days, or analgesics [aspirin, NSAIDs, acetaminophen] on ≥ 15 days, or any combination of triptans, ergotamines or analgesics on ≥ 10 days) during the screening/baseline phase were also included.
h. Patients with treatment failure of 2–4 of the following drugs with different mechanisms of action: beta-blockers (propranolol/metoprolol), anticonvulsants (topiramate), calcium channel blockers (flunarizine), valproate/divalproex, tricyclic antidepressants (amitriptyline), venlafaxine, lisinopril, angiotensin II receptor blockers (candesartan), locally approved products (e.g.

- oxeterone or pizotifen) AND
- treatment failure of one and treatment failure of or unsuitability for a second of the following drugs with different mechanisms of action: beta-blockers (propranolol or metoprolol), topiramate, flunarizine AND
- treatment failure of or unsuitability of valproate or divalproex

i. Following the double-blind treatment phase, patients had the option to receive further treatment with erenumab for 156 weeks in the open-label extension part of the study. Patients who discontinued treatment during the double-blind treatment phase or who did not participate in the extension part of the study had a follow-up visit 16 weeks after the last dose of study medication.
j. Date of the last study visit of the double-blind treatment phase of the last patients included: 27 October 2017.
k. Episodic migraine is defined in the study as ≥ 6 to < 15 headache days per month, of which ≥ 4 migraine days; chronic migraine is defined as ≥ 15 headache days per month, of which ≥ 8 migraine days.
l. Also included were patients with medication overuse (defined as taking acute medication for the treatment of headache on ≥ 15 days/month or migraine-specific acute medication or a combined medication on ≥ 10 days/month).
m. Inclusion of patients with treatment failure of the following drugs with different mechanisms of action: 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, or valproic acid.
n. Data on non-response to treatments more than 10 years ago was not recorded in the study.
o. In the study arm with monthly fremanezumab administration, patients with chronic migraine received an initial dose of 675 mg. This does not comply with the recommendations of the SmPC (see benefit assessment of fremanezumab [32]). See also following text for details.
p. Following the double-blind treatment phase, all study participants received further treatment with 225 mg fremanezumab monthly, for a total of 3 doses, in an open-label treatment phase. The subsequent follow-up visit took place 6 months after the last dose of study intervention.

AE: adverse event; BID: twice daily; EMA: European Medicines Agency; NSAID: non-steroidal anti-inflammatory drug; n: relevant subpopulation; N: number of randomized patients; QD: once daily; RCT: randomized controlled trial; SmPC: summary of product characteristics

Table 7: Characteristics of the interventions – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Study	Intervention	Comparison
Atogepant vs. placebo		
ELEVATE	atogepant 60 mg QD, orally	placebo QD, orally
	Dose modification was not possible	
	Required prior treatment ▪ 2–4 failed migraine prevention medications[a] with the following drugs with different mechanisms of action: beta-blockers (propranolol/metoprolol/atenolol/bisoprolol/timolol/nadolol), anticonvulsants (topiramate), calcium channel blockers (flunarizine), valproate/divalproex, tricyclic antidepressants (amitriptyline/nortriptyline), venlafaxine/desvenlafaxine, lisinopril, angiotensin II receptor blockers (candesartan), locally approved products (e.g. oxeterone or pizotifen), including at least one failed treatment with one of the following drugs: beta-blockers (propranolol/metoprolol), topiramate, flunarizine or amitriptyline **Disallowed prior treatment** ▪ Within 30 days before the start of the study and during the baseline phase: ▫ Migraine prevention medications or non-drug migraine prevention ▪ Within 3 months before the start of the study and during the baseline phase: ▫ Opioid-containing analgesics and barbiturates > 2 days/month ▫ Ergotamines or triptans ≥ 10 days/month ▫ Classic analgesics (NSAIDs, acetaminophen, aspirin[b]) ≥ 15 days/month ▪ Within 6 months before the start and during the baseline phase: ▫ Treatment with botulinum toxin into areas of the head and neck ▫ CGRP antibodies, CGRP receptor antagonists **Allowed concomitant treatment** ▪ Pharmacological interventions for the acute treatment of a migraine attack (e.g. triptans, ergotamine derivatives, other analgesics [including paracetamol, metamizole], NSAID agents and antiemetics) ▪ Non-pharmacological interventions (e.g. biofeedback, psychotherapy, acupuncture, vagus nerve stimulation, transcutaneous supraorbital nerve stimulation, single-pulse transcranial magnetic stimulator or other locally accepted or endorsed non-invasive interventions for acute migraine) **Disallowed concomitant treatment** ≤ 4 weeks before the start of the study and during the study: ▪ Strong and moderate CYP3A4 inhibitors/inducers, strong P-gp inhibitors, strong OATP1B1/OATP1B3 inhibitors, drugs with narrow therapeutic margins with theoretical potential for CYP-drug interactions, CBD oil, cannabis ▪ Drugs with efficacy for the prophylaxis of migraine: beta-blockers (propranolol/metoprolol/atenolol/bisoprolol/timolol/nadolol), anticonvulsants (topiramate), calcium channel blockers (flunarizine), valproate/divalproex, tricyclic antidepressants (amitriptyline/nortriptyline), venlafaxine/desvenlafaxine, lisinopril, angiotensin II receptor blockers (candesartan), locally approved drugs (e.g. oxeterone or pizotifen)	

Table 7: Characteristics of the interventions – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Study	Intervention	Comparison
	▪ Cranial traction, nociceptive trigeminal inhibition, occipital nerve block treatments, or dental splints for headache ▪ Acupuncture, non-invasive neuromodulation devices (e.g. transcutaneous supraorbital neurostimulator, single-pulse transcranial magnetic stimulator, vagus nerve stimulator, etc.) for the prophylaxis of migraine ▪ Treatment with botulinum toxin A into areas of the head and neck ▪ Any opioid-containing medication during the study (except for surgery)	
ADVANCE	atogepant 60 mg once daily, orally	placebo once daily, orally
	Dose modification was not possible	
	Allowed prior treatment ▪ ≤ 4 failed migraine prevention medications[a], including 2 drugs with different mechanisms of action: beta-blockers (propranolol/metoprolol/bisoprolol/atenolol/nadolol/timolol), anticonvulsants (topiramate), calcium channel blockers (flunarizine), valproate/divalproex, tricyclic antidepressants (amitriptyline/nortriptyline), venlafaxine, lisinopril, angiotensin II receptor blockers (candesartan), locally approved drugs (e.g. oxeterone or pizotifen) **Disallowed prior treatment** ▪ Within 3 months before the start and during the baseline phase: ▫ Analgesics containing opioids or barbiturates > 2 days/month ▫ Ergotamines or triptans ≥ 10 days/month ▫ Classic analgesics (NSAIDs, acetaminophen, aspirin[b]) ≥ 15 days/month ▪ Within 6 months before the start and during the baseline phase: ▫ Treatment with botulinum toxin into areas of the head and neck ▫ CGRP antibodies, CGRP receptor antagonists **Allowed concomitant treatment** ▪ Drugs for the acute treatment of a migraine attack (e.g. triptans, ergotamine derivatives, opioids, other analgesics [including acetaminophen], NSAID agents and antiemetics) **Disallowed concomitant treatment** ≤ 4 weeks before the start of the study and during the study: ▪ Strong and moderate CYP3A4 inhibitors/inducers, strong OATP1B1 inhibitors, drugs with narrow therapeutic margins with theoretical potential for CYP-drug interactions, CBD oil ▪ Drugs with efficacy for the prevention of migraine (e.g. amitriptyline, topiramate, propranolol) ▪ Treatment with botulinum toxin into areas of the head and neck ▪ Non-pharmacological interventions, e.g. acupuncture, non-invasive neuromodulation devices (e.g. transcutaneous supraorbital neurostimulator, single-pulse transcranial magnetic stimulator, vagus nerve stimulator, etc.), cranial traction, nociceptive trigeminal inhibition, occipital nerve block treatments, or dental splints for headache	

Table 7: Characteristics of the interventions – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Study	Intervention	Comparison
PROGRESS	atogepant 60 mg QD, orally (in the morning) + placebo QD, orally (in the evening)	placebo BID, orally (in the morning and evening)
	Dose modification was not possible	
	Allowed prior treatment ▪ ≤ 4 failed migraine prevention medications[a], including 2 drugs with different mechanisms of action: beta-blockers (propranolol/metoprolol/bisoprolol/atenolol/nadolol/timolol), anticonvulsants (topiramate), calcium channel blockers (flunarizine/lomerizine/verapamil), valproate/divalproex, tricyclic antidepressants (amitriptyline/nortriptyline), venlafaxine/desvenlafaxine, lisinopril, angiotensin II receptor blockers (candesartan), locally approved drugs (e.g. oxeterone or pizotifen) **Disallowed prior treatment** ▪ Within 3 months before the start and during the baseline phase: ▫ Opioid-containing analgesics or barbiturates > 4 days/month ▪ Within 6 months before the start and during the baseline phase: ▫ Treatment with botulinum toxin into areas of the head and neck ▪ ≤ 30 days before the start of the study and during the study: ▫ CGRP antibodies, CGRP receptor antagonists **Allowed concomitant treatment** ▪ Pharmacological interventions for the acute treatment of a migraine attack (e.g. any triptans, ergotamine derivatives, opioids, analgesics [including paracetamol], NSAID agents [including aspirin] and antiemetics) ▪ One drug with efficacy for the prevention of migraine[c] (e.g. amitriptyline, topiramate, propranolol) provided that dose has been stable and the medication has been well-tolerated for ≥ 12 weeks and continuation of use is planned ▪ Aspirin up to 325 mg/day for cardiac prophylaxis **Disallowed concomitant treatment** ▪ Drugs with efficacy for the prevention of migraine (e.g. amitriptyline, topiramate, propranolol) for the treatment of indications other than migraine ▪ ≤ 4 weeks before the start of the study and during the study: ▫ Strong and moderate CYP3A4 inhibitors/inducers, strong OATP1B1 inhibitors, drugs with narrow therapeutic margins with theoretical potential for CYP-drug interactions, CBD oil, cannabis ▫ Non-pharmacological interventions, e.g. acupuncture, non-invasive neuromodulation devices (e.g. transcutaneous supraorbital neurostimulator, single-pulse transcranial magnetic stimulator, vagus nerve stimulator, etc.), cranial traction, nociceptive trigeminal inhibition, occipital nerve block treatments, or dental splints for headache	

Table 7: Characteristics of the interventions – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Study	Intervention	Comparison
Erenumab vs. placebo		
LIBERTY	erenumab twice 70 mg SC (total dose of 140 mg) every 4 weeks	placebo twice SC every 4 weeks
	Dose modification was not allowed.	
	Required prior treatment ▪ 2–4 failed migraine prevention medications[d] with the following drugs with different mechanisms of action: beta-blockers (propranolol/metoprolol), anticonvulsants (topiramate), calcium channel blockers (flunarizine), valproate/divalproex, tricyclic antidepressants (amitriptyline), venlafaxine, lisinopril, angiotensin II receptor blockers (candesartan), locally approved drugs (e.g. oxeterone or pizotifen), including at least one failed treatment with one, and treatment failure of or unsuitability for a second of the following drugs: beta-blockers (propranolol / metoprolol), topiramate, flunarizine ▪ Failed or unsuitable prophylaxis of migraine with valproate or divalproex **Disallowed prior treatment** ▪ Within 1 month before the start and during the screening/baseline phase: ▫ Migraine prevention medications or non-drug migraine prevention ▫ Ergotamines or triptans ≥ 10 days/month ▫ Classic analgesics (NSAIDs, acetaminophen, paracetamol) ≥ 15 days/month ▫ Opioid- or butalbital-containing analgesics ≥ 4 days/month ▪ Within 4 months before the start and during the baseline phase: ▫ Treatment with botulinum toxin A into areas of the head and neck **Allowed concomitant treatment** ▪ Pharmacological interventions for the acute treatment of a migraine attack ▪ non-pharmacological interventions (e.g. biofeedback, psychotherapy, acupuncture or other locally accepted and endorsed interventions for migraine) **Disallowed concomitant treatment** ▪ Drugs with efficacy for the prevention of migraine (beta-blockers, topiramate, flunarizine, valproate/divalproex, amitriptyline, venlafaxine/desvenlafaxine, lisinopril, candesartan, oxetorone/pizotifen/methysergide), unless they were used for a different condition at stable doses for ≥ 3 months prior to enrolment ▪ Non-pharmacological interventions (e.g. nerve blocks, occipital nerve stimulators, transcranial magnetic stimulation) for prophylaxis of migraine ▪ Treatment with botulinum toxin A into areas of the head and neck	

