IQWiG Reports – Commission No. A19-28

Galcanezumab (migraine) –

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

Extract

[1] Translation of Sections 2.1 to 2.7 of the dossier assessment *Galcanezumab (Migräne) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 June 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Galcanezumab (migraine) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
29 March 2019

Internal Commission No.:
A19-28

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

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

Medical and scientific advice:

- Thomas Henze, practice for neurology Dr. Blersch, Regensburg, Germany

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.

IQWiG employees involved in the dossier assessment:

- Lisa Junge
- Katharina Biester
- Judith Gibbert
- Charlotte Guddat
- Michaela Florina Kerekes
- Stefan Kobza
- Cornelia Rüdig
- Dorothea Sow

Keywords: galcanezumab, migraine disorders, benefit assessment, NCT02614183, NCT02614196, NCT02614261

Table of contents

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CI	confidence interval
EF	Emotional Function
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICHD-3	International Classification of Headache Disorders, 3rd edition
IPD	individual patient data
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
MMRM	mixed-effects model repeated measures
MSQ	Migraine-Specific Quality of Life Questionnaire
PGI-I	Patient Global Impression of Improvement
PGI-S	Patient Global Impression of Severity
RCT	randomized controlled trial
RFR	Role Function-Restrictive
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug galcanezumab. 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 29 March 2019.

Research question

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

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

Table 2: Research questions of the benefit assessment of galcanezumab

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

a: Presentation of the respective ACT specified by the G-BA.
b: All 4 drug classes specified as ACTs for research question 1 (beta-blockers, flunarizine, topiramate or amitriptyline) must have been considered before the patients fall under research question 2.
c: According to Appendix VI to Section K of the Pharmaceutical Directive: if treatment with all other drugs approved for this indication has been unsuccessful or is contraindicated.
d: In compliance with the approval only for chronic migraine.
e: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

Research questions 1, 2 and 3 of the present benefit assessment concur with the company's research questions A, B and C. For easier presentation and better readability, the present benefit assessment uses the following terms for the research questions in the running text:

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

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

Results

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

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

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

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

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

The studies EVOLVE-1, EVOLVE-2 and REGAIN were included for the assessment of the added benefit of galcanezumab in adult patients for whom BSC is the only treatment option. The studies EVOLVE-1 and EVOLVE-2 enrolled adults with episodic migraine, and the REGAIN study enrolled adults with chronic migraine.

Study design

Studies EVOLVE-1 and EVOLVE-2 (episodic migraine)

The studies EVOLVE-1 and EVOLVE-2 were randomized, double-blind approval studies on the comparison of galcanezumab + BSC with placebo + BSC for 6 months in adult patients with at least 12 months of documented migraine. Adults with and without prior treatment with migraine prevention drugs were enrolled. Patients with failure to respond to ≥ 3 adequately

dosed treatments from different drug classes were excluded from study participation. In addition, the patients had to have a history of both 4 to 14 migraine days/month on average and ≥ 2 migraine attacks/month on average within the past 3 months.

A total of 862 patients in the EVOLVE-1 study and of 922 patients in the EVOLVE-2 study were randomly allocated in a 1:1:2 ratio to treatment with galcanezumab 120 mg, galcanezumab 240 mg[3] or placebo. Of the patients who had received at least 1 dose of the study medication, 213 (EVOLVE-1) and 231 (EVOLVE-2) were allocated to the relevant galcanezumab arms (120 mg); 433 (EVOLVE-1) and 461 patients (EVOLVE-2) were allocated to the placebo arms. Only a subpopulation was relevant for both studies (see below).

In the relevant study arm, galcanezumab, in accordance with the Summary of Product Characteristics (SPC), was administered subcutaneously. Patients were allowed to use additional medications for the acute treatment of migraine attacks.

Primary outcome of the study was the change in the number of migraine days/month from the baseline phase, averaged over the 6-month double-blind treatment phase. Key secondary outcomes were further outcomes on morbidity, health-related quality of life and adverse event (AE) outcomes.

Study REGAIN (chronic migraine)

The REGAIN study was a randomized, double-blind approval study on the comparison of galcanezumab + BSC with placebo + BSC for 3 months in adult patients with chronic migraine according to the International Classification of Headache Disorders, 3rd edition (ICHD-3). For study inclusion, the patients additionally had to have ≥ 1 headache-free calendar day/month within the past 3 months and in the baseline phase. Patients who had been on a stable dose of either topiramate or propranolol for ≥ 2 months prior to the baseline phase were allowed to continue to take that preventive medication alongside the study medication. Patients with medication overuse headache in the baseline phase were also enrolled.

A total of 1117 patients were randomly allocated in a ratio of 1:1:2 to treatment with galcanezumab 120 mg (N = 279), galcanezumab 240 mg[3] (N = 279) or placebo (N = 559). Only a subpopulation was relevant also for the REGAIN study (see below).

In the relevant study arm, galcanezumab, in accordance with the SPC, was administered subcutaneously. Patients were allowed to use additional medications for the acute treatment of migraine attacks.

[3] A dosage of 240 mg every 4 weeks is not approved in Germany and is therefore not considered further in the present benefit assessment.

Primary outcome of the study was the change in the number of migraine days/month from the baseline phase, averaged over the 3-month double-blind treatment phase. Key secondary outcomes were further outcomes on morbidity, health-related quality of life and AE outcomes.

Implementation of the appropriate comparator therapy BSC

BSC treatment in the therapeutic indication of migraine includes both drug and non-drug interventions.

The studies EVOLVE-1, EVOLVE-2 and REGAIN allowed the use of acute medications (particularly analgesics and antiemetics) for the treatment of migraine attacks during treatment with the study medication. The patients could choose from a list of different analgesics (drugs and drug classes) for the acute treatment of migraine headache. However, this list does not include all treatment options approved or recommended in Germany. In addition, not all drug options for the treatment of migraine were available to the patients. Acupuncture, chiropractic, physiotherapy and transcutaneous electrical nerve stimulation in the head and neck region were not allowed.

Despite the limitations described with regard to the permitted concomitant treatments in the included studies EVOLVE-1, EVOLVE-2 and REGAIN, treatment in the placebo arms of the studies was regarded as an approximation to the ACT BSC, since the patients had basically different drug and non-drug treatment options available to them to ensure the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

Subpopulation relevant for the benefit assessment

The company presented analyses on subpopulations of the 3 studies for research question 3 of the benefit assessment. These subpopulations included patients who, in accordance with the patient groups defined by the G-BA, had been pretreated with at least 2 of the following therapies (drug classes): propranolol/metoprolol, flunarizine, topiramate or amitriptyline. For the benefit assessment, the subpopulations presented by the company were used for answering research question 3. However, since patients with failure to respond to ≥ 3 adequately dosed treatments from different drug classes were excluded from participation in all 3 studies, it cannot be ruled out that for some of the patients, in principle, another one of the above-mentioned approved therapies and not only BSC could have been an option. The relevant subpopulations of the studies EVOLVE-1, EVOLVE-2 and REGAIN were regarded as an approximation to the patient population of research question 3. The relevant subpopulations of the studies for the present benefit assessment comprised 17 patients for the EVOLVE-1 study, 55 patients for the EVOLVE-2 study, and 146 patients for the REGAIN study. The results of the studies EVOLVE-1 and EVOLVE-2 were summarized in a meta-analysis on the basis of individual patient data (IPD) (hereinafter referred to as “EVOLVE-1/-2”).

Quantitative interpretation of the results of the studies on episodic migraine and chronic migraine

The therapeutic indication of galcanezumab comprises adults with at least 4 migraine days/month. Hence, the therapeutic indication includes both patients with episodic migraine and patients with chronic migraine. Since there is no indication that the effects of treatment differ between patients with episodic and those with chronic migraine, the present benefit assessment summarizes the results of EVOLVE-1/-2 and the results of the REGAIN study despite different double-blind treatment durations in a meta-analysis, unless otherwise indicated.

Unless stated otherwise, hereinafter, the designation "meta-analysis" refers to the meta-analytical summary of the results of EVOLVE-1/-2 and the REGAIN study.

Risk of bias

The risk of bias across outcomes for the results of the studies EVOLVE-1, EVOLVE-2 and REGAIN was rated as low in each case.

The risk of bias of the results for the outcome "all-cause mortality" as well as for the harm outcomes "serious AEs (SAEs)" and "discontinuation due to AEs" from the studies EVOLVE-1, EVOLVE-2 and REGAIN was rated as low in each case.

The risk of bias of the individual study results was rated as high for each of the following outcomes: symptoms (migraine days/month), disease severity (Patient Global Impression of Severity [PGI-S], health status – change of migraine status under treatment (Patient Global Impression of Improvement [PGI-I]), and health-related quality of life (Migraine-Specific Quality of Life Questionnaire [MSQ]). The high risk of bias for the outcome "symptoms" (migraine days/month) resulted from the fact that the type of analysis used by the company deviated from the prespecified analysis without justification, and, for the results of the studies EVOLVE-1 and EVOLVE-2 additionally from the large number of missing values imputed using last observation carried forward (LOCF). However, due to the size of the observed effects, the certainty of results in this outcome was not downgraded despite the high risk of bias. The high risk of bias of the results of the individual studies for the outcomes "disease severity" (PGI-S), "health status – change of migraine status under treatment" (PGI-I) and "health-related quality of life" (MSQ) resulted from the large proportion of missing values.

Overall assessment of the certainty of conclusions

There were different uncertainties in the studies EVOLVE-1, EVOLVE-2 and REGAIN regarding the implementation of the ACT and the patients' pretreatment. As a result of these uncertainties, at most indications, e.g. of an added benefit, can be derived also in the meta-analytical summary of the results of EVOLVE-1/-2 and the REGAIN study. The outcome-specific assessment can deviate from this.