Table 7: Characteristics of the interventions – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Study	Intervention	Comparison
Fremanezumab vs. placebo		
FOCUS	▪ fremanezumab, monthly: ▫ Starting dose - for chronic migraine: 675 mg, SC - for episodic migraine: 225 mg, SC ▫ followed by 225 mg SC every 4 weeks (for another 2 doses in total) or ▪ fremanezumab, quarterly: ▫ for episodic and chronic migraine: 1 dose: 675 mg, SC ▫ followed by placebo doses every 4 weeks (for 2 doses in total)	▪ placebo every 4 weeks (3 doses in total)
	Dose modification was not allowed.	
	Required prior treatment ▪ 2–4 failed migraine prevention medications[a] with the following drugs with different mechanisms of action: beta-blockers (propranolol, metoprolol, atenolol and bisoprolol), anticonvulsants (topiramate), tricyclic antidepressants (amitriptyline), calcium channel blockers (flunarizine), angiotensin II receptor blockers (candesartan), clostridium botulinum toxin type A[e], valproic acid **Disallowed prior treatment** ▪ Procedure or intervention for migraine (e.g. planned nerve blocks and transcranial magnetic stimulation) within 2 months prior to screening ▪ Botulinum toxin A injections in the head and neck region within 3 months prior to screening ▪ Analgesics containing opioids or barbiturates ≥ 4 days during the screening phase ▪ Ergotamines or triptans for the prophylaxis of migraine ▪ NSAIDs for the prophylaxis of migraine ▪ CGRP antibodies	
	Allowed concomitant treatment[f] ▪ Pharmacological interventions for the acute treatment of a migraine attack ▪ Other drugs in the same drug classes that are not included in the list under “required prior treatment” are allowed for other therapeutic indications. ▪ Other prescription drugs must have been used at stable doses for at least 2 months at screening and remain unchanged during the double-blind treatment period. ▪ Over-the-counter drugs or nutritional supplements **Disallowed concomitant treatment** ▪ Initiation of migraine prophylaxis (see under “required prior treatment”) during the screening/baseline phase[g] and for the duration of the study[h]	

Table 7: Characteristics of the interventions – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Study	Intervention	Comparison
a. Treatment failure was assessed by the investigator on the basis of lack of efficacy, intolerability and/or unsuitability/contraindication (see text below for details). b. Aspirin up to 325 mg/day (ELEVATE, ADVANCE) and low-dose 81 mg (FOCUS) for cardiac prophylaxis was allowed. c The proportion of patients with concomitant use of a drug with efficacy for the prevention of migraine was limited to about 15%. d. Patients could also be included who had failed treatment with only one migraine prevention medication before inclusion and who were additionally unsuitable for treatment with a second drug from the following: beta-blockers (propranolol/metoprolol), topiramate or flunarizine. Treatment failure was assessed by the investigator on the basis of documented intolerance, unsuitability or lack of efficacy (in the 5 years prior to screening). e. If botulinum toxin A was used as a previous prophylactic medication, at least 2 injections must have been administered and 3 months must have passed since the last injection prior to screening. f. Information on allowed non-drug concomitant treatments is not available in the study documents (see text below). g. At least 5 half-lives of the previous migraine prophylactic medication must have passed at the time of screening. h. Also disallowed for the treatment of therapeutic indications other than migraine (except if given as topical agents or eye drops). BID: twice daily; CBD: cannabidiol; CGRP: calcitonin gene-related peptide; CYP3A4: cytochrome P450 3A4; ND: no data; NSAID: non-steroidal anti-inflammatory drug; OATP1B1/OATP1B3: organic anion transporting polypeptide; QD: once daily; P-gp: P-glycoprotein; RCT: randomized controlled trial; SC: subcutaneous		

Studies with atogepant (ELEVATE, ADVANCE, PROGRESS)

ELEVATE study

The ELEVATE study is a double-blind RCT comparing atogepant with placebo. Patients with episodic migraine were included in the study. The study consisted of a 4-week screening/baseline phase, a 12-week double-blind, placebo-controlled treatment phase, and a 4-week follow-up phase.

Adult patients aged 18 to 80 years with a history of migraine (defined according to the International Classification of Headache Disorders, third edition [ICHD-3] [41]) of at least 12 months were included. Patients had to have been younger than 50 years when first experiencing migraine and had to have 4 to 14 migraine days per month in the 3 months prior to study inclusion and in the screening/baseline phase. The extent to which the inclusion criterion regarding the number of migraine days/month was met was verified on the basis of the patients' entries in an electronic migraine diary during the 4-week screening/baseline phase. For the transition to the randomized treatment phase, patients had to have completed the electronic migraine diary on at least 20 out of 28 days.

Another inclusion criterion was documented treatment failure of 2 to 4 of the following drugs with different mechanisms of action: beta-blockers (propranolol/metoprolol/atenolol/

bisoprolol/timolol/nadolol), anticonvulsants (topiramate), calcium channel blockers (flunarizine), valproate/divalproex, tricyclic antidepressants (amitriptyline/nortriptyline), venlafaxine/desvenlafaxine, lisinopril, angiotensin II receptor blockers (candesartan), locally approved products (e.g. oxeterone or pizotifen). This included ≥ 1 treatment failure due to insufficient efficacy or tolerability of beta-blockers (propranolol/metoprolol), topiramate, flunarizine or amitriptyline. Treatment failure was defined as no clinically meaningful improvement of migraine after at least 2 months of preventive migraine treatment at generally accepted therapeutic doses during the past 7 years, or discontinuation of treatment due to AEs at any previous time. Contraindications did not count as treatment failure. Patients with medication overuse, defined as treatment of acute migraine with triptans or ergotamines on ≥ 10 days/month or classic analgesics (non-steroidal anti-inflammatory drugs [NSAIDs], acetaminophen, aspirin) on ≥ 15 days/month [42] within 3 months prior to baseline or during the screening/baseline phase, were not included.

In the ELEVATE study, a total of 315 patients were randomly allocated in a 1:1 ratio to treatment with 60 mg atogepant (N = 157) or placebo (N = 158). Randomization was stratified based on number of migraine days per month (4 to < 8 versus > 8), number of failed prophylactic treatments with drugs with different mechanisms of action (2 versus > 2) and region (North America versus Europe versus Asia/Pacific).

Treatment with atogepant was administered orally once daily, which was in compliance with the SmPC [43]. The additional treatment of acute migraine attacks with pharmacological or non-pharmacological interventions was possible during the course of the study.

The primary outcome of the study was migraine days/month operationalized as the change from baseline in monthly migraine days across a 12-week period. Secondary outcomes were further outcomes in the categories morbidity and health-related quality, as well as AE outcomes.

The company presented the results of a subpopulation of those patients who previously did not respond to ≥ 2 of the following drugs with different mechanisms of action, who did not tolerate these, or who had a contraindication: beta-blockers (metoprolol/propranolol), flunarizine, amitriptyline, topiramate or valproic acid. The subpopulation comprised 126 patients in the intervention arm and 129 in the comparator arm. This subpopulation presented by the company was used for this benefit assessment.

ADVANCE study

The ADVANCE study is a 4-arm, double-blind RCT comparing atogepant at 3 different doses and placebo, conducted exclusively in the United States. Patients with episodic migraine were included in the study. The study consisted of a 4-week screening/baseline phase, a 12-week double-blind, placebo-controlled treatment phase, and a 4-week follow-up phase.

As in the ELEVATE study, adult patients aged 18 to 80 years with a history of migraine (defined according to the ICHD-3 [41]) of at least 12 months were included. Patients had to have been younger than 50 years when first experiencing migraine and had to have a history of 4 to 14 migraine days/month in the 3 months prior to study inclusion, in the investigator's judgement. In the 4-week screening/baseline phase, electronic migraine diaries were used to check the inclusion criterion of 4 to 14 migraine days/month and the patients' compliance to complete the diaries. The diary had to be completed on at least 20 out of 28 days.

In contrast to the ELEVATE study, adults with and without prior migraine prevention medication were enrolled. According to the study protocol, approximately 70% of patients had to have taken at least one prior migraine prevention medication with proven efficacy. However, non-response was not a prerequisite for participation in the study. However, patients were excluded who had failed > 4 medications for the prophylaxis of migraine, including 2 drugs with different mechanisms of action, out of the following drugs: beta-blockers (propranolol/metoprolol/bisoprolol/atenolol/nadolol/timolol), anticonvulsants (topiramate), calcium channel blockers (flunarizine), valproate/divalproex, tricyclic antidepressants (amitriptyline/nortriptyline), venlafaxine, lisinopril, angiotensin II receptor blockers (candesartan), locally approved drugs (e.g. oxeterone or pizotifen). Study participation was also not possible for patients with medication overuse, defined as treatment of acute migraine with triptans or ergotamines on ≥ 10 days/month or classic analgesics (NSAIDs, acetaminophen, aspirin) on ≥ 15 days/month [42] within 3 months prior to baseline or during the screening/baseline phase.

A total of 910 patients were randomly allocated in a ratio of 1:1:1:1 to treatment with atogepant 10 mg (N = 222), atogepant 30 mg (N = 230), atogepant 60 mg (N = 235) or placebo (N = 223). The doses of 10 mg and 30 mg atogepant were not relevant for the assessment and were therefore not considered further in this benefit assessment. Randomization was stratified based on prior exposure to a migraine prevention medication with proven efficacy (yes versus no).

In the relevant study arm, atogepant was administered orally once daily, which was in compliance with the SmPC [43]. Throughout the study, patients were allowed to take additional drugs to treat an acute migraine attack (e.g. triptans, ergotamine derivatives, opioids, other analgesics including acetaminophen, NSAIDs and antiemetics). Non-pharmacological interventions such as acupuncture or non-invasive neuromodulation devices were not allowed, however.

The primary outcome of the study was migraine days/month operationalized as the change from baseline in monthly migraine days across a 12-week period. Secondary outcomes were further outcomes in the categories morbidity and health-related quality, as well as AE outcomes.

The company presented the results of a subpopulation of those patients who previously did not respond to ≥ 2 of the following drugs with different mechanisms of action, who did not tolerate these, or who had a contraindication: beta-blockers (metoprolol/propranolol), flunarizine, topiramate, amitriptyline or valproic acid. The company identified a subpopulation of 27 patients in the relevant atogepant treatment arm (60 mg) and 18 patients in the placebo arm. This subpopulation presented by the company was used for this benefit assessment.

PROGRESS study

The PROGRESS study is a 3-arm, double-blind RCT with a 4-week screening/baseline phase, a 12-week double-blind, placebo-controlled treatment phase, and a 4-week follow-up phase comparing atogepant in 2 different dosing regimens and placebo. In contrast to the studies ELEVATE and ADVANCE, adult patients with an at least 1-year history of chronic migraine according to ICHD-3 [41] were included. According to the ICHD-3, chronic migraine is defined as "headache occurring on 15 or more days/month for more than 3 months, which, on at least 8 days/month, has the features of migraine headache" [41]. Participation in the study required a history of, on average, 15 headache days/month in the past 3 months in the opinion of the investigator. In addition, 15 or more headache days during the 4-week screening/baseline phase had to be recorded in the electronic diary, of which at least 8 were migraine days. Furthermore, there had to be entries in the electronic migraine diary on at least 20 out of 28 days during the screening/baseline phase.

Adults aged between 18 and 80 years with and without prior migraine prevention medication were allowed to participate in the study. According to the study protocol, approximately 70% of patients had to have taken at least one prior migraine prevention medication with proven efficacy. However, non-response was not a prerequisite for participation in the study. However, patients were excluded who had failed > 4 medications for the prophylaxis of migraine, including 2 drugs with different mechanisms of action, out of the following drugs: beta-blockers (propranolol/metoprolol/bisoprolol/atenolol/nadolol/timolol), anticonvulsants (topiramate), calcium channel blockers (flunarizine/lomerizine/verapamil), valproate/divalproex, tricyclic antidepressants (amitriptyline/nortriptyline), venlafaxine/desvenlafaxine, lisinopril, angiotensin II receptor blockers (candesartan), locally approved drugs (e.g. oxeterone or pizotifen). In contrast to the studies ELEVATE and ADVANCE, concomitant treatment with one migraine prevention medication with proven efficacy was allowed, provided that the dosage had been stable for at least 12 weeks prior to study inclusion and was well tolerated. The proportion of patients with this type of concomitant treatment was limited to 15%. In contrast to the studies ELEVATE and ADVANCE, participation in the PROGRESS study was possible for patients with medication overuse, defined as use of triptans or ergotamines on ≥ 10 days, use of classic analgesics (aspirin, NSAIDs, acetaminophen) on ≥ 15 days, or any combination of triptans, ergotamines, or classic analgesics on ≥ 10 days in the screening/baseline phase.

A total of 778 patients were randomly allocated in a ratio of 1:1:1 to treatment with atogepant 30 mg twice daily (N = 257), atogepant 60 mg once daily (N = 262) or placebo twice daily (N = 259). The 30 mg dose twice daily was not relevant for the assessment and was therefore not considered further in this benefit assessment. Randomization was stratified by region (North America versus Europe versus Japan versus China versus other), acute headache medication overuse (yes versus no), and migraine prevention medication exposure (current use versus past use versus never used). For patients with current or prior use, a further stratification was carried out based on the number of prior treatments (failed 0 medications or failed ≥ 1 medication(s) with the same mechanism of action versus failed 2 to 4 medications with different mechanisms of action).

In the relevant study arm, atogepant was administered orally once daily, which was in compliance with the SmPC [43]. To maintain blinding versus the atogepant arm with twice-daily doses of 30 mg, patients in the intervention arm received placebo doses in the morning and evening in addition to the 60 mg doses of atogepant. Patients in the placebo arm received placebo in the morning and in the evening.

During the course of the study, participants were allowed to take acute migraine medications. As described above, in contrast to the studies ELEVATE and ADVANCE, concomitant treatment with one migraine prevention medication with proven efficacy was allowed in around 15% of the patients included.

The primary outcome of the study was migraine days/month operationalized as the change from baseline in monthly migraine days across a 12-week period. Secondary outcomes were further outcomes in the categories morbidity and health-related quality, as well as AE outcomes.

The company presented the results of a subpopulation of those patients who previously did not respond to ≥ 2 of the following drugs with different mechanisms of action, who did not tolerate these, or who had a contraindication: beta-blockers (metoprolol/propranolol), flunarizine, topiramate, amitriptyline, clostridium botulinum toxin type A, or valproic acid. The subpopulation included 64 patients in the relevant atogepant treatment arm and 56 patients in the comparator arm. This subpopulation presented by the company was used for this benefit assessment.

LIBERTY study (study with erenumab)

The LIBERTY study is a randomized, double-blind study comparing erenumab with placebo over 12 weeks. Patients with episodic migraine were included in the study. Following the 12-week double-blind treatment phase, the patients could continue treatment with erenumab for 156 weeks in the open-label extension part of the study. The study was already described in detail in dossier assessment A18-71 [29]. Analyses of the 12-week double-blind

treatment phase were relevant for this assessment. The open-label extension part of the study is therefore not discussed further.

The LIBERTY study included adult patients aged 18 to 65 years with a documented history of migraine for at least 12 months according to ICHD-3 [41]. In addition, the patients had to have a history of 4 to 14 migraine days/month on average across the past 3 months and failed 2 to 4 prior migraine prophylaxis treatments. Treatment failure or unsuitability of valproic acid was another prerequisite for inclusion in the study. Treatment failure due to lack of efficacy was defined in the LIBERTY study as no meaningful reduction in headache frequency after administration of the respective medication for an adequate period of time at a generally accepted dose(s) within the last 5 years prior to screening, based on the investigator's assessment. In accordance with the European Headache Federation treatment guidelines [44], an adequate period of time was specified as 2 to 3 months . Treatment failure due to lack of tolerability was defined as documented discontinuation of the respective medication due to AEs at any time before screening.

Within the screening/baseline phase, electronic migraine diaries were used to check the migraine frequency of 4 to 14 migraine days/month as well as the patients' compliance to complete the diaries. For patients to transition to the randomized treatment phase, compliance had to be ≥ 80% within 4 weeks before randomization. Patients with medication overuse, defined as treatment of acute migraine with triptans or ergotamines on ≥ 10 days/month or classic analgesics (NSAIDs, acetaminophen, aspirin) on ≥ 15 days/month [42] within 1 month prior to baseline and during the screening/baseline phase, were not included.

A total of 246 patients were randomly allocated in a 1:1 ratio to treatment with erenumab (N = 121) or placebo (N = 125). Randomization was stratified by the migraine frequency determined in the screening/baseline phase (4 to 7 migraine days/month versus 8 to 14 migraine days/month).

The study staff administered 140 mg erenumab or placebo subcutaneously every 4 weeks at scheduled visits. A dose of 70 mg erenumab is recommended in the SmPC. However, some patients may benefit from a dose of 140 mg [45]. The use of 140 mg in the LIBERTY study was therefore covered by the marketing authorization. As part of the early benefit assessment procedure for erenumab, the regulatory authorities also confirmed that the patient population included in the LIBERTY study was a group that may benefit from treatment with 140 mg erenumab according to the SmPC [24]. In addition, acute treatment of migraine attacks with pharmacological or non-pharmacological interventions was permitted during the study.

The primary outcome of the study was migraine days/month, operationalized as a ≥ 50% reduction in migraine days/month in Week 12. Relevant secondary outcomes were further outcomes in the category morbidity and AE outcomes.

The company presented the results of a subpopulation of those patients who previously did not respond to ≥ 2 of the following drugs with different mechanisms of action or did not tolerate them: beta-blockers (propranolol/metoprolol), flunarizine, topiramate or amitriptyline. The subpopulation also included those patients who responded inadequately to only one of these drugs and had a contraindication to another drug with a different mechanism of action. In addition, the company only included in the subpopulation those patients with a prior treatment with valproic acid for whom valproic acid was the last treatment regimen prior to study inclusion. The subpopulation included 88 patients in the intervention arm and 105 in the comparator arm. This subpopulation presented by the company was used for this benefit assessment.

FOCUS study (study with fremanezumab)

The FOCUS study is a 3-arm, double-blind, randomized study comparing 2 different doses of fremanezumab with placebo. The study was already described in detail in dossier assessment A19-44 [38] and its addendum A19-82 [39]. Patients with chronic or episodic migraine were included in the study. The study consisted of a 4-week screening/baseline phase, a 12-week double-blind, placebo-controlled treatment phase, and a subsequent 12-week open-label phase, in which all patients received fremanezumab. Analyses of the 12-week double-blind treatment phase were relevant for this benefit assessment. The open-label phase of the study is therefore not discussed further.

The study included adult patients aged 18 to 70 years with a documented history of chronic or episodic migraine for at least 12 months (defined according to ICHD-3 [41]. Patients with episodic migraine had to have an average of ≥ 6 and ≤ 14 headache days during the screening/baseline phase, of which ≥ 4 were migraine days. Patients with chronic migraine had to have an average of > 14 headache days during the screening/baseline phase, of which ≥ 8 were 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/baseline phase or with opioid or barbiturate use for migraine treatment on > 4 days were also not included in the study. Patients with medication overuse were not excluded from study participation.

The extent to which the inclusion criterion regarding the number of headache or migraine days/month was met was verified on the basis of the patients' entries in their electronic migraine diaries during the 4-week screening/baseline phase. At the same time, the

compliance of patients for filling out the diary was also checked. Compliance in the screening/baseline phase had to be ≥ 85% for transition to the randomized treatment phase.

Adults with treatment failure of 2 to 4 of the following drugs with different mechanisms of action in the past 10 years were included: 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 AEs, or treatment contraindicated or unsuitable for the prophylactic treatment of migraine for the patient.

In the 12-week double-blind treatment phase, a total of 838 patients with episodic or chronic migraine were randomly assigned in a ratio of 1:1:1 to receive either monthly fremanezumab (N = 283), quarterly fremanezumab (N = 276) or placebo (N = 279).

The quarterly fremanezumab dose consisted 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 administration of fremanezumab in patients with episodic migraine (a total of 3 doses of 225 mg) was in compliance with the marketing authorization. The dosing regimen of fremanezumab used in patients with chronic migraine (initial dose of 675 mg followed by 2 doses at 225 mg) deviated from the dosage described in the SmPC [46]. The SmPC 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 [46]. Since the European Medicines Agency considers the 2 dosing regimens (with and without an initial dose of 675 mg in patients with chronic migraine) to be comparable in the given therapeutic indication, the dosing regimen was considered to be adequate in the early benefit assessment of fremanezumab [32]. In this benefit assessment, monthly and quarterly fremanezumab administration was therefore also considered equivalent and considered jointly.

Patients in the study were allowed to use acute medication to treat acute migraine attacks, as needed. No data were available on the use of non-drug interventions, or these data had not been documented. Since non-drug interventions were not explicitly excluded, however, it was assumed in the benefit assessment procedure for fremanezumab [32] that their use was possible in principle.

The primary outcome of the study was migraine days/month operationalized as the change from baseline in the monthly average number of migraine days. Secondary outcomes were further outcomes in the categories morbidity and health-related quality, as well as AEs.

The company used the results of a subpopulation of those patients who previously did not respond to ≥ 2 treatments (drug classes) or did not tolerate them: beta-blockers (propranolol or metoprolol), flunarizine, topiramate or amitriptyline. The subpopulation included 388 patients in the intervention arm and 195 in the comparator arm. This subpopulation presented by the company was used for this benefit assessment.

Patient characteristics

Table 8 shows the patient characteristics of the subpopulations of the included studies.