Mortality

All-cause mortality

No deaths occurred in the studies EVOLVE-1, EVOLVE-2 and REGAIN. There was no hint of an added benefit of galcanezumab + BSC in comparison with BSC; an added benefit is therefore not proven.

Morbidity

Symptoms (migraine days/month)

For the outcome "symptoms" (migraine days/month), responder analyses were used for a reduction of migraine days by ≥ 50% from the baseline phase, averaged over the treatment period. The meta-analysis showed a statistically significant difference in favour of galcanezumab + BSC. This advantage was also shown in the operationalization of migraine hours/month (change from the baseline phase, averaged over the treatment period) presented as additional information. This resulted in an indication of an added benefit of galcanezumab + BSC in comparison with BSC for the outcome "symptoms" (migraine days/month).

Disease severity (PGI-S)

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "disease severity" (PGI-S). As a result, there was no hint of an added benefit of galcanezumab + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

Health status – change of migraine status under treatment (PGI-I)

The meta-analysis showed a statistically significant difference in favour of galcanezumab + BSC for the outcome "health status – change of migraine status under treatment" (PGI-I). The standardized mean difference (SMD) in the form of Hedges' g was considered to check the relevance of the result. The 95% confidence interval (CI) was completely below the irrelevance threshold of –0.2. This was interpreted to be a relevant effect. There was an indication of an added benefit of galcanezumab + BSC in comparison with BSC.

Health-related quality of life

MSQ

The meta-analysis showed a statistically significant difference in favour of galcanezumab + BSC for each of the MSQ domains Role Function-Restrictive (RFR), Role Function-Preventive (RP) and Emotional Function (EF). The SMD in the form of Hedges' g was considered to check the relevance of the result. In each case, the 95% CI of the SMD for the 3 domains was not completely outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effects are relevant in each case. There was no hint of an added benefit of galcanezumab + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

Side effects

Serious adverse events and discontinuation due to adverse events

No SAEs occurred in the EVOLVE-1 study. There was 1 patients with event in the placebo arm of the EVOLVE-2 study and 1 patient with event in the galcanezumab arm of the REGAIN study.

There were no discontinuations due to AEs in the studies EVOLVE-1 and EVOLVE-2. There was 1 patient with event in the placebo arm of the REGAIN study.

A meta-analytical summary of the results of EVOLVE-1/-2 and the REGAIN study was not performed for these outcomes due to the absence or the only very low number of events that occurred.

There was no hint of greater or lesser harm of galcanezumab + BSC in comparison with BSC for any of these outcomes. Greater or lesser harm is therefore not proven for these outcomes.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[4]

Based on the results presented, probability and extent of the added benefit of the drug galcanezumab in comparison with the ACT are assessed as follows:

Research questions 1 and 2

No data were available for the assessment of the added benefit for research question 1 (adult patients for whom treatment with metoprolol or propranolol or flunarizine or topiramate or amitriptyline is an option) and for research question 2 (adult patients for whom treatment with valproic acid or clostridium botulinum toxin type A is an option). An added benefit of galcanezumab versus the ACT is therefore not proven for these patients.

Research question 3

In the overall assessment based on the studies EVOLVE-1, EVOLVE-2 and REGAIN, there are only positive effects for adult patients who have at least 4 migraine days/month and for whom BSC is the only treatment option. These were shown both for adults with episodic migraine (4 to 14 migraine days/month) and for adults with chronic migraine, each in the outcome category of morbidity.

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

In summary, there is an indication of major added benefit of galcanezumab versus BSC for adult patients who have at least 4 migraine days/month and for whom BSC is the only treatment option.

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

Table 3: Galcanezumab – probability and extent of added benefit

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

a: Presentation of the respective ACT specified by the G-BA.
b: All 4 drug classes specified as ACTs for research question 1 (beta-blockers, flunarizine, topiramate or amitriptyline) must have been considered before the patients fall under research question 2.
c: According to Appendix VI to Section K of the Pharmaceutical Directive: if treatment with all other drugs approved for this indication has been unsuccessful or is contraindicated.
d: In compliance with the approval only for chronic migraine.
e: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
f: Both for adults with episodic migraine and for adults with chronic migraine.
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

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

2.2 Research question

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

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

Table 4: Research questions of the benefit assessment of galcanezumab

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

a: Presentation of the respective ACT specified by the G-BA.
b: All 4 drug classes specified as ACTs for research question 1 (beta-blockers, flunarizine, topiramate or amitriptyline) must have been considered before the patients fall under research question 2.
c: According to Appendix VI to Section K of the Pharmaceutical Directive: if treatment with all other drugs approved for this indication has been unsuccessful or is contraindicated.
d: In compliance with the approval only for chronic migraine.
e: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

Research questions 1, 2 and 3 of the present benefit assessment concur with the company's research questions A, B and C. For easier presentation and better readability, the present benefit assessment uses the following terms for the research questions in the running text:

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

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

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum

treatment duration of 3 months were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on galcanezumab (status: 4 February 2019)
- bibliographical literature search on galcanezumab (last search on 12 February 2019)
- search in trial registries for studies on galcanezumab (last search on 4 February 2019)

To check the completeness of the study pool:

- search in trial registries for studies on galcanezumab (last search on 8 April 2019)

The check identified no additional relevant study.

2.3.1 Studies included

The studies listed in the following Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: galcanezumab vs. ACT

Research question	Study	Study category		
		Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
1	No data presented			
2	No data presented			
3	CGAG (EVOLVE-1[b])	Yes	Yes	No
	CGAH (EVOLVE-2[b])	Yes	Yes	No
	CGAI (REGAIN[b])	Yes	Yes	No

a: Study sponsored by the company.
b: In the following tables, the study is referred to with this abbreviated form.
ACT: appropriate comparator therapy; RCT: randomized controlled trial; vs.: versus

For research questions 1 and 2, no directly comparative data were available for the benefit assessment of galcanezumab in comparison with the ACT. The assessment of the data situation concurs with that of the company. The company did not perform any indirect comparisons.

For research question 3, the studies EVOLVE-1, EVOLVE-2 and REGAIN were used for the benefit assessment of galcanezumab in comparison with the ACT BSC. This concurs with the company's approach. In each case, treatment with galcanezumab + BSC was compared with placebo + BSC. The studies EVOLVE-1 and EVOLVE-2 enrolled adults with episodic migraine, and the REGAIN study enrolled adults with chronic migraine. All 3 studies are suitable to derive, in each case based on a subpopulation, conclusions on the added benefit of galcanezumab for adult patients for whom BSC is the only treatment option (see Section 2.6.1).

Section 2.6.4 contains a reference list for the studies included for research question 3.

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

2.4.1 Results on added benefit (research question 1)

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

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

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

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

2.4.3 List of included studies (research question 1)

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

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

2.5.1 Results on added benefit (research question 2)

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

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

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

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

2.5.3 List of included studies (research question 2)

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

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

For research question 3, the studies EVOLVE-1, EVOLVE-2 and REGAIN were included in the benefit assessment.

2.6.1 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, direct comparison: galcanezumab + BSC vs. placebo + BSC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
EVOLVE-1	RCT, double-blind, parallel	Adults (18–65 years) with episodic migraine (4–14 migraine days/months) and ≥ 2 migraine attacks/month on average within the past 3 months	Galcanezumab 120 mg + BSC (N^b = 213) galcanezumab 240 mg + BSC[c] (N^b = 212) placebo + BSC (N^b = 433) Relevant subpopulation thereof[d]: galcanezumab 120 mg + BSC (n = 7) placebo + BSC (n = 10)	Screening: 3–45 days Baseline phase[e]: 30–40 days Treatment: 6 months Observation: 4 months[f]	90 centres in Canada, Puerto Rico and USA 1/2016–3/2017	Primary: change in monthly migraine days from the baseline phase, averaged over months 1 to 6 Secondary: morbidity, health-related quality of life, AEs
EVOLVE-2	RCT, double-blind, parallel	Adults (18–65 years) with episodic migraine (4–14 migraine days/months) and ≥ 2 migraine attacks/month on average within the past 3 months	Galcanezumab 120 mg + BSC (N^b = 231) galcanezumab 240 mg + BSC[c] (N^b = 223) placebo + BSC (N^b = 461) Relevant subpopulation thereof[d]: galcanezumab 120 mg + BSC (n = 27) placebo + BSC (n = 28)	Screening: 3–45 days Baseline phase[e]: 30–40 days Treatment: 6 months Observation: 4 months[f]	109 centres in Argentina, Czech Republic, Germany, Great Britain, Israel, Korea, Mexico, Netherlands, Spain, Taiwan, USA 1/2016–3/2017	Primary: change in monthly migraine days from the baseline phase, averaged over months 1 to 6 Secondary: morbidity, health-related quality of life, AEs

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison: galcanezumab + BSC vs. placebo + BSC (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
REGAIN	RCT, double-blind, parallel	Adults (18–65 years) with chronic migraine (≥ 15 headache days/month, of which ≥ 8 migraine days/month for ≥ 3 months)	Galcanezumab 120 mg + BSC (N[b] = 278) galcanezumab 240 mg + BSC[c] (N[b] = 277) placebo + BSC (N[b] = 558) Relevant subpopulation thereof[d]: galcanezumab 120 mg + BSC (n = 36) placebo + BSC (n = 110)	Screening: 3–45 days Baseline phase[g]: 30–40 days Treatment: 3 months[h] Observation: 4 months	116 centres in Argentina, Canada, Czech Republic, Germany, Great Britain, Israel, Italy, Mexico, Netherlands, Spain, Taiwan, USA 1/2016–3/2017	Primary: change in monthly migraine days from the baseline phase, averaged over months 1 to 3 Secondary: morbidity, health-related quality of life, AEs

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b: Number of randomized patients who received at least 1 dose of the study medication. A total of 862 patients in the EVOLVE-1 study, of 922 patients in the EVOLVE-2 study, and of 1117 patients in the REGAIN study were randomly allocated to the treatment arms.
c: The arm is not relevant for the assessment and is no longer presented in the following tables.
d: Patients who have not responded to ≥ 2 migraine prevention drugs (drug classes) (metoprolol/propranolol, flunarizine, topiramate, amitriptyline). Patients without response to ≥ 3 classes of migraine prevention drugs with high evidence level (A or B) according to the American Academy of Neurology's Evidence-based guidelines [3] and to clostridium botulinum toxin type A or B were excluded from study participation.
e: Within the baseline phase, the inclusion criterion of migraine frequency (4–14 migraine days and ≥ 2 migraine attacks) and the compliance in completing the electronic migraine diary (≥ 80%) were checked.
f: 1 month after the end of the double-blind treatment phase, patients with deterioration of symptoms could initiate a new migraine prevention drug at the investigator's discretion.
g: Within the baseline phase, the inclusion criterion of migraine frequency (≥ 15 migraine days/month, of which ≥ 8 migraine days/month and at least 1 headache-free day) and the compliance in completing the electronic migraine diary (≥ 80%) were checked.
h: Following the double-blind treatment phase, the patients could receive further optional galcanezumab treatment of 9 months in an open-label extension phase.
AE: adverse event; BSC: best supportive care; ICHD: International Classification of Headache Disorders; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: galcanezumab + BSC vs. placebo + BSC

Study	Intervention	Comparison
EVOLVE-1	Galcanezumab: initial dose of 2x 120 mg (total dose of 240 mg), SC then 120 mg 1x/month, SC + placebo 1x/month, SC	Placebo 1x/month, SC (2 injections)
	Permitted concomitant treatment ▪ acute medication for the treatment of migraine (paracetamol, NSAIDs, triptans, ergotamine and derivatives, isometheptene, fixed combinations of dichloralphenazone and paracetamol, further combinations of the mentioned drugs) ▪ antiemetics ▪ opiates or barbiturate-containing analgesics ≤ 3x/month ▪ one single steroid injection during the study for emergency treatment **Non-permitted concomitant treatment** ▪ oral corticosteroids ▪ anticonvulsants/antiepileptics ▪ antipsychotics ▪ beta-blockers[a] ▪ botulinum toxin in the head and neck region ▪ cannabis/cannabinoids ▪ non-drug interventions: ▫ acupuncture ▫ chiropractic, physiotherapy, TENS or other electrical procedures on the head and neck ▪ herbs with anti-inflammatory or sympathomimetic effect ▪ flunarizine ▪ triptans for the treatment of menstrual migraine: frovatriptan, naratriptan, zolmitriptan ▪ antidepressants (TCAs, MAO inhibitors, $5HT_{2a/2c}$ antagonists, venlafaxine)	
	Permitted pretreatment ▪ failed migraine prevention with < 3 drug classes with evidence level A or B of Table 1 of the American Academy of Neurology's Evidence-based guidelines[b] and clostridium botulinum toxin type A or B[c] **Non-permitted pretreatment** ▪ CGRP antibodies ▪ therapeutic antibodies (e.g. adalimumab, infliximab, trastuzumab, bevacizumab) within 12 months before the start and during the baseline phase as well as during the study ▪ migraine prevention drugs within 1 months before the start and during the baseline phase; treatment with botulinum toxin A and B in the head and neck region within 4 months before the start and during the baseline phase as well as during the study ▪ opiates or barbiturate-containing analgesics > 2x/month[d] in more than 2 of the last 6 months before the start of the baseline phase (exception: opiate for emergency use)	
EVOLVE-2	See information on EVOLVE-1	

(continued)

Table 7: Characteristics of the interventions – RCT, direct comparison: galcanezumab + BSC vs. placebo + BSC (continued)

Study	Intervention	Comparison
REGAIN	Galcanezumab: initial dose of 2x 120 mg (total dose of 240 mg), SC then 120 mg 1x/month, SC + placebo 1x/month, SC	Placebo 1x/month, SC (2 injections)
	Concomitant treatment ▪ continuation of migraine prevention with topiramate or propranolol at a stable dose if this had been taken at a stable dose for ≥ 2 months prior to the baseline phase ▪ further permitted/non-permitted concomitant treatment: see information on EVOLVE-1	
	Pretreatment ▪ permitted/non-permitted pretreatment: see information on EVOLVE-1	

a: Permitted for the treatment of other diseases than migraine.
b: Antiepileptics (divalproex sodium, sodium valproate, topiramate), beta-blockers (metoprolol, propranolol, timolol, atenolol, nadolol), only for the prevention of menstruation-associated migraine: triptans (frovatriptan, naratriptan, zolmitriptan), antidepressants (amitriptyline, venlafaxine).
c: Treatment ≥ 2 months in the maximum tolerated dose; lack of response due to lack of tolerability was not rated as treatment failure.
d: Study REGAIN: > 3x/months
5-HT: 5-hydroxytryptamine; BSC: best supportive care; CGRP: calcitonin gene-related peptide; MAO: monoamine oxidase; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; TCA: tricyclic antidepressant; TENS: transcutaneous electrical nerve stimulation; vs.: versus

Study design

Studies EVOLVE-1 and EVOLVE-2 (episodic migraine)

EVOLVE-1 and EVOLVE-2 were studies with identical design, which were conducted in different regions. They were randomized, double-blind approval studies comparing galcanezumab + BSC with placebo + BSC over 6 months.

The studies enrolled adult patients with at least 12 months of documented migraine according to the ICHD-3 [4]. In addition, the patients had to have a history of both 4 to 14 migraine days/month on average and ≥ 2 migraine attacks/month on average within the past 3 months. Adults with and without prior treatment with migraine prevention drugs were enrolled. Patients with failure to respond to ≥ 3 adequately dosed treatments from different drug classes were excluded from study participation. Permitted pretreatments were drugs with evidence level A or B according to the classification of the American Academy of Neurology and American Headache Society (antiepileptics [divalproex sodium, sodium valproate, topiramate], beta-blockers [metoprolol, propranolol, timolol, atenolol, nadolol], only for prevention of menstruation-associated migraine: triptans [frovatriptan, naratriptan, zolmitriptan], antidepressants [amitriptyline, venlafaxine]) [3] and botulinum toxin A or B. Adequate dosage was defined as the maximum tolerated dose of a drug for ≥ 2 months; lack of response due to intolerance was not rated as treatment failure.

In a 4-week so-called baseline phase after screening, 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. Compliance in the baseline phase had to be ≥ 80% for transition to the randomized treatment phase. A total of 862 patients in the EVOLVE-1 study and of 922 patients in the EVOLVE-2 study were randomly allocated in a 1:1:2 ratio to treatment with galcanezumab 120 mg, galcanezumab 240 mg[5] or placebo. Of the patients who had received at least 1 dose of the study medication, 213 (EVOLVE-1) and 231 (EVOLVE-2) were allocated to the relevant galcanezumab treatment arms (120 mg); 433 (EVOLVE-1) and 461 patients (EVOLVE-2) were allocated to placebo. Randomization was stratified by the migraine frequency recorded in the baseline phase (< 8 migraine days/month versus ≥ 8 migraine days/month) and geographical region (EVOLVE-1: eastern half of the USA versus western half of the USA versus Puerto Rico versus Canada) or country (EVOLVE-2). The EVOLVE-1 study was only conducted in the USA, Canada and Puerto Rico; the EVOLVE-2 study had study centres also in Europe.

In the relevant study arm, galcanezumab, in accordance with the SPC [5], was administered subcutaneously in the framework of the planned study visits. To maintain blinding, patients in the galcanezumab 120 mg arm received 1 subcutaneous administration of placebo in addition to their study medication, and patients in the placebo arm received 2 injections of placebo. Patients were allowed to use additional medications for the acute treatment of migraine attacks (see below).

Primary outcome of the study was the change in the number of migraine days/month from the baseline phase, averaged over the 3-month double-blind treatment phase. Key secondary outcomes were further outcomes on morbidity, health-related quality of life and AE outcomes.

Only a subpopulation was relevant for both studies (see below). The present assessment was based on analyses of the double-blind treatment (6 months).

Study REGAIN (chronic migraine)

The study design of the REGAIN study was similar to that of the EVOLVE studies. Differences are described below.

The REGAIN study enrolled adult patients with chronic migraine according to ICHD-3 [4], which defines chronic migraine 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" [4]. For study inclusion, the patients additionally had to have ≥ 1 headache-free calendar day/month within the past 3 months and in the baseline phase. Patients who had been on a stable dose of either topiramate or propranolol for ≥ 2 months prior to the baseline phase were allowed to continue to take that preventive medication alongside the study medication. This applied to

[5] A dosage of 240 mg every 4 weeks is not approved in Germany and is therefore not considered further in the present benefit assessment.

about 14% of the patients in the study (about 13% of the relevant subpopulation [see below]). Patients with medication overuse headache in the baseline phase were also enrolled. The REGAIN study also used electronic migraine diaries to determine the eligibility of the patients for study participation.

The double-blind treatment duration was 3 months. Following the double-blind treatment phase, the patients could continue treatment with galcanezumab for 9 months in the open-label extension part of the study.

A total of 1117 patients were randomly allocated in a ratio of 1:1:2 to treatment with galcanezumab 120 mg (N = 279), galcanezumab 240 mg[6] (N = 279) or placebo (N = 559). Randomization was stratified by country, overuse of acute medication for headache determined in the baseline phase (yes versus no) and concomitant treatment with migraine prevention drugs (yes versus no).