Table 8: Characteristics of the relevant subpopulations as well as study/treatment discontinuation – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Study	ELEVATE		ADVANCE		PROGRESS		LIBERTY		FOCUS	
Characteristic Category	Atogepant	Placebo	Atogepant	Placebo	Atogepant	Placebo	Erenumab	Placebo	Fremanezumab	Placebo
	N[a] = 123	N[a] = 127	N[a] = 26	N[a] = 17	N[a] = 63	N[a] = 54	N[b] = 86	N[b] = 104	N[c] = 388	N[c] = 195
Age [years], mean (SD)	41 (10)	43 (10)	41 (12)	40 (13)	39 (11)	43 (13)	44 (11)	45 (11)	45 (11)	46 (11)
Sex [F/M], %	89/11	91/9	88/12	82/18	87/13	89/11	81/19	88/12	85/15	87/13
Family origin, n (%)										
White	116 (94)	122 (96)	25 (96)	16 (94)	43 (68)	42 (78)	77 (90)	95 (91)	361 (93)	182 (93)
Black	3 (2)	3 (2)	1 (4)	0 (0)	2 (3)	1 (2)	–	–	2 (< 1)	2 (< 1)
Asian	2 (2)	2 (2)	0 (0)	1 (6)	17 (27)	11 (20)	0 (0)	1 (< 1)	3 (< 1)	1 (< 1)
Other[d]	2 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	9 (11)	8 (8)	3 (< 1)	0 (0)
Not reported	–	–	–	–	–	–	–	–	19 (5)	10 (5)
Geographical region										
North America	16 (13)	16 (13)	26 (100)[e]	17 (100)[e]	18 (29)	18 (33)	0 (0)[f]	0 (0)[f]	ND[g]	ND[g]
Europe	107 (87)	111 (87)	0 (0)	0 (0)	28 (44)	26 (48)	84 (98)[f]	104 (100)[f]	ND[g]	ND[g]
Asia/Pacific	0 (0)	0 (0)	0 (0)	0 (0)	17 (27)	10 (19)	2 (2)[f]	0 (0)[f]	0 (0)	0 (0)
Disease duration: time since diagnosis of migraine [years], mean (SD)	20.3 (11.3)	19.9 (11.2)	22.1 (13.3)	20.2 (12.7)	20.6 (10.6)	20.7 (11.8)	26.1 (12.2)[h]	23.8 (11.0)[h]	23.4 (13.1)	22.9 (13.1)
Type of migraine, n (%)										
EM	123 (100)	127 (100)	26 (100)	17 (100)	0 (0)	0 (0)	86 (100)	104 (100)	149 (38)	76 (39)
CM	0 (0)	0 (0)	0 (0)	0 (0)	63 (100)	54 (100)	0 (0)	0 (0)	239 (62)	119 (61)
Number of migraine days [days/months], mean (SD)	9.4 (2.5)	9.4 (2.2)	8.0 (2.6)	9.0 (2.9)	18.0 (7.0)	16.6 (6.1)	9.1 (2.3)	9.1 (2.5)	14.3 (5.4)	14.2 (5.9)
Number of headache days[i] [days/months], mean (SD)	10.3 (2.4)	10.1 (2.4)	9.9 (2.9)	11.6 (2.0)	22.9 (5.1)	21.9 (4.9)	9.9 (2.5)	9.9 (2.5)	14.2 (5.8)	14.2 (6.1)

Table 8: Characteristics of the relevant subpopulations as well as study/treatment discontinuation – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Study	ELEVATE		ADVANCE		PROGRESS		LIBERTY		FOCUS	
Characteristic Category	Atogepant	Placebo	Atogepant	Placebo	Atogepant	Placebo	Erenumab	Placebo	Fremanezumab	Placebo
	N[a] = 123	N[a] = 127	N[a] = 26	N[a] = 17	N[a] = 63	N[a] = 54	N[b] = 86	N[b] = 104	N[c] = 388	N[c] = 195
Failed migraine prevention medications[j], n (%)										
1	0 (0)	0 (0)	0 (0)[f]	0 (0)[f]	ND[k]	ND[k]	6 (7)[h, l]	2 (2)[h, l]	0 (0)	0 (0)
2	59 (48)	59 (46)	22 (85)	15 (88)	28 (44)	23 (43)	44 (50)[h]	66 (63)[h]	296 (76)	143 (73)
3	52 (42)	53 (42)	3 (12)	2 (12)	18 (29)	14 (26)	33 (38)[h]	28 (27)[h]	83 (21)	49 (25)
4	12 (10)	15 (12)	1 (4)	0 (0)	8 (13)	7 (13)	5 (6)[h]	9 (9)[h]	9 (2)	3 (2)
Acute headache medication, n (%)										
None	0 (0)	3 (2)	0 (0)	0 (0)	0 (0)	1 (2)	3 (4)	1 (< 1)	ND	ND
Any acute medication	123 (100)	124 (98)	26 (100)	17 (100)	63 (100)	53 (98)	83 (97)	103 (99)	ND	ND
Migraine-specific[m]	101 (82)	105 (83)	11 (42)	14 (82)	48 (76)	41 (76)	70 (81)	90 (87)	ND[n]	ND[n]
Number of days of use of migraine-specific acute medication [days/month], mean (SD)	ND[o]	ND[o]	ND[o]	ND[o]	16.6 (7.4)	15.9 (7.4)	4.6 (2.9)	4.4 (2.8)	9 (6.4)	9.2 (6.7)
Any non-drug prophylaxis of migraine, n (%)	ND	ND	ND	ND	ND	ND	6 (7)	9 (9)	ND	ND
Medication overuse, n (%)	–	–	–	–	ND[p]	ND[p]	–	–	204 (53[f])	91 (47[f])
Concomitant migraine prophylaxis	–	–	–	–	9 (14)	10 (19)	–	–	–	–
General impact of headache, measured using the HIT-6, mean (SD)	64.6 (4.3)	64.8 (4.1)	63.1 (4.8)	64.6 (3.9)	64.5 (4.7)	66.3 (3.5)	62.5 (3.9)	62.2 (5.2)	64.2 (4.4)	64.0 (5.2)

Table 8: Characteristics of the relevant subpopulations as well as study/treatment discontinuation – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Study Characteristic Category	ELEVATE		ADVANCE		PROGRESS		LIBERTY		FOCUS	
	Atogepant	Placebo	Atogepant	Placebo	Atogepant	Placebo	Erenumab	Placebo	Fremanezumab	Placebo
	N[a] = 123	N[a] = 127	N[a] = 26	N[a] = 17	N[a] = 63	N[a] = 54	N[b] = 86	N[b] = 104	N[c] = 388	N[c] = 195
Treatment discontinuation, n (%)	10 (8)	4 (3)	4 (15)[p]	1 (6)[p]	4 (6)	7 (13)	ND	ND	ND	ND
Study discontinuation, n (%)	ND[q]	ND[q]	ND[q]	ND[q]	ND[q]	ND[q]	3 (3)[h]	3 (3)[h]	ND	ND

a. Number of randomized patients in the relevant subpopulation who received at least 1 dose of the respective study medication and who have a usable screening/baseline phase as well as entries in the electronic diary for at least one usable 4-week period after baseline (Weeks 1 to 4, 5 to 8, or 9 to 12) during the double-blind treatment period (mITT population).
b. Number of randomized patients in the relevant subpopulation who received at least 1 dose of the study medication and have a post-baseline value of monthly migraine days for at least 1 month in the double-blind treatment phase (FAS population).
c. Number of randomized patients in the relevant subpopulation who received at least 1 dose of the study medication and for whom a recording on migraine is available on at least 10 days (mITT population).
d. In the atogepant studies, patients with multiple family origins fall into this category.
e. The ADVANCE study is a study that was only conducted at study centres in the United States.
f. Institute's calculation.
g. In relation to the overall population of the FOCUS study, 14% of patients came from the United States and 86% from Europe.
h. Based on the 88 vs. 105 randomized patients in the relevant subpopulation.
i. For the atogepant studies, this is the average number of headache days per month in the past 3 months; for LIBERTY and FOCUS, the number of headache days in the last month.
j. Treatment failure was assessed by the investigator on the basis of lack of efficacy, intolerability and/or unsuitability/contraindication.
k. Data are only available for 54 of 63 vs. 44 of 54 patients, although the characteristic was used to form the relevant subpopulation. However, according to the definition of the relevant subpopulation, the missing 9 vs. 10 patients should not have received only one failed migraine prevention medication; patients with more than 4 treatments were not included in the study.
l. Additionally at least one unsuitability for treatment with propranolol/metoprolol, topiramate, flunarizine, amitriptyline.
m. Number or proportion of patients in the relevant subpopulation who received triptans.
n. Data are only available for the total population, fremanezumab vs. placebo: 86% vs. 85%.
o. Data are only available for the total population (mITT); mean (SD) [days], atogepant vs. placebo: 7.5 (3.0) vs. 7.7 (3.4) in ELEVATE; 6.9 (3.2) vs. 6.5 (3.2) in ADVANCE.
p. Data are only available for the total population, atogepant vs. placebo: 63% vs. 64%.

Table 8: Characteristics of the relevant subpopulations as well as study/treatment discontinuation – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Study	ELEVATE		ADVANCE		PROGRESS		LIBERTY		FOCUS	
Characteristic Category	Atogepant	Placebo	Atogepant	Placebo	Atogepant	Placebo	Erenumab	Placebo	Fremanezumab	Placebo
	N[a] = 123	N[a] = 127	N[a] = 26	N[a] = 17	N[a] = 63	N[a] = 54	N[b] = 86	N[b] = 104	N[c] = 388	N[c] = 195

q. In relation to 27 vs. 18 patients (with at least 1 dose of study medication; atogepant vs. placebo).
r. Data are only available for the total population (with at least 1 dose of the study medication), atogepant vs. placebo: 8% vs. 4% in ELEVATE; 13% vs. 10% in ADVANCE; 11% vs. 11% in PROGRESS.

CM: chronic migraine; EM: episodic migraine; F: female; FAS: full analysis set; HIT: Headache Impact Test; M: male; mITT: modified intention to treat; n: number of patients in the category; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The characteristics of the relevant subpopulations were largely balanced between the arms of the individual studies. The mean patient age in all studies was about 40 to 45 years; most of them were female and white. Most study participants were enrolled in Europe and North America; only the PROGRESS study was also conducted in Asian study centres. The ADVANCE study was only conducted in the United States.

Patients in all 5 studies had had migraine for about 20 years and had mostly received 2 to 3 migraine prevention medications prior to inclusion in the study. They mainly required acute medication for the treatment of headaches and, as shown by the information provided in the HIT-6 questionnaire at baseline, headaches had a severe impact on their lives.

There was a clear difference between the studies in the proportion of patients with chronic migraine: While the studies ELEVATE and ADVANCE, as well as the LIBERTY study, only included patients with episodic migraine, the proportion of patients with chronic migraine was around 60% in the FOCUS study. The PROGRESS study exclusively investigated patients with chronic migraine. Individual disease characteristics associated with the underlying type of migraine also differed accordingly, in particular the number of migraine days/month, which was generally smaller in the studies with episodic migraine than in the studies that also included patients with chronic migraine (FOCUS study) or that exclusively included these patients (PROGRESS study). In addition, the number of days with use of acute medication to treat migraine was accordingly also higher in these studies. The studies PROGRESS and FOCUS also included patients with medication overuse, which is expected to be more common in patients with chronic migraine than in patients with episodic migraine. The PROGRESS study also included around 15% of patients with one concomitant prophylactic treatment for migraine. A detailed discussion of the differences between the studies is provided in Section I 4.1.3 describing the similarity of the patient populations for the indirect comparison.

Information on study or treatment discontinuations was only partially available for the relevant subpopulations of the studies. The proportion of treatment discontinuations was low in the atogepant studies ELEVATE, ADVANCE and PROGRESS. The proportion of study discontinuations was also low in relation to the total populations of these 3 studies and for the LIBERTY study.

I 4.1.3 Similarity of the studies for the indirect comparison

The following text discusses key aspects of the similarity of the studies for conducting an adjusted indirect comparison beyond the study characteristics described in Section I 4.1.2.

Study design

All 5 studies presented by the company for an adjusted indirect comparison were multicentre, double-blind RCTs with a mostly comparable study design, which included adult patients with chronic and/or episodic migraine with ≥ 4 migraine days per month.

The outcomes on morbidity and health-related quality of life were recorded and analysed over the course of a 12-week placebo-controlled treatment phase. Results for the outcomes in the side effects category were available for the 12-week treatment phase in the studies LIBERTY and FOCUS, while in the atogepant studies ELEVATE, ADVANCE and PROGRESS, these included a 4-week follow-up phase in addition to the 12-week treatment phase. However, due to the comparably small number of events, this was of no consequence for the indirect comparison in the given data situation.

The periods in which the studies were conducted differed marginally, but did not call into question the comparability of the studies for the indirect comparison. While the double-blind treatment phases in the studies on the comparator side, LIBERTY and FOCUS, were started and completed between 2017 and 2018, the studies on the intervention side were conducted between 2018 and 2022.