In the relevant study arm, galcanezumab, in accordance with the SPC [5], was administered subcutaneously in the framework of the planned study visits. Administration of placebo to maintain blinding was analogous to the approach in the studies EVOLVE-1 and EVOLVE-2. Patients were allowed to use additional medications for the acute treatment of migraine attacks (see below).

Primary outcome of the study was the change in migraine days/month from the baseline phase, averaged over the 3 months of double-blind treatment. Key secondary outcomes were further outcomes on morbidity, health-related quality of life and AE outcomes.

Only a subpopulation was relevant for the study (see below). The present assessment was based on analyses of the double-blind treatment (3 months).

Implementation of the appropriate comparator therapy BSC

BSC treatment in the therapeutic indication of migraine comprises drug and non-drug interventions [6-8].

The studies EVOLVE-1, EVOLVE-2 and REGAIN allowed the use of acute medications (particularly analgesics and antiemetics) for the treatment of migraine attacks during treatment with the study medication. The patients recorded the drugs for the acute treatment of migraine with drug name, dose and type of application in their electronic migraine diaries. Different analgesics (drugs and drug classes) for the acute treatment of migraine headache (and other pain conditions) were prespecified in the 3 studies (see Table 7). However, the list of allowed acute medications does not include all treatment options approved or recommended in Germany [6]. Thus, metamizole is not on the list. In addition, both EVOLVE studies excluded the use of the triptans frovatriptan, naratriptan and zolmitriptan for the treatment of menstruation-

[6] A dosage of 240 mg every 4 weeks is not approved in Germany and is therefore not considered further in the present benefit assessment.

associated migraine. All 3 studies limited the use of opiates and barbiturate-containing analgesics to a maximum of 3 administrations per month. One single steroid injection for emergency treatment was allowed during the study period. Opiates, barbiturates and injected steroids could be used regardless of whether it was for the treatment of migraine headache or other pain conditions.

In addition to acute medication for migraine attacks, treatment with BSC in the therapeutic indication of migraine also includes non-drug therapies such as psychological therapies, acupuncture or endurance sports [6-8]. In all 3 studies, the use of acupuncture, chiropractic, physiotherapy and transcutaneous electrical nerve stimulation in the head and neck area was not permitted during treatment with the study medication. However, other non-drug interventions than those mentioned above were not explicitly excluded and were therefore basically possible.

Despite the limitations described with regard to the permitted concomitant therapies in the included studies EVOLVE-1, EVOLVE-2 and REGAIN, the treatment in the placebo arms of the studies was regarded as an approximation to the ACT BSC. In principle, patients had various drug and non-drug treatment options at their disposal in order to guarantee the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. However, the described limitations in the implementation of the ACT BSC were taken into account in the derivation of the added benefit of galcanezumab versus BSC.

Subpopulation relevant for the benefit assessment

Regarding prior treatment with migraine prevention drugs, the studies EVOLVE-1, EVOLVE-2 and REGAIN included both treatment-naive and pretreated adults. Patients with failure to respond to ≥ 3 adequately dosed treatments from different drug classes were excluded from study participation. Lack of response due to intolerance was not rated as treatment failure and therefore not considered in the number of prior therapies with treatment failure.

Since the patients in the studies were treated with a large number of drugs approved and not approved in Germany, the company presented analyses on subpopulations of the 3 studies for research question 3 of the benefit assessment. These subpopulations included patients who, in accordance with the patient groups defined by the G-BA, had been pretreated with at least 2 of the following therapies (drug classes): propranolol/metoprolol, flunarizine, topiramate or amitriptyline.

Some patients in the relevant subpopulations (EVOLVE-1: 2 of 17 [11.8%]; EVOLVE-2: 16 of 55 [29.1%]; REGAIN: 44 of 146 [30.1%]) had received pretreatment with valproic acid before enrolment. According to the Pharmaceutical Directive (Appendix VI to Section K [9]), valproic acid for the prophylaxis of migraine in adults is only prescribable “if treatment with other drugs approved for this indication has been unsuccessful or is contraindicated”. Thus only those patients would be relevant for whom the administration of valproic acid was the last therapy

with migraine prevention drugs prior to inclusion in the study. This was not clear from the data presented, however.

In addition, patients in the REGAIN study who had been on a stable dose of either topiramate or propranolol for ≥ 2 months prior to the baseline phase were allowed to continue to take this medication alongside the study medication in the double-blind treatment phase.

The company summarized the results of the studies EVOLVE-1 and EVOLVE-2 in a meta-analysis using IPD. It used these results of the meta-analyses under the designation "EVOLVE-1/-2-IPD meta-analysis" (excluding results on the MSQ) for adults with episodic migraine. The company included the REGAIN study for adults with chronic migraine. Analogous to the company, the results of the EVOLVE-1/-2-IPD meta-analysis (hereinafter referred to as "EVOLVE-1/-2) were used. Deviating from the company's approach, the results of the studies on episodic and chronic migraine were summarized in a meta-analysis.

For the benefit assessment, the subpopulations presented by the company were used for answering research question 3. However, since patients with failure to respond to ≥ 3 adequately dosed treatments from different drug classes were excluded from participation in all 3 studies, it cannot be ruled out that for some of the patients, in principle, another one of the above-mentioned approved therapies and not only BSC could have been an option. The proportion of patients who received ≥ 1 further migraine prevention drug that had to be discontinued due to a lack of tolerability was unclear. Treatment discontinuation for this reason was not rated as treatment failure in the studies (see above). In addition, it was unclear whether, in patients who received pretreatment with valproic acid, this was the last therapy (see above). The relevant subpopulations of the studies EVOLVE-1, EVOLVE-2 and REGAIN were regarded as an approximation to the patient population of research question 3, however. The described limitations were taken into account in the derivation of the added benefit of galcanezumab in comparison with BSC.

The relevant subpopulations of the studies for the present benefit assessment comprised 17 patients for the EVOLVE-1 study, 55 patients for the EVOLVE-2 study, and 146 patients for the REGAIN study.

Patient characteristics

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

Table 8: Characteristics of the study populations – RCT, direct comparison: galcanezumab + BSC vs. placebo + BSC

Study Characteristics Category	EVOLVE-1		EVOLVE-2		REGAIN	
	Galcanezumab + BSC	Placebo + BSC	Galcanezumab + BSC	Placebo + BSC	Galcanezumab + BSC	Placebo + BSC
	N[a] = 7	N[a] = 10	N[a] = 27	N[a] = 28	N[a] = 36	N[a] = 110
Age [years], mean (SD)	45 (15)	42 (11)	45 (10)	46 (7)	44 (12)	45 (11)
Sex [F/M], %	100/0	90/10	89/11	93/7	94/6	88/12
Ethnicity, n (%)						
White	6 (85.7)	10 (100)	18 (66.7)	21 (75.0)	32 (88.9)	92 (83.6)
Black	1 (14.3)	0 (0)	0 (0)	0 (0)	1 (2.8)	1 (0.9)
Asian	0 (0)	0 (0)	6 (22.2)	6 (21.4)	1 (2.8)	3 (2.7)
Other	0 (0)	0 (0)	3 (11.1)	1 (3.6)	2 (5.6)[b]	14 (12.7)[b]
Duration of disease [years], mean (SD)	23.7 (14.9)	21.6 (15.2)	23.6 (13.0)	21.7 (13.4)	23.6 (13.6)	24.6 (13.1)
Migraine days/month						
Mean (SD)	9.4 (2.4)	7.6 (2.1)	9.0 (3.1)	9.1 (3.0)	20.5 (4.8)	19.3 (4.7)
< 8 migraine days/month, n (%)	1 (14.3)	6 (60.0)	8 (29.6)	8 (28.6)	0 (0)	0 (0)
≥ 8 migraine days/month, n (%)	6 (85.7)	4 (40.0)	19 (70.4)	20 (71.4)	36 (100)	110 (100)
Migraine attacks/month	ND	ND	ND	ND	ND	ND
Headache days/month, mean (SD)	10.2 (2.6)	10.3 (3.3)	10.7 (3.4)	10.3 (2.9)	21.8 (4.9)	21.8 (3.9)
Moderate/severe headache days/month, mean (SD)	7.5 (3.9)	5.7 (2.2)	7.4 (3.4)	7.0 (3.3)	16.8 (6.0)	16.0 (5.1)
Failed migraine prevention drugs[c], n (%)						
2	6 (85.7)	7 (70.0)	11 (40.7)	14 (50.0)	16 (44.4)	48 (43.6)
3	1 (14.3)	0 (0)	6 (22.2)	11 (39.3)	14 (38.9)	38 (34.5)
≥ 4	0 (0)	3 (30.0)	10 (37.0)[b]	3 (10.7)[b]	6 (16.7)[b]	24 (21.8)[b]

(continued)

Table 8: Characteristics of the study populations – RCT, direct comparison: galcanezumab + BSC vs. placebo + BSC (continued)

Study Characteristics Category	EVOLVE-1		EVOLVE-2		REGAIN	
	Galcanezumab + BSC	Placebo + BSC	Galcanezumab + BSC	Placebo + BSC	Galcanezumab + BSC	Placebo + BSC
	N[a] = 7	N[a] = 10	N[a] = 27	N[a] = 28	N[a] = 36	N[a] = 110
Days with migraine-specific acute medication [days/month], mean (SD)	7.9 (4.2)	6.0 (3.1)	7.8 (3.7)	7.2 (3.5)	17.3 (5.4)	15.4 (6.1)
Any non-drug prophylaxis of migraine, n (%)	ND	ND	ND	ND	ND	ND
Patients with prophylaxis of migraine during the study[f], n (%)	–	–	–	–	5 (13.9)	14 (12.7)
Medication overuse, n (%)	–	–	–	–	28 (77.8)	69 (63.3)
Treatment discontinuation[d], n (%)	0 (0)	2 (20.0[b])	0 (0)	3 (10.7[b])	2 (5.6[b])	3 (2.7[b])
Study discontinuation, n (%)	ND	ND	ND	ND	ND	ND

a: Number of analysed patients in the relevant subpopulation. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Institute's calculation.
c: Includes treatment failure both due to lacking efficacy and due to lacking tolerability.
c: It was not clear from the information in Module 4 A whether this is treatment and/or study discontinuation.
BSC: best supportive care; F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Overall, the patient characteristics of the 3 studies were sufficiently balanced between the treatment groups, also against the background of the small sample sizes.

The mean age of the patients across the individual studies and study arms was about 45 years, most of them were white and women.

The studies EVOLVE-1 and EVOLVE-2 enrolled only adults with episodic migraine (4 to 14 migraine days/month), and the REGAIN study included adults with chronic migraine (see section describing the REGAIN study for the definition). The patients in both EVOLVE studies had about 9 migraine days/month on average. Prior to inclusion in the study, the majority had received 2 migraine prevention drugs; in the EVOLVE-1 study, this accounted for the largest proportion of patients (85% in the galcanezumab arm and 70% in the placebo arm). In the EVOLVE-2 study, the proportion of patients with 2 prior migraine prevention drugs was lower (about 45% on average).

The REGAIN study enrolled adults with chronic migraine. The mean number of migraine days/month was about 20. At the start of the study, 66% of the patients included had medication overuse, and about 13% of the patients received prophylaxis of migraine with topiramate or propranolol during the study. Patients with medication overuse were excluded from participation in both EVOLVE studies. In the EVOLVE studies, patients were also not allowed to take a further migraine prevention drug alongside the study medication.

It was unclear whether the information referred to treatment discontinuations or study discontinuations. No information was provided on the use of non-drug migraine prevention such as endurance sports or psychotherapy.

Quantitative interpretation of the results of the studies on episodic migraine and chronic migraine

The therapeutic indication of galcanezumab comprises adults with at least 4 migraine days/month. Hence, the therapeutic indication includes both patients with episodic migraine and patients with chronic migraine.

The studies EVOLVE-1, EVOLVE-2 and REGAIN provide data both on patients with episodic migraine and on patients with chronic migraine.

Authors of a publication on differences between episodic and chronic migraine consider the relationship between episodic and chronic migraine to be complex [10]. Episodic migraine can develop into chronic migraine and vice versa. The same authors describe that there is no clear differentiation between episodic and chronic migraine, but point out that the corresponding groups differ from each other (e.g. in terms of epidemiology, symptoms and comorbidities) [10].

Since there is no indication that the effects of treatment differ between patients with episodic and those with chronic migraine, the present benefit assessment summarizes the results of

EVOLVE-1/-2 and of the REGAIN study despite different double-blind treatment durations (EVOLVE-1, EVOLVE-2: 6 months; REGAIN: 3 months) in a meta-analysis, unless otherwise indicated. If heterogeneity was observed between the results of individual outcomes, however, the results were assessed separately for both populations.

This deviates from the company's approach, which considered the results of the studies on episodic and chronic migraine in qualitative terms.

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, direct comparison: galcanezumab + BSC vs. placebo + BSC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
EVOLVE-1	Yes	Yes	Yes	Yes	Yes	Yes/	Low
EVOLVE-2	Yes	Yes	Yes	Yes	Yes	Yes/	Low
REGAIN	Yes	Yes	Yes	Yes	Yes	Yes/	Low
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes for the studies EVOLVE-1, EVOLVE-2 and REGAIN was rated as low in each case. This concurs with the company's assessment.

2.6.2 Results on added benefit

2.6.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.8.4.3.2 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - symptoms, measured with migraine days/month
  - disease severity, measured with the PGI-S
  - health status – change of migraine status under treatment, measured with the PGI-I

- Health-related quality of life, measured with the MSQ
- Side effects
  - SAEs
  - discontinuation due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.8.4.3.2 of the full dossier assessment).

Table 10 shows for which outcomes data were available in the studies included.

Table 10: Matrix of outcomes – RCT, direct comparison: galcanezumab + BSC vs. placebo + BSC

Study	Outcomes						
	All-cause mortality	**Symptoms (migraine days/month)**	**Disease severity (PGI-S)**	**Health status – change of migraine status under treatment (PGI-I)**	**Health-related quality of life (MSQ)**	**SAEs**	**Discontinuation due to AEs**
EVOLVE-1	Yes	Yes	Yes	Yes	Yes	Yes	Yes
EVOLVE-2	Yes	Yes	Yes	Yes	Yes	Yes	Yes
REGAIN	Yes	Yes	Yes	Yes	Yes	Yes	Yes

AE: adverse event; BSC: best supportive care; MSQ: Migraine-Specific Quality of Life Questionnaire; PGI-I: Patient Global Impression of Improvement; PGI-S: Patient Global Impression of Severity; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

2.6.2.2 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, direct comparison: galcanezumab + BSC vs. placebo + BSC

Study	Study level	Outcomes						
		all-cause mortality	Symptoms (migraine days/month)	Disease severity (PGI-S)	Health status – change of migraine status under treatment (PGI-I)	Health-related quality of life (MSQ)	SAEs	Discontinuation due to AEs
EVOLVE-1	L	L	H[a, b]	H[a]	H[a]	H[a]	L	L
EVOLVE-2	L	L	H[a, b]	H[a]	H[a]	H[a]	L	L
REGAIN	L	L	H[b]	H[a]	H[a]	H[a]	L	L

a: Large proportion of imputed or missing values.
b: Unjustified deviation from the analysis planned in the statistical analysis plan (see following text).
AE: adverse event; BSC: best supportive care; H: high; L: low; MSQ: Migraine-Specific Quality of Life Questionnaire; PGI-I: Patient Global Impression of Improvement; PGI-S: Patient Global Impression of Severity; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The risk of bias of the results for the outcome "all-cause mortality" as well as for the harm outcomes "SAEs" and "discontinuation due to AEs" from the studies EVOLVE-1, EVOLVE-2 and REGAIN was rated as low in each case. This concurs with the company's assessment.

The risk of bias of the results of the individual studies was rated as high for the outcomes "symptoms" (migraine days/month), "disease severity" (PGI-S), "health status – change of migraine status under treatment" (PGI-I) and "health-related quality of life" (MSQ). The high risk of bias for the outcome "symptoms" (migraine days/month) resulted from the fact that the type of analysis used by the company ("grouped logit model for binomially distributed data" with LOCF imputation of missing values) deviated from the prespecified analysis without justification, and, for the results of the studies EVOLVE-1 and EVOLVE-2 additionally from the large number of LOCF imputations. However, due to the size of the observed effects, the certainty of results in this outcome was not downgraded despite the high risk of bias in each case. The high risk of bias of the results of the individual studies for the outcomes "disease severity" (PGI-S), "health status – change of migraine status under treatment" (PGI-I) and "health-related quality of life" (MSQ) resulted from the large proportion of missing values (see also Section 2.8.4.2 of the full dossier assessment). This assessment deviates from that of the company, which assumed a low risk of bias for the results on all outcomes.

Overall assessment of the certainty of conclusions

There were different uncertainties in the studies EVOLVE-1, EVOLVE-2 and REGAIN. These are explained below.

Implementation of the appropriate comparator therapy

In the 3 studies, patients did not have all available or recommended [6] drug and non-drug treatment options at their disposal in order to guarantee the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. Hence, treatment in the placebo arm was only considered as an approximation to the ACT BSC.

Pretreatment of the patients

Pretreated patients with failure to respond to ≥ 3 adequately dosed treatments from different drug classes were excluded from participation in the studies. Lack of response due to intolerance was not rated as treatment failure. Hence, it was not excluded that, in principle, one of the other approved therapies mentioned above and not only BSC could have been an option for some of the patients. In addition, it was unclear whether, in patients who received pretreatment with valproic acid, this was the last therapy (see Section 2.6.1). The relevant subpopulations of the studies EVOLVE-1, EVOLVE-2 and REGAIN were regarded as an approximation to the patient population of research question 3, however.

Conclusions

The certainty of conclusions of the results from the 3 included studies was reduced due to the described uncertainties. As a result, at most indications, e.g. of an added benefit, can be derived also in the meta-analytical summary of the results of the studies EVOLVE-1, EVOLVE-2 and REGAIN. The outcome-specific assessment can deviate from this.

2.6.2.3 Results

Table 12, Table 13 and Table 14 summarize the results on the comparison of galcanezumab + BSC in comparison with placebo + BSC in adult patients with at least 4 migraine days per month.

The meta-analytical summary of the results of the studies EVOLVE-1 and EVOLVE-2 (EVOLVE-1/-2) on the relevant subpopulations were used in the present benefit assessment. In addition, the results on patients with episodic migraine (EVOLVE-1/-2) and chronic migraine (study REGAIN) were summarized in a meta-analysis (see Section 2.6.1 for reasons and for the approach in case of observed heterogeneity). Forest plots of the meta-analyses calculated by the Institute can be found in Appendix A.1 of the full dossier assessment. Where necessary, data from the company's dossier were supplemented with the Institute's calculations.

The tables on common AEs that occurred in the 3 studies are presented in Appendix A.2 of the full dossier assessment. Since only very few SAEs (2 patients with event) and AEs that led to discontinuation (1 patient with event) occurred in the 3 studies, their frequencies are not

presented. The AEs that commonly occurred in the relevant subpopulations of the studies EVOLVE-1 and EVOLVE-2 are summarized for both studies due to the low number of events that occurred.