Similarity of the patient population

For the studies ELEVATE, LIBERTY and FOCUS, failure of 2 to 4 previous treatments for migraine prophylaxis was an inclusion criterion. In contrast, patients were included in the studies ADVANCE and PROGRESS regardless of whether they had previously received migraine prevention medication or whether they had responded to or had not tolerated previous prophylactic treatment. According to the protocols of these 2 studies, approximately 70% of respective study populations had to have taken at least one prior migraine prevention medication with proven efficacy.

To form the relevant subpopulations for the indirect comparison, the company used comparable definitions for all 5 studies to ensure sufficient similarity of the patients considered. In line with the previous benefit assessment procedures on erenumab [24] and fremanezumab [32], the company considered metoprolol, propranolol, flunarizine, amitriptyline, clostridium botulinum toxin type A (only for chronic migraine) as well as valproic acid and topiramate as possible options for failed migraine prophylaxis. The company considered valproic acid and topiramate in addition to the treatments relevant for the research question at hand (see Table 4), as no analyses without consideration of these drugs were available for the studies LIBERTY and FOCUS.

Information on the patient characteristics of the relevant subpopulations of the 3 studies ELEVATE, ADVANCE and PROGRESS on the intervention side and the 2 studies LIBERTY and FOCUS on the comparator side can be found in Section I 4.1.2.

The demographic and clinical characteristics of the relevant subpopulations in the 5 studies were largely comparable. However, there were differences between the studies in the included patients' types of migraine and the associated characteristics. The studies ELEVATE and ADVANCE on the intervention side and LIBERTY on the comparator side only included patients with episodic migraine with 4 to 14 migraine days per month. In contrast, the atogepant study PROGRESS only investigated study participants with chronic migraine. The FOCUS study included both types of migraine, with the proportion of patients with chronic migraine in the relevant subpopulation being around 60%. The mean number of migraine days per month also differed between the studies depending on the underlying migraine type. At baseline, it was around 9 days for patients with episodic migraine, almost twice as many (18.0 and 16.6 days respectively) in the PROGRESS study for chronic migraine, and 14 days in the FOCUS study with a mixed patient group in terms of migraine type. There are also comparable differences in the number of headache days at baseline.

There was a clear difference, which was also associated with the migraine type, in the proportion of patients with medication overuse, defined as treatment of acute migraine with triptans or ergotamines on ≥ 10 days/month or classic analgesics (NSAIDs, acetaminophen, aspirin) on ≥ 15 days/month. Participation in the studies ELEVATE, ADVANCE and LIBERTY on episodic migraine was not possible for patients with medication overuse, whereas participation in the studies PROGRESS and FOCUS was possible for this patient group. The proportion of these patients was 64% in the overall population of the PROGRESS study, and around 50% in the relevant subpopulation of the FOCUS study [40].

Similarity of the common comparator

The common comparator in the presented indirect comparison was placebo. Additional concomitant medications for the acute treatment of headaches or migraine attacks were permitted in all 5 studies. In addition, exclusively in the PROGRESS study, approximately 15% of the patient population had the option of receiving one migraine prevention medication with proven efficacy during the study, provided that it had been taken at stable doses for at least 12 weeks prior to the start of the study and had been well tolerated, according to the study protocol. In all other studies presented for the indirect comparison, however, concomitant preventive migraine treatment was generally excluded. Only very limited information for all 5 studies was available on non-drug interventions for acute treatment or as migraine prophylaxis in prior therapy or during the study. In some cases, there were different specifications for acute treatment and prophylaxis (see Table 7 for details). No information on the use of non-drug interventions was available for the FOCUS study, but their use was not excluded (see Section I 4.1.2 for details).

Summary on the comparability of the studies

Similarity is a key requirement for the consideration of studies in an adjusted indirect comparison. The 5 studies ELEVATE, ADVANCE, PROGRESS, LIBERTY and FOCUS had a similar study design. The patient populations of the presented studies showed differences, which mainly resulted from the difference in the underlying disease characteristic migraine type (episodic or chronic migraine) and their associated features. Overall, however, these differences did not call into question an adequate similarity of the studies and thus the possibility of conducting an indirect comparison via the common comparator placebo, taking into account all 5 studies.

Authors of a publication on differences between episodic and chronic migraine considered the relationship between episodic and chronic migraine to be complex [47]. Episodic migraine can develop into chronic migraine and vice versa. The same authors described that there is no clear differentiation between episodic and chronic migraine, but pointed out that the corresponding groups differ from each other (e.g. in terms of epidemiology, symptoms and comorbidities) [47].

To address the uncertainty caused by the differences described above, in addition to the analyses of the indirect comparison across all 5 studies, this benefit assessment considered analyses of the indirect comparison that only included studies exclusively with patients with episodic migraine (ELEVATE and ADVANCE on the intervention side and LIBERTY on the comparator side). In principle, indirect comparisons according to migraine type would be of interest as sensitivity analyses in the given data situation, i.e. also separate analyses for patients with chronic migraine. However, as no separate analyses of patients with episodic and chronic migraine were available from the FOCUS study for the relevant subpopulation, it was not possible to conduct such analyses.

Analyses presented by the company

In contrast to the approach in this benefit assessment, the company conducted a separate indirect comparison for each of the 2 ACT options it had selected and used these analyses as the main analyses for its assessment. For the adjusted indirect comparison of atogepant with erenumab, the company only considered the ELEVATE study on the intervention side. It excluded the ADVANCE study from this analysis on the grounds that the ELEVATE and LIBERTY studies showed the greatest possible comparability in terms of study design and that the relevant subpopulation from the ADVANCE study did not carry much weight compared with the ELEVATE study. The company additionally presented an indirect comparison taking into account ELEVATE and ADVANCE on the intervention side and LIBERTY on the comparator side, pointing to consistent results in a homogeneous data situation in Appendix 4-G to Module 4 A of the dossier.

For the adjusted indirect comparison of atogepant with fremanezumab, the company argued that due to the inclusion of patients with different migraine types (episodic and chronic migraine) in the FOCUS study on the comparator side, an approximation of the similarity of the studies on both sides of the indirect comparison was possible if, in addition to the relevant subpopulation of the ELEVATE study on the intervention side, the relevant subpopulations of the ADVANCE and PROGRESS studies were also taken into account. The resulting study pool thus contained about 70% of patients with episodic migraine and about 30% with chronic migraine on the intervention side. In contrast, the relevant subpopulation of the FOCUS study contained around 40% with episodic migraine and around 60% with chronic migraine.

The company refrained from joint consideration of the studies on the 2 comparators erenumab and fremanezumab selected on the comparator side in a joint indirect comparison, as it considered the similarity of the studies to be insufficient, particularly with regard to the proportion of patients with chronic migraine. For this reason, the company presented an indirect comparison considering all 5 studies on the intervention and comparator side only as supplementary information in Appendix 4-G to Module 4 A of the dossier. However, in view of the fact that the company summarized studies on the different types of migraine in its indirect comparison versus fremanezumab on the intervention side, it remained unclear why it did not also provide such a summary on the comparator side. In addition, a joint consideration of the studies LIBERTY and FOCUS further increased the similarity of the populations in terms of migraine type on both sides of the indirect comparison, with respective proportions of patients with episodic or chronic migraine of around 50% on the comparator side.

Deviating from the company, the indirect comparison of atogepant versus erenumab or fremanezumab, taking all 5 studies into account, was considered as the main analysis, as described above.

I 4.1.4 Methods for conducting the indirect comparison

The company described that Bucher's methodological approach was used to conduct the adjusted indirect comparisons [6].

For a meta-analytical summary of study results on the intervention or comparator side, the company chose a fixed-effect model using the inverse variance method. It determined the variance between the studies on the basis of the Paule-Mandel method. The company checked the presence of heterogeneity using the Q-test.

The company justified the choice of the fixed-effect model on the atogepant side with a sufficient similarity of the 3 studies ELEVATE, ADVANCE and PROGRESS. Even if the overall similarity of the studies presented for the indirect comparison was not called into question, the relevant subpopulations used nevertheless showed differences with regard to the

underlying disease characteristic migraine type (episodic or chronic migraine) and other associated disease characteristics, as described in Section I 4.1.3. Therefore, a method that takes random effects into account would be adequate for carrying out the indirect comparison.

Since in the given data situation, even using a fixed-effect model for the meta-analytical summary on the atogepant side, the analyses on the indirect comparison presented by the company did not show a statistically significant and relevant effect for any of the outcomes in the adjusted indirect comparison as per Bucher, the company's approach was of no consequence for the conclusion of this benefit assessment. It could be deduced from the results that even when conducting an indirect comparison with a method that took random effects into account, no statistically significant and relevant effect could be expected (see Section I 4.2.3).

I 4.1.5 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: atogepant vs. erenumab or fremanezumab

Comparison Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
Atogepant vs. placebo							
ELEVATE	Yes	Yes	Yes	Yes	Yes	Yes	Low
ADVANCE	Yes	Yes	Yes	Yes	Yes	Yes	Low
PROGRESS	Yes	Yes	Yes	Yes	Yes	Yes	Low
Erenumab or fremanezumab vs. placebo							
LIBERTY	Yes	Yes	Yes	Yes	Yes	Yes	Low
FOCUS	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for all 5 studies.

Transferability of the study results to the German health care context

The company presumed good transferability of the results of the studies and of the indirect comparison to the German health care context. According to the company, this was supported

by the characteristics of the patients in the ELEVATE, ADVANCE and PROGRESS studies and by key aspects of how the studies were conducted. It added that the studies were conducted in North American and European study centres, and that patients were considered who had failed ≥ 2 migraine prophylactics approved in Germany or recommended in the German guidelines as drugs with a high level of evidence, or who were unsuitable for these prophylactics. According to the company, this limited the respective subpopulation to those patients who best represented the German health care context. Atogepant was used in compliance with the German SmPC, the company explained, and the studies used valid instruments to assess treatment response, which were also used in everyday clinical practice in Germany and were mentioned in the German migraine guideline, among others. The company also saw no important deviations in the key inclusion criteria of the study population compared with the relevant target population in Germany of adults with at least 4 migraine days per month. According to the company, the patients' baseline values essentially concurred with the values described in the literature, e.g. the common onset of migraine between the ages of 20 and 50. and the fact that women were more often affected than men. This age and sex distribution was also reflected in the baseline data from the ELEVATE, ADVANCE and PROGRESS studies, the company said.

It noted that the LIBERTY and FOCUS studies had already been used for the benefit assessment of erenumab and fremanezumab. Due to the demographic and disease-specific characteristics of the study populations, the company concluded that the study data were transferable to the German health care context.

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 as migraine days/month
  - General impact of headache, measured using the HIT-6
  - Health status, measured using the EQ-5D VAS
- Health-related quality of life

- Health-related quality of life, measured with the MSQ

- Side effects
  - Serious adverse events (SAEs)
  - Discontinuation due to AEs
  - Other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A).

Table 10 shows for which outcomes data were available in the included studies (yes/no) and whether an indirect comparison was possible based on the available data (yes/no).