Table 12: Results (mortality, side effects) – RCT, direct comparison: galcanezumab + BSC vs. placebo + BSC

Outcome category **Outcome** **Study**	**Galcanezumab + BSC**		**Placebo + BSC**		**Galcanezumab + BSC vs. placebo + BSC**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
Mortality					
All-cause mortality					
EVOLVE-1	*7*	*0 (0)*	*10*	*0 (0)*	–
EVOLVE-2	*27*	*0 (0)*	*28*	*0 (0)*	–
EVOLVE-1/-2[b]	34	0 (0)	38	0 (0)	–
REGAIN	36	0 (0)	110	0 (0)	–
Side effects					
AEs (additional information)					
EVOLVE-1	*7*	*6 (85.7)*	*10*	*7 (70.0)*	–
EVOLVE-2	*27*	*23 (85.2)*	*28*	*21 (75.0)*	–
EVOLVE-1/-2[b]	34	29 (85.3)	38	28 (73.7)	–
REGAIN	36	25 (69.4)	110	58 (52.7)	–
SAEs					
EVOLVE-1	*7*	*0 (0)*	*10*	*0 (0)*	–
EVOLVE-2	*27*	*0 (0)*	*28*	*1 (3.6)*	*0.34 [0.01 8.76]; 0.510*
EVOLVE-1/-2[b]	34	0 (0)	38	1 (2.6)	0.36 [0.01 9.20]; 0.533
REGAIN	36	1 (2.8)	110	0 (0)	5.64 [0.21 153.10]; 0.302
Discontinuation due to AEs					
EVOLVE-1	*7*	*0 (0)*	*10*	*0 (0)*	–
EVOLVE-2	*27*	*0 (0)*	*28*	*0 (0)*	–
EVOLVE-1/-2[b]	34	0 (0)	38	0 (0)	–
REGAIN	36	0 (0)	110	1 (0.9)	0.54 [0.02 14.70]; 0.713

a: RR, 95% CI and p-value: logistic regression with a term for treatment.
b: IPD meta-analysis; logistic regression with terms for treatment and study.

AE: adverse event; BSC: best supportive care; IPD: individual patient data; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 13: Results (morbidity, dichotomous) – RCT, direct comparison: galcanezumab + BSC vs. placebo + BSC

Outcome category Outcome Study	Galcanezumab + BSC N	Galcanezumab + BSC Mean proportion[a] of patients with improvement % [95% CI]	Placebo + BSC N	Placebo + BSC Mean proportion[a] of patients with improvement % [95% CI]	Galcanezumab + BSC vs. placebo + BSC RR [95% CI]; p-value[a]
Morbidity					
Symptoms: migraine days/month, reduction by ≥ 50% from the baseline phase, change averaged over the treatment period[b]					
EVOLVE-1	*7*	*42.86 [27.84; 59.31]*	*10*	*15.00 [7.55; 27.61]*	*2.86 [1.34; 6.09]; 0.010*
EVOLVE-2	*27*	*65.43 [57.61; 72.50]*	*28*	*14.29 [9.67; 20.59]*	*4.58 [3.08; 6.81]; < 0.001*
EVOLVE-1/-2[c]	34	60.88 [53.85; 67.49]	38	14.22 [10.20; 19.50]	4.28 [3.03; 6.04]; < 0.001
REGAIN	36	41.67 [35.22; 48.41]	110	10.00 [7.92; 12.56]	4.17 [3.15; 5.51]; < 0.001
Total[d]					4.21 [3.39; 5.24]; < 0.001

a: Mean proportion with 95% CI (per treatment group) and RR with 95% CI and p-value (group comparison): according to the company, grouped logit model for binomially distributed data with a term for treatment (see Section 2.8.4.2 of the full dossier assessment); imputation of missing values using LOCF.
b: Months 1–6 (EVOLVE-1/-2) or months 1–3 (REGAIN).
c: IPD meta-analysis; according to the company, grouped logit model for binomially distributed data with terms for treatment and study (see Section 2.8.4.2 of the full dossier assessment); imputation of missing values using LOCF.
d: Institute's calculation; meta-analysis with fixed effect.
AE: adverse event; BSC: best supportive care; CI: confidence interval; IPD: individual patient data; LOCF: last observation carried forward; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: galcanezumab + BSC vs. placebo + BSC

Outcome category Outcome Study	Galcanezumab + BSC			Placebo + BSC			Galcanezumab + BSC vs. placebo + BSC
	N[a]	Values at baseline[b] mean (SD)	Change[c] mean (SE)[d]	N[a]	Values at baseline[b] mean (SD)	Change[c] mean (SE)[d]	MD [95% CI]; p-value[d]
Morbidity							
Symptoms: migraine hours/month (additional information)							
EVOLVE-1	*7*	*67.7 (64.23)*	*−28.70 (7.59)*	*10*	*55.2 (36.05)*	*2.84 (6.58)*	*−31.54 [−53.15 −9.93]; 0.007*
EVOLVE-2	*27*	*51.7 (30.94)*	*−29.21 (6.60)*	*28*	*62.5 (46.11)*	*−1.02 (6.98)*	*−28.19 [−46.95 −9.42]; 0.005*
EVOLVE-1/-2[e]	34	55.0 (39.34)	−27.25 (6.45)	38	60.6 (43.34)	0.33 (5.74)	−27.58 [−41.76; −13.40]; < 0.001
REGAIN	36	144.8 (99.73)	−60.32 (11.02)	109	144.1 (90.61)	−3.06 (7.55)	−57.25 [−79.23; −35.28]; < 0.001
Total[f]	Heterogeneity: Q = 4.94; df = 1; p = 0.026; I^2 = 79.8%						
Disease severity (PGI-S[g])							
EVOLVE-1	*7*	*4.7 (1.38)*	*−1.28 (0.54)*	*8*	*5.0 (0.82)*	*−0.59 (0.45)*	*−0.69 [−2.30; 0.93]; 0.373*
EVOLVE-2	*26*	*4.1 (1.40)*	*−0.93 (0.23)*	*21*	*4.8 (0.97)*	*−0.92 (0.27)*	*−0.01 [−0.68; 0.66]; 0.975*
EVOLVE-1/-2[e]	33	4.2 (1.39)	−0.87 (0.25)	29	4.9 (0.92)	−0.68 (0.25)	−0.19 [−0.79; 0.41]; 0.527
REGAIN	30	5.0 (1.11)	−0.62 (0.24)	96	5.0 (1.22)	−0.50 (0.15)	−0.12 [−0.61; 0.37]; 0.632
Total[f]							−0.15 [−0.53; 0.23]; 0.445
Health status – change of migraine status under treatment (PGI-I[g])							
EVOLVE-1	*7*	*–*	*2.55 (0.38)*	*10*	*–*	*3.52 (0.29)*	*−0.97 [−2.03 0.09]; 0.069*
EVOLVE-2	*27*	*–*	*2.31 (0.19)*	*26*	*–*	*3.40 (0.22)*	*−1.09 [−1.64; −0.55]; < 0.001*
EVOLVE-1/-2[e]	34	–	2.25 (0.21)	36	–	3.37 (0.19)	−1.12 [−1.60; −0.64]; < 0.001
REGAIN	34	–	2.94 (0.18)	102	–	3.63 (0.12)	−0.69 [−1.04; −0.34]; < 0.001
Total[f]		–			–		−0.84 [−1.12; −0.56]; < 0.001 Hedges' g [95% CI][h]: −0.87 [−1.17; −0.57]

(continued)

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: galcanezumab + BSC vs. placebo + BSC (continued)

Outcome category Outcome Study	Galcanezumab + BSC			Placebo + BSC			Galcanezumab + BSC vs. placebo + BSC
	N[a]	Values at baseline[b] mean (SD)	Change[c] mean (SE)[d]	N[a]	Values at baseline[b] mean (SD)	Change[c] mean (SE)[d]	MD [95% CI]; p-value[d]
Health-related quality of life							
MSQ[i]							
Role Function-Restrictive domain							
EVOLVE-1	*7*	*46.5 (25.27)*	*21.42 (10.55)*	*8*	*48.9 (14.41)*	*16.14 (8.57)*	*5.28 [−26.30; 36.87]; 0.720*
EVOLVE-2	*26*	*53.0 (13.22)*	*25.74 (3.77)*	*21*	*48.3 (12.98)*	*13.79 (4.25)*	*11.95 [1.37; 22.53]; 0.028*
EVOLVE-1/-2[e]	33	51.7 (16.15)	23.99 (4.28)	29	48.4 (13.18)	14.06 (4.10)	9.93 [0.19; 19.67]; 0.046
REGAIN	30	40.4 (18.89)	20.07 (3.67)	96	38.1 (18.26)	12.01 (2.43)	8.07 [0.51 15.62]; 0.037
Total[f]							8.77 [2.80 14.74]; 0.004 Hedges' g [95% CI][h]: 0.44 [0.14; 0.75]
Role Function-Preventive domain							
EVOLVE-1	*7*	*60.0 (27.39)*	*8.72 (9.73)*	*8*	*68.5 (14.35)*	*15.28 (8.09)*	*−6.56 [−35.46 22.35]; 0.630*
EVOLVE-2	*26*	*69.8 (15.09)*	*17.62 (3.68)*	*21*	*64.8 (15.41)*	*9.14 (4.23)*	*8.48 [−1.91; 18.87]; 0.107*
EVOLVE-1/-2[e]	33	67.8 (18.22)	14.74 (4.19)	29	65.8 (15.02)	9.01 (4.02)	5.74 [−3.76; 15.23]; 0.231
REGAIN	30	54.1 (21.48)	16.52 (3.47)	96	55.1 (21.08)	9.29 (2.29)	7.23 [0.05; 14.42]; 0.049
Total[f]							6.69 [0.96 12.42]; 0.022 Hedges' g [95% CI][h]: 0.35 [0.05; 0.66]
Emotional Function domain							
EVOLVE-1	*7*	*50.5 (38.08)*	*20.38 (13.76)*	*8*	*54.7 (20.07)*	*14.27 (11.26)*	*6.11 [−34.91; 47.13]; 0.751*
EVOLVE-2	*26*	*69.6 (19.94)*	*15.12 (3.60)*	*21*	*62.7 (19.06)*	*12.83 (4.18)*	*2.29 [−7.96; 12.54]; 0.654*
EVOLVE-1/-2[e]	33	65.7 (25.27)	13.67 (4.66)	29	60.5 (19.40)	11.06 (4.48)	2.61 [−8.01; 13.23]; 0.624
REGAIN	30	45.9 (23.43)	22.94 (4.51)	96	44.9 (24.88)	10.37 (2.96)	12.57 [3.20; 21.95]; 0.009
Total[f]							8.21 [1.18 15.24]; 0.022 Hedges' g [95% CI][h]: 0.35 [0.05; 0.66]

(continued)

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: galcanezumab + BSC vs. placebo + BSC (continued)

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b: Migraine hours/month: baseline phase; PGI-S and MSQ: values at start of treatment; PGI-I: no recording of change at start of treatment.
c: Migraine hours/month and PGI-I: averaged over months 1–6 (EVOLVE-1/-2) or months 1–3 (REGAIN); PGI-S and MSQ: averaged over months 4–6 (EVOLVE-1/-2) or at month 3 (REGAIN).
d: MMRM with terms for treatment, geographical region, value at the start of treatment (PGI-I: PGI-S value) and time point (month) as well as for the interactions treatment x time point and value at the start of treatment x time point. In EVOLVE-1 and EVOLVE-2 additionally (except for migraine hours/month) with a term for number of migraine days/month (< 8/≥ 8); in REGAIN additionally with terms for medication overuse and prophylaxis of migraine during the study.
e: IPD meta-analysis; MMRM with terms for treatment, number of migraine days/month (< 8/≥ 8; term omitted for migraine hours/month), geographical region, baseline value (PGI-I: PGI-S value), time point (month) and study as well as for the interactions treatment x time point and value at start of treatment x time point.
f: Institute's calculation; meta-analysis with fixed effect.
g: Lower values indicate better health status; negative group differences indicate an advantage of galcanezumab.
h: Institute's calculation.
i: A higher score indicates better health-related quality of life of the patient; positive group differences indicate an advantage of galcanezumab.

BSC: best supportive care; CI: confidence interval; IPD: individual patient data; MD: mean difference; MMRM: mixed-effects model repeated measures; MSQ: Migraine-Specific Quality of Life Questionnaire; N: number of analysed patients; PGI-I: Patient Global Impression of Improvement; PGI-S: Patient Global Impression of Severity; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

On the basis of the available data, the limitations described in Sections 2.6.1 and 2.6.2.2 regarding the implementation of the ACT and the patient population considered allow the at most indications, e.g. of an added benefit, to be determined for all outcomes with the meta-analytical summary of the results of EVOLVE-1/-2 and the REGAIN study. This deviates from the approach of the company, which considered the results on episodic migraine (EVOLVE-1/-2) and chronic migraine (REGAIN) in qualitative terms and derived proof for individual outcomes.

Unless stated otherwise, hereinafter, the designation "meta-analysis" refers to the meta-analytical summary of the results of EVOLVE-1/-2 and the REGAIN study.

Mortality

All-cause mortality

No deaths occurred in the studies EVOLVE-1, EVOLVE-2 and REGAIN. There was no hint of an added benefit of galcanezumab + BSC in comparison with BSC; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Symptoms (migraine days/month)

For the outcome "symptoms" (migraine days/month), responder analyses were used for a reduction of migraine days by ≥ 50% from the baseline phase, averaged over the treatment period. The meta-analysis showed a statistically significant difference in favour of galcanezumab + BSC.

This advantage was also shown in the operationalization of migraine hours/month (change from the baseline phase averaged over the treatment period) presented as additional information. With effects in the same direction, there was heterogeneity between the results from EVOLVE-1/-2 and the REGAIN study for the operationalization of migraine hours/month ($p < 0.05$). This could be expected due to the consideration of the absolute effect measure, and a meta-analytical summary of the results of this operationalization is not meaningful.

This resulted in an indication of an added benefit of galcanezumab + BSC in comparison with BSC for the outcome "symptoms" (migraine days/month).

This deviates from the approach of the company, which derived proof of an added benefit of galcanezumab on the basis of the responder analyses for a reduction in migraine days by ≥ 50%, ≥ 75% and 100% (EVOLVE-1/-2) or ≥ 30%, ≥ 50% and ≥ 75% (study REGAIN). The company included the operationalization of migraine hours/month as independent outcome in its assessment and also derived proof of an added benefit for it.

Disease severity (PGI-S)

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "disease severity" (PGI-S). As a result, there was no hint of an added benefit of galcanezumab + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company arrived at the same result on the basis of a different type of analysis (analysis of covariance with LOCF imputation).

Health status – change of migraine status under treatment (PGI-I)

The meta-analysis showed a statistically significant difference in favour of galcanezumab + BSC for the outcome "change of migraine status under treatment" (PGI-I). The SMD in the form of Hedges' g was considered to check the relevance of the result. The 95% CI was completely below the irrelevance threshold of –0.2. This was interpreted to be a relevant effect. There was an indication of an added benefit of galcanezumab + BSC in comparison with BSC.

This deviates from the assessment of the company, which derived proof of an added benefit for this outcome on the basis of a different type of analysis (analysis of covariance with LOCF imputation).

Health-related quality of life

MSQ

The meta-analysis showed a statistically significant difference in favour of galcanezumab + BSC for each of the MSQ domains RFR, RP and EF. The SMD in the form of Hedges' g was considered to check the relevance of the result. In each case, the 95% CI of the SMD for the 3 domains was not completely outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effects are relevant in each case. There was no hint of an added benefit of galcanezumab + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

This deviates from the approach of the company, which used responder analyses and derived an indication of an added benefit of galcanezumab both for patients with episodic migraine for the RFR domain and the RP domain based on the results of the EVOLVE-2 study, and for patients with chronic migraine for the RP domain based on the results of the REGAIN study.

Side effects

Serious adverse events and discontinuation due to adverse events

No SAEs occurred in the EVOLVE-1 study. There was 1 patient with event in the placebo arm of the EVOLVE-2 study and 1 patient with event in the galcanezumab arm of the REGAIN study.

There were no discontinuations due to AEs in the studies EVOLVE-1 and EVOLVE-2. There was 1 patient with event in the placebo arm of the REGAIN study.

A meta-analytical summary of the results of EVOLVE-1/-2 and the REGAIN study was not performed for these outcomes due to the absence or the only very low number of events that occurred.

There was no hint of greater or lesser harm of galcanezumab + BSC in comparison with BSC for any of these outcomes. Greater or lesser harm is therefore not proven for these outcomes.

This concurs with the company's assessment.

2.6.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered in the benefit assessment (see Section 2.8.4.3.4 of the full dossier assessment):

- sex (female/male)
- region (North America/Europe/other)
- disease severity at baseline (< 8 migraine days/month/≥ 8 migraine days/month)

Additionally for patients with chronic migraine:

- prophylaxis of migraine during the study (yes/no)
- medication overuse at baseline (yes/no)

The choice of potential effect modifiers deviated from that of the company.

All subgroup characteristics used in the present benefit assessment were prespecified, but only for the primary outcome. The subgroup characteristic "age" was not considered in the present benefit assessment because it had not been prespecified in the 3 studies and the company did not provide sufficient justification as to why it used the cut-off values it presented.

The company conducted separate interaction tests for EVOLVE-1/-2 and the REGAIN study. For this reason, an interaction test at the meta-level using a Q test was subsequently performed for the present assessment, provided that both analyses (for EVOLVE-1/-2 and REGAIN) each resulted in a significant effect modification to the level of 0.2. If the Q test determines a significant interaction to the level of 0.05, separate conclusions on the benefit were derived for the subgroups. Moreover, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Subgroup analyses for the type of analysis used in the present benefit assessment (mixed-effects model repeated measures [MMRM]) were available only for the outcome "symptoms" (migraine days/month). No corresponding analyses were available for the outcomes "disease severity" (PGI-S), "health status – change of migraine status under treatment" (PGI-I) and "health-related quality of life" (3 domains of the MSQ). No subgroup analyses were conducted for the outcomes "all-cause mortality", "SAEs" and "discontinuation due to AEs" due to the absence or the very low number of events that occurred.

In accordance with the methods described above, no relevant effect modification was identified for the present research question. This concurs with the approach of the company insofar as it also observed no relevant effect modifications on the basis of the considered subgroup characteristics.

2.6.3 Probability and extent of added benefit

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

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

2.6.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.6.2 (see Table 15).

Determination of the outcome category for the outcomes on morbidity

It could not be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Symptoms (migraine days/month)

The outcome "symptoms" (migraine days/month) was allocated to the outcome category "serious/severe symptoms/late complications". This is because the results of the relevant subpopulations with episodic and chronic migraine were considered together, and adults with chronic migraine represent the majority of the patients included in the present benefit assessment (see Table 8). Due to the high burden of disease of these patients with 20 migraine days/month on average, the outcome was therefore overall allocated to the outcome category "serious/severe symptoms/late complications". The assessment of the outcome category concurred with that of the company, which did not justify its assessment, however.

Health status – change of migraine status under treatment (PGI-I)

The PGI-I instrument in the therapeutic indication of migraine is an instrument for the subjective recording of the change in migraine status under treatment. Since the PGI-I only records the change in symptoms under treatment and not the severity of the symptoms, it was allocated to the outcome category "non-serious/non-severe symptoms/late complications". This concurs with the company's assessment.