Table 10: Matrix of outcomes – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab

Comparison / Study	Outcomes							
	All-cause mortality[a]	Symptoms (migraine days/month)	General impact of headache (HIT-6)	Health status (EQ-5D VAS)	Health-related quality of life (MSQ)	SAEs	Discontinuation due to AEs	Specific AEs
Atogepant vs. placebo								
ELEVATE	Yes[b]	Yes	Yes	Yes	Yes	Yes	Yes	No[c]
ADVANCE	Yes[b]	Yes	Yes	Yes	Yes	Yes[b]	Yes	No[c]
PROGRESS	Yes[b]	No[d]	Yes	Yes	Yes	Yes	Yes	No[c]
Erenumab or fremanezumab vs. placebo								
LIBERTY	Yes[b]	Yes	Yes	Yes	No[e]	Yes	Yes	No[f]
FOCUS	Yes[b]	Yes	Yes	Yes	Yes	Yes	Yes	No[g]
Indirect comparison feasible	No[h]	No[i]	Yes	Yes	Yes	Yes	Yes	No

a. The results on all-cause mortality are based on the information on fatal AEs.
b. No event for this outcome occurred in the relevant subpopulation.
c. The company stated that it did not present the AEs according to SOCs and PTs for the ELEVATE, ADVANCE and PROGRESS studies, as only incomplete analyses of AEs were available for the comparator side.
d. There are no results for the relevant operationalization (≥ 50% reduction in migraine days/month from baseline in Month 3).
e. Outcome not recorded.
f. No specific AEs were identified based on the AEs occurring in the study.
g. No complete analyses of AEs available. Data is only available at SOC level and not at PT level, so it is not possible to select specific AEs based on complete data.
h. No event for this outcome occurred in the relevant subpopulation in any of the studies. An indirect comparison was therefore not conducted.
i. The requirement for the certainty of results to perform an adjusted indirect comparison is not met (see following text, Table 11 and Section I 4.2.2).

AE: adverse event; HIT-6: 6-Item Headache Impact Test; MSQ: Migraine-Specific Quality of Life Questionnaire; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

All-cause mortality

No events for this outcome occurred in the relevant subpopulations of any of the 5 studies. An indirect comparison was therefore not conducted for this outcome.

Symptoms – migraine days/month

In this benefit assessment, the outcome of symptoms was assessed on the basis of migraine days/month. The patients in all 5 studies recorded this information daily in their electronic patient diaries. Against the background of the patients' symptom burden in the studies, a ≥ 50% reduction in migraine days/month was an appropriate response criterion, regardless of whether the patients had episodic or chronic migraine. Therefore, the ≥ 50% reduction in migraine days/month was used for the derivation of the added benefit. The reduction from baseline in Month 3 is shown, as analyses for this operationalization were available for both studies on the comparator side. Analyses of this operationalization were also possible in principle for the intervention side, but were only presented by the company for the ELEVATE and ADVANCE studies, and not for the PROGRESS study. This would mean that only patients with episodic migraine would be included on the intervention side, whereas the comparator side would also include patients with chronic migraine from the FOCUS study. To achieve sufficient similarity in the indirect comparison, only the results of the comparison of atogepant with erenumab based on ELEVATE and ADVANCE versus LIBERTY could therefore be considered for this outcome. Since the results on this outcome from the LIBERTY study did not fulfil the requirement for the certainty of results for conducting an adjusted indirect comparison (see Table 11 and Section I 4.2.2), the indirect comparison for this outcome was not used for the benefit assessment, however.

No analyses across all 5 studies were possible for the ≥ 75% or 100% reduction in migraine days/month because only analyses of different operationalizations were available for the 2 studies on the comparator side (LIBERTY: analyses of the reduction from baseline in Month 3; FOCUS: analyses of the reduction from baseline averaged over 12 weeks). Since the risk of bias of the results was assessed as high for the analyses of the studies on the comparator side, the requirement for the certainty of results for conducting an adjusted indirect comparison was not met for the results of both operationalizations. This means that the adjusted indirect comparison for these operationalizations was also not suitable for the benefit assessment. As an analysis of the indirect comparison for the reduction in migraine days/month was only possible if all 5 studies were included in the analyses, the results of the individual studies on the ≥ 75% or 100% reduction in migraine days/month are not presented in this assessment.

Continuous analyses of the change from baseline in Month 3 using a mixed-effects model with repeated measures as well as analyses of the ≥ 50% reduction in migraine days/month in Month 3 were available for both studies on the comparator side, but were not presented by the company for the PROGRESS study. An indirect comparison was therefore also not feasible for this operationalization.

Notes on outcomes in the side effects category

SAEs and discontinuation due to AEs

In the relevant subpopulations of all studies, very few events occurred overall for the outcomes SAEs and discontinuation due to AEs. In this data situation, the sensitivity analyses for the indirect comparison, which only took into account studies that exclusively included patients with episodic migraine (ELEVATE and ADVANCE on the intervention side and LIBERTY on the comparator side) were therefore not considered.

Specific AEs

The company stated that it did not present the AEs according to System Organ Classes (SOCs) and Preferred Terms (PTs) for the ELEVATE, ADVANCE and PROGRESS studies, as only incomplete analyses of AEs were available for the comparator side. Although data on common AEs with a threshold value of 10% were available for the LIBERTY study on erenumab in the previous benefit assessment, no specific AEs were identified based on the AEs that occurred in the study. [29]. For the FOCUS study on fremanezumab, only data on AEs at SOC level were available for the relevant subpopulation. Data on PTs were not available [32]. It was therefore not possible to select specific AEs based on complete data.

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: atogepant vs. erenumab or fremanezumab

Comparison Study	Study level	Outcomes							
		All-cause mortality[a]	Symptoms (migraine days/month)	General impact of headache (HIT-6)	Health status (EQ-5D VAS)	Health-related quality of life (MSQ)	SAEs	Discontinuation due to AEs	Specific AEs
Atogepant vs. placebo									
ELEVATE	L	L	H[b]	L	H[c]	L	L	L	–[d]
ADVANCE	L	L	H[b, e]	L	L	L	L	L	–[d]
PROGRESS	L	L	–[f]	L	H[c]	L	L	L	–[d]
Erenumab or fremanezumab vs. placebo									
LIBERTY	L	L	H[b, g]	L	L	–[h]	L	L	–[i]
FOCUS	L	L	H[b]	L	L	L	L	L	–[j]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. For the relevant subpopulation, there is insufficient information on the frequency or distribution of missing values in the electronic diary; see the following text section for an explanation.
c. Presumably high proportion of patients not included in the analysis (> 10%); it is assumed that only patients with a baseline value and at least one post-baseline value were included in the analysis; in the ELEVATE and PROGRESS studies, baseline values were only available for 60% vs. 64% and 50% vs. 41% of the patients randomized to the relevant subpopulation; due to the similar proportions in both arms and the double-blind study design, the absence of values is not considered to be closely associated with the treatment. The results are therefore used, but their risk of bias is still assessed as high in each case.
d. The company stated that it did not present the AEs according to SOCs and PTs for the ELEVATE, ADVANCE and PROGRESS studies, as only incomplete analyses of AEs were available for the comparator side.
e. High proportion of patients not included in the analysis, which differs between the treatment arms.
f. There are no results for the relevant operationalization (≥ 50% reduction in migraine days/month from baseline in Month 3).
g. No information on the proportion of NRI-imputed values.
h. Outcome not recorded.
i. No specific AEs were identified based on the AEs occurring in the study.
j. No complete analyses of AEs available. Data is only available at SOC level and not at PT level, so it is not possible to select specific AEs based on complete data.

AE: adverse event; H: high; HIT-6: 6-Item Headache Impact Test; L: low; NRI: non-responder imputation; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of the results for the symptom outcome (migraine days/month) was assessed as high for each of the studies ELEVATE, ADVANCE, LIBERTY and FOCUS, as there was

insufficient information on the frequency or distribution of missing values in the electronic diary.

The outcome was recorded in all studies via the electronic migraine diary, which patients had to fill out daily.

In the atogepant studies, patients qualified for randomization if they were in the screening/baseline phase for at least 28 days and had completed the diary on at least 20 days during this time. After randomization, recordings had to be available for at least 14 days per time window in 3 successive 4-week (i.e. 28-day) time windows. If recordings were available for fewer than 14 days, the patient's number of migraine days for that 4-week window was considered as missing. If recordings were available for at least 14 but less than 28 days in a patient's 4-week window, the proportion of migraine days was determined in relation to the days with recordings and then transferred to the 4-week window.

The company only provided information on the number of patients with an available value for the respective 4-week window. However, recordings for up to 14 days may have been missing for these patients. The company did not provide a breakdown of the number of days without recordings. If recordings were missing on many days for a high proportion of patients, this could lead to a major bias, as the monthly migraine days were allocated to the corresponding 4-week window concurring with the proportion of migraine days among the documented days.

In the atogepant studies, randomized patients who received at least 1 dose of the respective study medication and who had entries in the electronic diary on at least 14 days in at least one 4-week window after baseline were included in the analysis of morbidity outcomes. In the ELEVATE study, 3 patients (2.4%) randomized to the atogepant arm vs. 2 patients (1.6%) randomized to the placebo arm were not included in the analysis for this reason; in the ADVANCE study, this concerned one patient each (3.7% vs. 5.6%).

In the analysis of the reduction in migraine days/month, the company additionally imputed missing values in some of the studies if there were 3 entries in the electronic diary on less than 14 days per month. In the ELEVATE study, for example, the analysis was carried out using a non-responder imputation (NRI) in patients who had 3 entries in the electronic diary on less than 14 days per month (9 versus 3). Hence, 9.5% versus 3.9% of the randomized patients had the missing value imputed or were not included in the analysis.

In the ADVANCE study, no imputation was performed for patients with 3 entries in the electronic diary on less than 14 days per month (3 versus 0). This means that a total of 14.8% versus 5.6% of the randomized patients were not included in the analysis of the reduction in migraine days/month. This high proportion patients excluded from the analysis, which

differed between the treatment arms, was an additional aspect of bias for the results of the ADVANCE study.

Data on the number of days without recordings were also not available for the studies LIBERTY and FOCUS, which was already described in the benefit assessments on erenumab [29] and fremanezumab [39].

In the LIBERTY study, the analysis was carried out using an NRI in patients with 3 entries in the electronic diary on less than 14 days per month (there was no information on the proportions). In the FOCUS study, the analysis was carried out using a last-observation-carried-forward imputation in patients with 3 entries in the electronic diary on less than 10 days per month (in relation to the relevant subpopulation 2.6% vs. 4.6%). The missing information on the proportion of imputed values was a further aspect of bias for the result from the LIBERTY study.

For the outcome health status (EQ-5D VAS), the results from the studies ELEVATE and PROGRESS were used despite the high proportion of missing values, particularly at baseline, because due to the similar proportions in both arms and the double-blind study design, the absence of values was not considered to be closely associated with the treatment. However, the risk of bias was still assessed as high in both cases. The risk of bias for the other studies was assessed as low.

The risk of bias of the results of the other outcomes was assessed as low in each case.

I 4.2.3 Results

Table 12 and Table 13 summarize the results of the comparison of atogepant versus erenumab or fremanezumab for prophylaxis of migraine in adult patients who have at least 4 migraine days per month and who are not candidates for conventional migraine prophylaxis. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Forest plots of the presented meta-analyses can be found in Appendix A of the full dossier assessment.

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Outcome category Outcome Comparison Study	Atogepant or erenumab or fremanezumab N	 Patients with event n (%)	Placebo N	 Patients with event n (%)	Group difference RR [95% CI]; p-value[a]
Mortality					
All-cause mortality[b, c]					
Atogepant vs. placebo					
ELEVATE	125	0 (0)	128	0 (0)	–
ADVANCE	27	0 (0)	18	0 (0)	–
PROGRESS	64	0 (0)	56	0 (0)	–
Total					–
Erenumab or fremanezumab vs. placebo					
LIBERTY	86	0 (0)	104	0 (0)	–
FOCUS	388	0 (0)	195	0 (0)	–
Total					–
Indirect comparison using common comparators:					
Atogepant vs. erenumab or fremanezumab					–
Morbidity					
Symptoms: migraine days/month					
≥ 50% reduction from baseline in Month 3					
Atogepant vs. placebo					
ELEVATE[d]	123	67 (54.4)	127	39 (30.7)	1.77 [1.30; 2.41]; < 0.001[e]
ADVANCE[d]	23	16 (69.6)	17	4 (23.5)	2.96 [1.20; 7.26]; 0.004[e]
PROGRESS	ND	ND	ND	ND	ND
Total					ND
Erenumab or fremanezumab vs. placebo					
LIBERTY[f]	86	26 (30.2)	104	14 (13.5)	2.25 [1.25; 4.03]; 0.005
FOCUS[f]	387[g]	152 (39.3)[g]	195	33 (17)	2.32 [1.66; 3.24]; < 0.001[h]
Total					ND
Indirect comparison using common comparators:					
Atogepant vs. erenumab or fremanezumab					ND[i]

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Outcome category Outcome Comparison Study	Atogepant or erenumab or fremanezumab N	 Patients with event n (%)	Placebo N	 Patients with event n (%)	Group difference RR [95% CI]; p-value[a]
Sensitivity analysis					
Atogepant vs. placebo					
ELEVATE/ADVANCE, total					*1.87 [1.40; 2.50]; < 0.001*[j]
Erenumab vs. placebo					
LIBERTY	*86*	*26 (30.2)*	*104*	*14 (13.5)*	*2.25 [1.25; 4.03]; 0.005*
Indirect comparison using common comparators:					
Atogepant vs. erenumab					–[k]
Side effects[c]					
AEs (supplementary information)					
Atogepant vs. placebo					
ELEVATE	125	68 (54.4)	128	70 (54.7)	–
ADVANCE	27	12 (44.4)	18	13 (72.2)	–
PROGRESS	64	39 (60.9)	56	31 (55.4)	–
Total					–
Erenumab or fremanezumab vs. placebo					
LIBERTY	86	52 (60.5)	104	61 (58.7)	–
FOCUS	388	208 (53.6)	195	101 (51.8)	–
Total					–
SAEs					
Atogepant vs. placebo					
ELEVATE	125	4 (3.2)	128	0 (0)	9.21 [0.50; 169.38][l]; 0.044[e]
ADVANCE	27	0 (0)	18	0 (0)	–
PROGRESS	64	1 (1.6)	56	0 (0)	2.63 [0.11; 63.31][l]; 0.515[e]
ELEVATE/PROGRESS, total					5.20 [0.61; 44.56]; 0.132[j]
Erenumab or fremanezumab vs. placebo					
LIBERTY	86	2 (2.3)	104	1 (1.0)	2.42 [0.22; 26.22]; 0.592
FOCUS	388	4 (1.0)	195	3 (1.5)	0.67 [0.15; 2.96]; 0.625
Total					0.96 [0.27; 3.40]; 0.950[j]
Indirect comparison using common comparators[m]:					
Atogepant vs. erenumab or fremanezumab					5.42 [0.45; 65.54]; 0.184

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Outcome category Outcome Comparison Study	Atogepant or erenumab or fremanezumab N	 Patients with event n (%)	Placebo N	 Patients with event n (%)	Group difference RR [95% CI]; p-value[a]
Discontinuation due to AEs					
Atogepant vs. placebo					
ELEVATE	125	2 (1.6)	128	1 (0.8)	2.05 [0.19; 22.30]; 0.601[e]
ADVANCE	27	1 (3.7)	18	1 (5.6)	0.67 [0.04; 9.99]; 0.808[e]
PROGRESS	64	2 (3.1)	56	2 (3.6)	0.88 [0.13; 6.01]; 0.975[e]
Total					1.07 [0.29; 3.98]; 0.920[j]
Erenumab or fremanezumab vs. placebo					
LIBERTY	86	0 (0)	104	2 (1.9)	0.24 [0.01; 4.96][l]; 0.228
FOCUS	388	3 (0.8)	195	2 (1.0)	0.75 [0.13; 4.47]; 0.829
Total					0.57 [0.12; 2.64]; 0.470[j]
Indirect comparison using common comparators[m]:					
Atogepant vs. erenumab or fremanezumab					1.89 [0.25; 14.24]; 0.538

a. p-value at study level: unconditional exact test (CSZ method according to [48]).
b. The results on all-cause mortality are based on the data on fatal AEs.
c. Includes events that occurred within the 12-week double-blind treatment phase; for ELEVATE/ADVANCE/PROGRESS: events that occurred within the 4-week follow-up phase are also included.
d. ELEVATE: The analysis was carried out using a non-responder imputation in patients who had 3 entries in the electronic diary on less than 14 days per month (see Section I 4.2.2 for details).
ADVANCE: The analysis was carried out without imputation in patients who had 3 entries in the electronic diary on less than 14 days per month (see Section I 4.2.2 for details).
e. Institute's calculation of p-value.
f. LIBERTY: The analysis was carried out using a non-responder imputation in patients who had 3 entries in the electronic diary on less than 14 days per month (see Section I 4.2.2 for details).
FOCUS: The analysis was carried out using a last observation carried forward imputation in patients who had 3 entries in the electronic diary on less than 10 days per month (see Section I 4.2.2 for details).
g. Institute's calculation.
h. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [48]).
i. The company did not present any analyses for the PROGRESS study and therefore also for the indirect comparison across all 5 studies (see Section I 4.2.1 for an explanation).
j. Meta-analysis, fixed-effect model (method with inverse variance).
k. Requirement for the certainty of results to perform an adjusted indirect comparison is not met (see Table 11 and Section I 4.2.2).
l. Calculation of RR and CI with correction factor 0.5 in both study arms. Possible discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
m. Indirect comparison according to Bucher [6].

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Table 13: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Outcome category	Atogepant or erenumab or fremanezumab			Placebo			Group difference
Outcome Comparison Study	N[a]	Values at baseline mean (SD)	Change in Month 3 or Week 12 mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change in Month 3 or Week 12 mean (SE)[b]	MD [95% CI]; p-value[b]
Morbidity							
Symptoms: migraine days/month (change from baseline in Month 3) (supplementary information)							
Atogepant vs. placebo							
ELEVATE	*123*	*8.9 (2.4)*	*−4.1 (0.4)*	*127*	*9.5 (2.3)*	*−2.3 (0.4)*	*−1.80 [−2.91; −0.69]; 0.002*
ADVANCE	*26*	*8.5 (2.5)*	*−4.2 (0.9)*	*17*	*7.9 (2.0)*	*−1.1 (1.1)*	*−3.11 [−5.91; −0.31]; 0.030*
PROGRESS	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Total							*ND*
Erenumab or fremanezumab vs. placebo							
LIBERTY	*86*	*9.1 (2.3)*	*−1.6 (0.5)*	*104*	*9.1 (2.5)*	*−0.1 (0.4)*	*−1.51 [−2.73; −0.28]; 0.016*
FOCUS	*387[c]*	*14.3 (5.4)[c]*	*−4.1 (0.3)[c]*	*195*	*14.2 (5.9)*	*−1.0 (0.5)*	*−3.1 [−4.26; −1.94]; < 0.001[c]*
Total							*ND*
Indirect comparison using common comparators:							
Atogepant vs. erenumab or fremanezumab							ND[d]
Sensitivity analysis							
Atogepant vs. placebo							
ELEVATE/ADVANCE, total							*−1.98 [−3.01; −0.95]; < 0.001[e]*
Erenumab vs. placebo							
LIBERTY	*86*	*9.1 (2.3)*	*−1.6 (0.5)*	*104*	*9.1 (2.5)*	*−0.1 (0.4)*	*−1.51 [−2.73; −0.28]; 0.016*
Indirect comparison using common comparators:							
Atogepant vs. erenumab							*–[f]*

Table 13: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Outcome category	Atogepant or erenumab or fremanezumab			Placebo			Group difference
Outcome Comparison Study	N[a]	Values at baseline mean (SD)	Change in Month 3 or Week 12 mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change in Month 3 or Week 12 mean (SE)[b]	MD [95% CI]; p-value[b]
General impact of headache (HIT-6[g]) (Week 12)							
Atogepant vs. placebo							
ELEVATE	ND[h]	64.6 (4.3)	−10.8 (0.8)	ND[h]	64.8 (4.1)	−4.8 (0.8)	−5.99 [−8.02; −3.96]; < 0.001
ADVANCE	ND[h]	63.1 (4.8)	−9.1 (1.3)	ND[h]	64.6 (3.9)	−3.3 (1.6)	−5.83 [−10.01; −1.64]; 0.007
PROGRESS	ND[h]	64.5 (4.7)	−7.8 (1.0)	ND[h]	66.3 (3.5)	−4.1 (1.1)	−3.67 [−6.50; −0.83]; 0.012
Total							−5.29 [−6.82; −3.75]; < 0.001[e]
Erenumab or fremanezumab vs. placebo							
LIBERTY	86	62.5 (3.9)	−6.1 (0.7)	104	62.2 (5.2)	−2.5 (0.5)	−3.60 [−5.30; −1.90]; < 0.001
FOCUS	388	64.2 (4.4)	−6.05 (0.5)[c]	195	64.0 (5.2)	−2.3 (0.7)	−3.37 [−4.45; −2.30]; < 0.001
Total							−3.44 [−4.34; −2.53]; < 0.001[e]
Indirect comparison using common comparators[i]:							
Atogepant vs. erenumab or fremanezumab							−1.85 [−3.64; −0.07]; 0.042 SMD[j, k]: −0.17 [−0.33; −0.01]
Sensitivity analysis							
Atogepant vs. placebo							
ELEVATE/ADVANCE, total							*−5.96 [−7.79; −4.13]; < 0.001[e]*
Erenumab vs. placebo							
LIBERTY	*86*	*62.5 (3.9)*	*−6.1 (0.7)*	*104*	*62.2 (5.2)*	*−2.5 (0.5)*	*−3.60 [−5.30; −1.90]; < 0.001*
Indirect comparison using common comparators[i]:							
Atogepant vs. erenumab							*−2.36 [−4.85; 0.14]; 0.064*

Table 13: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Outcome category	Atogepant or erenumab or fremanezumab			Placebo			Group difference
Outcome Comparison Study	N[a]	Values at baseline mean (SD)	Change in Month 3 or Week 12 mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change in Month 3 or Week 12 mean (SE)[b]	MD [95% CI]; p-value[b]
Health status (EQ-5D VAS[l]) (Week 12)							
Atogepant vs. placebo							
ELEVATE	ND[m]	77.1 (12.9)	7.0 (1.4)	ND[m]	75.9 (14.0)	5.0 (1.4)	1.97 [−1.80; 5.74]; 0.304
ADVANCE	ND[m]	79.0 (16.2)	3.2 (2.5)	ND[m]	83.8 (15.5)	3.31 (3.0)	−0.10 [−7.89; 7.70]; 0.980
PROGRESS	ND[m]	59.8 (23.0)	7.6 (3.2)	ND[m]	62.1 (15.9)	5.1 (3.6)	2.58 [−6.55; 11.71]; 0.575
Total							1.70 [−1.48; 4.88]; 0.295[e]
Erenumab or fremanezumab vs. placebo							
LIBERTY	86	79.7 (16.8)	2.1 (2.1)	104	77.5 (19.9)	0.8 (1.8)	1.35 [−4.18; 6.88]; 0.630
FOCUS	388	69.6 (21.2)	5.45 (1.3)[n, c]	195	70.1 (20.1)	1.2 (1.8)[n]	4.22 [1.28; 7.17]; 0.005[n]
Total							3.59 [0.99; 6.19]; 0.007[e]
Indirect comparison using common comparators[i]:							
Atogepant vs. erenumab or fremanezumab							−1.89 [−5.99; 2.22]; 0.368
Sensitivity analysis							
Atogepant vs. placebo							
ELEVATE/ADVANCE, total							*1.58 [−1.82; 4.97]; 0.362[e]*
Erenumab vs. placebo							
LIBERTY	*86*	*79.7 (16.8)*	*2.1 (2.1)*	*104*	*77.5 (19.9)*	*0.8 (1.8)*	*1.35 [−4.18; 6.88]; 0.630*
Indirect comparison using common comparators[i]:							
Atogepant vs. erenumab							*0.23 [−6.26; 6.72]; 0.945*

Table 13: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Outcome category	Atogepant or erenumab or fremanezumab			Placebo			Group difference
Outcome Comparison Study	N[a]	Values at baseline mean (SD)	Change in Month 3 or Week 12 mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change in Month 3 or Week 12 mean (SE)[b]	MD [95% CI]; p-value[b]
Health-related quality of life							
MSQ[l] (Week 12)							
Role function–Restrictive							
Atogepant vs. placebo							
ELEVATE	ND[h]	41.5 (16.5)	32.3 (1.9)	ND[h]	42.8 (15.7)	15.0 (2.0)	17.27 [12.09; 22.45]; < 0.001
ADVANCE	ND[h]	50.4 (16.4)	31.1 (4.1)	ND[h]	43.2 (16.6)	15.2 (5.0)	15.89 [3.04; 28.74]; 0.016
PROGRESS	ND[h]	42.2 (18.5)	22.9 (2.9)	ND[h]	35.6 (18.5)	14.3 (3.2)	8.59 [0.37; 16.81]; 0.041
Total							14.92 [10.77; 19.06]; < 0.001[e]
Erenumab or fremanezumab vs. placebo							
LIBERTY	–	–	–	–	–	–	–
FOCUS	388	47.6 (17.4)	17.7 (1.4)[c]	195	47.6 (19.0)	8.7 (1.9)	9.06 [5.77; 12.35]; < 0.001
Total							–
Indirect comparison using common comparators[i]:							
Atogepant vs. erenumab or fremanezumab							5.86 [0.56; 11.15]; 0.030 SMD[j, k]: 0.18 [0.02; 0.35]

Table 13: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Outcome category	Atogepant or erenumab or fremanezumab			Placebo			Group difference
Outcome Comparison Study	N[a]	Values at baseline mean (SD)	Change in Month 3 or Week 12 mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change in Month 3 or Week 12 mean (SE)[b]	MD [95% CI]; p-value[b]
MSQ[l] (Week 12)							
Role function–Preventive							
Atogepant vs. placebo							
ELEVATE	ND[h]	53.6 (21.9)	28.3 (1.8)	ND[h]	56.0 (21.1)	14.6 (1.9)	13.72 [8.83; 18.62]; < 0.001
ADVANCE	ND[h]	67.6 (17.4)	23.0 (3.5)	ND[h]	60.3 (23.9)	15.5 (4.2)	7.44 [−3.55; 18.43]; 0.182
PROGRESS	ND[h]	56.0 (22.9)	21.9 (2.7)	ND[h]	53.6 (24.4)	12.1 (3.1)	9.79 [1.94; 17.64]; 0.015
Total							11.97 [8.09; 15.86]; < 0.001[e]
Erenumab or fremanezumab vs. placebo							
LIBERTY	–	–	–	–	–	–	–
FOCUS	388	63.2 (20.4)	13.8 (1.3)[c]	195	64.2 (21.0)	8.0 (1.7)	5.81 [2.82; 8.80]; < 0.001
Total							–
Indirect comparison using common comparators[i]:							
Atogepant vs. erenumab or fremanezumab							6.16 [1.26; 11.07]; 0.014 SMD[j, k]: 0.21 [0.04; 0.38]

Table 13: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Outcome category	Atogepant or erenumab or fremanezumab			Placebo			Group difference
Outcome Comparison Study	N[a]	Values at baseline mean (SD)	Change in Month 3 or Week 12 mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change in Month 3 or Week 12 mean (SE)[b]	MD [95% CI]; p-value[b]
MSQ[l] (Week 12)							
Emotional Function							
Atogepant vs. placebo							
ELEVATE	ND[h]	57.1 (26.5)	25.4 (2.0)	ND[h]	58.1 (24.7)	13.1 (2.0)	12.35 [7.04; 17.66]; < 0.001
ADVANCE	ND[h]	54.8 (27.0)	29.7 (4.6)	ND[h]	57.1 (20.8)	15.8 (5.6)	13.88 [−0.59; 28.35]; 0.060
PROGRESS	ND[h]	50.3 (27.3)	22.9 (2.9)	ND[h]	48.2 (27.9)	13.6 (3.3)	9.28 [0.92; 17.65]; 0.030
Total							11.68 [7.40; 15.96]; < 0.001[e]
Erenumab or fremanezumab vs. placebo							
LIBERTY	–	–	–	–	–	–	–
FOCUS	388	60.6 (23.9)	15.2 (1.5)[c]	195	60.6 (25.3)	6.1 (2.1)	9.14 [5.52; 12.77]; < 0.001
Total							–
Indirect comparison using common comparators[i]:							
Atogepant vs. erenumab or fremanezumab							2.54 [−3.07; 8.15]; 0.375

a. Number of patients taken into account in the effect estimation; baseline values (and values in Month 3/Week 12) may be based on different patient numbers.
b. Unless stated otherwise, mean and SE (per treatment group) as well as MD, CI and p-value (group comparison): MMRM
- ELEVATE: adjusted for baseline value, number of failed previous prophylactic treatment classes (2/> 2) and number of migraine days (4 to < 8/≥ 8) (not applicable, for the symptom outcome: migraine days/month)
- ADVANCE: adjusted for baseline value
- PROGRESS: adjusted for baseline value, region and medication overuse
- LIBERTY: adjusted for baseline value and disease severity (4 to 7 migraine days/month/8 to 14 migraine days/month)
- FOCUS: adjustment is assumed for baseline value, sex, geographical region, treatment failure, migraine type, and years since migraines started

c. Institute's calculation.
d. The company did not present any analyses for the PROGRESS study and therefore also for the indirect comparison across all 5 studies (see Section I 4.2.1 for an explanation).
e. Meta-analysis, fixed-effect model (method with inverse variance).

Table 13: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison: atogepant vs. erenumab or fremanezumab (multipage table)

Outcome category	Atogepant or erenumab or fremanezumab			Placebo			Group difference
Outcome Comparison Study	N[a]	Values at baseline mean (SD)	Change in Month 3 or Week 12 mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change in Month 3 or Week 12 mean (SE)[b]	MD [95% CI]; p-value[b]

f. Requirement for the certainty of results to perform an adjusted indirect comparison is not met (see Table 11 and Section I 4.2.2).
g. Lower values indicate minor overall impact of headache (scale range: 36 to 78); in the direct comparison, a negative group difference corresponds to an advantage for atogepant, erenumab or fremanezumab. In the indirect comparison, a negative effect corresponds to an advantage for atogepant.
h. It is unclear how many patients were actually included in the analysis; it is assumed that those patients were included for whom the baseline value and at least one post-baseline value were available. Minimum number of patients included in the analysis because values at baseline and at Week 12 were available for them (atogepant vs. placebo): 116 vs. 123 in ELEVATE, 23 vs. 16 in ADVANCE, 60 vs. 47 in PROGRESS.
i: Indirect comparison according to Bucher [6].
j. The company determined the SMD based on the MD, including CI, resulting from the indirect comparison. It remains unclear whether the SMD was determined using only the number of patients whose recordings were also used to determine the MD.
The company's approach has no consequences, as the method used by the company to conduct the indirect comparison is anyway not appropriate in the given situation (see Section I 4.1.4).
k. 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.
l. Higher values indicate better health status (scale range: 0 to 100) or better health-related quality of life (scale range: Role function–Restrictive 7 to 42, Role function–Preventive 4 to 24, Emotional Function 3 to 18); in a direct comparison, a positive group difference corresponds to an advantage for atogepant or erenumab or fremanezumab. In the indirect comparison, a positive effect corresponds to an advantage for atogepant.
m. It is unclear how many patients were actually included in the analysis; it is assumed that those patients were included for whom the baseline value and at least one post-baseline value were available. Minimum number of patients included in the analysis because values at baseline and at Week 12 were available for them (atogepant vs. placebo): 69 vs. 73 in ELEVATE, 23 vs. 16 in ADVANCE, 27 vs. 21 in PROGRESS (see Section I 4.2.2 for details).
n. Mean and SE (per treatment group) as well as mean, CI and p-value (group comparison): ANCOVA; adjustment for baseline value, sex, geographical region, treatment failure, migraine type, and years since migraines started is assumed.

ANCOVA: analysis of covariance; CI: confidence interval; HIT-6: 6-Item Headache Impact Test; mITT: modified intent to treat; MMRM: mixed-effects model with repeated measures; MSQ: Migraine-Specific Quality of Life; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; VAS: visual analogue scale

As described in Section I 4.1.4, a method that takes random effects into account would have been adequate for conducting an indirect comparison in the given data situation. This is due to the fact that the 3 studies ELEVATE, ADVANCE and PROGRESS on the intervention side showed differences with regard to the underlying disease characteristic migraine type

(episodic or chronic migraine) and other associated disease features. In its indirect comparison, the company chose a fixed-effect model for the meta-analytical summary of the 3 studies on the atogepant side. However, since analyses presented by the company for the indirect comparison did not show a statistically significant and relevant effect for any of the outcomes even when using such a model (to determine relevance via the SMD, the associated confidence interval must be completely outside the irrelevance range [–0.2; 0.2]), the company's approach in the given data situation was of no consequence for the conclusion of the benefit assessment. The company presented an analysis of the indirect comparison, taking into account all studies on the intervention side, exclusively for the outcomes of general impact of headache (recorded using the HIT-6), health status (EQ-5D VAS), health-related quality of life (recorded using the MSQ) and discontinuation due to AEs. It could be deduced from the results for these outcomes that even when conducting an indirect comparison with a method that took random effects into account, no statistically significant and relevant effect could be expected.

Even in the sensitivity analyses shown in Table 12 and Table 13, which only included studies in patients with episodic migraine, the indirect comparison did not show a statistically significant and relevant effect for any of the outcomes.

Overall, there is no hint of an added benefit of atogepant versus the ACT for any of the outcomes in patients who have at least 4 migraine days per month and who are not candidates for conventional migraine prophylaxis; an added benefit is therefore not proven.

I 4.2.4 Subgroups and other effect modifiers

No subgroup analyses for the indirect comparison were available for this benefit assessment of atogepant. Thus, no conclusions regarding potential effect modifications could be drawn for the comparison of atogepant with erenumab or fremanezumab.

I 4.3 Probability and extent of added benefit

In summary, there is no hint of an added benefit of atogepant versus the ACT for patients who have at least 4 migraine days per month and who are not candidates for conventional migraine prophylaxis. An added benefit of atogepant in comparison with the ACT is therefore not proven for research question 2.

This assessment deviates from that of the company, which derived a hint of a non-quantifiable added benefit of atogepant versus the ACT for this patient group. This is due to the fact that although the company presented SMDs, it did not use them for the outcomes showing statistically significant differences between the treatment groups, for the assessment of whether these differences were relevant.

I 5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of atogepant in comparison with the ACT is summarized in Table 14.

Table 14: Atogepant – probability and extent of the added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults who have at least 4 migraine days per month and who are candidates for conventional migraine prophylaxis	Metoprolol or propranolol or flunarizine (if treatment with beta-receptor blockers is contraindicated or has not been sufficiently effective) or amitriptyline or clostridium botulinum toxin type A (only for chronic migraine[b]) or erenumab	Added benefit not proven
2	Adults who have at least 4 migraine days per month and who do not respond to any of the following drug treatments/drug classes, for whom they are unsuitable, or who do not tolerate them[c]: metoprolol, propranolol, flunarizine, 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 according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**.
b. Even in cases of chronic migraine, clostridium botulinum toxin type A is not a usual treatment option for all patients in research question 1.
c. In research question 2, treatment with biologics may be considered as part of a clinical study if patients have not responded to or have not tolerated at least 2 drug therapies (drug classes from research question 1). In cases where the drugs from research question 1 are not suitable for patients, this must be documented and justified.

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.

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

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