Table 15: Extent of added benefit at outcome level: galcanezumab + BSC vs. placebo + BSC

Outcome category **Outcome**	**Galcanezumab + BSC vs. placebo + BSC** **(Mean) proportion (%) or mean change** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	Proportion: 0% vs. 0% RR: –	Lesser benefit/added benefit not proven
Morbidity		
Symptoms: migraine days/month, reduction by ≥ 50% from the baseline phase, change averaged over the treatment period	Mean proportion: 41.67–60.88% vs. 10.00–14.22%[c] RR: 4.21 [3.39; 5.24] RR: 0.24 [0.19; 0.29][d] p < 0.001 probability: "indication"	Outcome category: serious/severe symptoms/late complications CI_u < 0.75 and risk ≥ 5% added benefit: "major"
Disease severity (PGI-S)	Mean: −0.62 to −0.87 vs. −0.50 to −0.68[c] MD: −0.15 [−0.53; 0.23]; p = 0.445	Lesser benefit/added benefit not proven
Health status – change of migraine status under treatment (PGI-I)	Mean: 2.25–2.94 vs. 3.37–3.63[c] MD: −0.84 [−1.12; −0.56]; p < 0.001 Hedges' g[e]: −0.87 [−1.17; −0.57] probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
Health-related quality of life		
MSQ		
Role Function-Restrictive domain	Mean: 20.07–23.99 vs. 12.01–14.06[c] MD: 8.77 [2.80; 14.74]; p = 0.004 Hedges' g[e]: 0.44 [0.14; 0.75]	Lesser benefit/added benefit not proven
Role Function-Preventive domain	Mean: 14.74–16.52 vs. 9.01–9.29[c] MD: 6.69 [0.96; 12.42]; p = 0.022 Hedges' g[e]: 0.35 [0.05; 0.66]	Lesser benefit/added benefit not proven
Emotional Function domain	Mean: 13.67–22.94 vs. 10.37–11.06[c] MD: 8.21 [1.18; 15.24]; p = 0.022 Hedges' g[e]: 0.35 [0.05; 0.66]	Lesser benefit/added benefit not proven
Side effects		
SAEs	Proportion: 0–2.8% vs. 0–2.6%[c] RR: –[f]	Greater/lesser harm not proven
Discontinuation due to AEs	Proportion: 0% vs. 0–0.9%[c] RR: –[f]	Greater/lesser harm not proven

(continued)

Table 15: Extent of added benefit at outcome level: galcanezumab + BSC vs. placebo + BSC (continued)

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Minimum and maximum proportions of events or mean changes per treatment arm in the included studies (EVOLVE-1/-2 [IPD meta-analysis] and REGAIN).
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
f: Due to the low number of patients with event, EVOLVE-1/-2 (IPD meta-analysis) and REGAIN were not summarized in a meta-analysis.
AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of the confidence interval; MD: mean difference; MSQ: Migraine-Specific Quality of Life Questionnaire; PGI-I: Patient Global Impression of Improvement; PGI-S: Patient Global Impression of Severity; RR: relative risk; SAE: serious adverse event; vs.: versus

2.6.3.2 Overall conclusion on added benefit

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

Table 16: Positive and negative effects from the assessment of galcanezumab + BSC compared with placebo + BSC

Positive effects	**Negative effects**
Outcome category: serious/severe symptoms/late complications: ▪ symptoms (migraine days/month), reduction by ≥ 50%: indication of added benefit, extent: "major"	–
Outcome category: non-serious/non-severe symptoms/late complications: ▪ Health status – change of migraine status under treatment (PGI-I): indication of added benefit, extent: "non-quantifiable"	
BSC: best supportive care; PGI-I: Patient Global Impression of Improvement	

In the overall assessment based on the studies EVOLVE-1, EVOLVE-2 and REGAIN, there are only positive effects for adult patients who have at least 4 migraine days/month and for whom BSC is the only treatment option. These were shown both for adults with episodic migraine (4 to 14 migraine days/month) and for adults with chronic migraine, each in the outcome category of morbidity.

In summary, there is an indication of major added benefit of galcanezumab versus BSC for adult patients who have at least 4 migraine days/month and for whom BSC is the only treatment option.

The assessment described above deviates from that of the company, which claimed proof of major added benefit.

2.6.4 List of included studies (research question 3)

EVOLVE-1

Eli Lilly. Evaluation of galcanezumab in the prevention of episodic migraine: the EVOLVE-1 study (EVOLVE-1); study details [online]. In: ClinicalTrials.gov. 29.11.2018 [Accessed: 10.04.2019]. URL: https://clinicaltrials.gov/ct2/show/NCT02614183.

Eli Lilly. Evaluation of galcanezumab in the prevention of episodic migraine: the EVOLVE-1 study (EVOLVE-1); study results [online]. In: ClinicalTrials.gov. 29.11.2018 [Accessed: 10.04.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02614183.

Eli Lilly. A phase 3, randomized, double-blind, placebo-controlled study of LY2951742 in patients with episodic migraine: the EVOLVE-1 study; study I5Q-MC-CGAG; clinical protocol [unpublished]. 2015.

Eli Lilly. A phase 3, randomized, double-blind, placebo-controlled study of LY2951742 in patients with episodic migraine: the EVOLVE-1 study; results from the double-blind treatment phase; study I5Q-MC-CGAG; clinical study report [unpublished]. 2017.

Eli Lilly. A phase 3, randomized, double-blind, placebo-controlled study of LY2951742 in patients with episodic migraine: studies I5Q-MC-CGAG and I5Q-MC-CGAH; statistical analysis plan [unpublished]. 2017.

Eli Lilly. A phase 3, randomized, double-blind, placebo-controlled study of LY2951742 in patients with episodic migraine: the EVOLVE-1 study; study I5Q-MC-CGAG; Zusatzanalysen [unpublished]. 2019.

Förderreuther S, Zhang Q, Stauffer VL, Aurora SK, Lainez MJA. Preventive effects of galcanezumab in adult patients with episodic or chronic migraine are persistent: data from the phase 3, randomized, double-blind, placebo-controlled EVOLVE-1, EVOLVE-2, and REGAIN studies. J Headache Pain 2018; 19(1): 121.

Nichols R, Doty E, Sacco S, Ruff D, Pearlman E, Aurora SK. Analysis of initial nonresponders to galcanezumab in patients with episodic or chronic migraine: results from the EVOLVE-1, EVOLVE-2, and REGAIN randomized, double-blind, placebo-controlled studies. Headache 2019; 59(2): 192-204.

Rosen N, Pearlman E, Ruff D, Day K, Nagy AJ. 100% response rate to galcanezumab in patients with episodic migraine: a post hoc analysis of the results from phase 3, randomized, double-blind, placebo-controlled EVOLVE-1 and EVOLVE-2 studies. Headache 2018; 58(9): 1347-1357.

Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of galcanezumab for the prevention of episodic migraine: the EVOLVE-1 randomized clinical trial. JAMA Neurol 2018; 75(9): 1080-1088.

EVOLVE-2

Eli Lilly. A phase 3, randomized, double-blind, placebo-controlled study of LY2951742 in patients with episodic migraine: the EVOLVE-2 study [online]. In: EU Clinical Trials Register. [Accessed: 10.04.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-001882-17.

Eli Lilly. Evaluation of efficay and safety of galcanezumab in the prevention of episodic migraine: the EVOLVE-2 study (EVOLVE-2); study details [online]. In: ClinicalTrials.gov. 07.01.2019 [Accessed: 10.04.2019]. URL: https://clinicaltrials.gov/ct2/show/NCT02614196.

Eli Lilly. Evaluation of efficay & safety of galcanezumab in the prevention of episodic migraine: the EVOLVE-2 study (EVOLVE-2); study results [online]. In: ClinicalTrials.gov. 07.01.2019 [Accessed: 10.04.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02614196.

Eli Lilly. A phase 3, randomized, double-blind, placebo-controlled study of LY2951742 in patients with episodic migraine: the EVOLVE-2 study; study I5Q-MC-CGAH; clinical protocol [unpublished]. 2015.

Eli Lilly. A phase 3, randomized, double-blind, placebo-controlled study of LY2951742 in patients with episodic migraine: studies I5Q-MC-CGAG and I5Q-MC-CGAH; statistical analysis plan [unpublished]. 2017.

Eli Lilly. A phase 3, randomized, double-blind, placebo-controlled study of LY2951742 in patients with episodic migraine: the EVOLVE-2 study; results from the double-blind treatment phase; study I5Q-MC-CGAH; clinical study report [unpublished]. 2017.

Eli Lilly. A phase 3, randomized, double-blind, placebo-controlled study of LY2951742 in patients with episodic migraine: the EVOLVE-2 study; study I5Q-MC-CGAH; Zusatzanalysen [unpublished]. 2019.

Förderreuther S, Zhang Q, Stauffer VL, Aurora SK, Lainez MJA. Preventive effects of galcanezumab in adult patients with episodic or chronic migraine are persistent: data from the phase 3, randomized, double-blind, placebo-controlled EVOLVE-1, EVOLVE-2, and REGAIN studies. J Headache Pain 2018; 19(1): 121.

Rosen N, Pearlman E, Ruff D, Day K, Nagy AJ. 100% response rate to galcanezumab in patients with episodic migraine: a post hoc analysis of the results from phase 3, randomized, double-blind, placebo-controlled EVOLVE-1 and EVOLVE-2 studies. Headache 2018; 58(9): 1347-1357.

Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, J.Y. Y. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. Cephalalgia 2018; 38(8): 1442-1454.

REGAIN

Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study. Neurology 2018; 91: e2211-e2221.

Eli Lilly. A phase 3, randomized, double-blind, placebo-controlled study of LY2951742 in patients with chronic migraine: the REGAIN study [online]. In: EU Clinical Trials Register. [Accessed: 10.04.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-001883-21.

Eli Lilly. Evaluation of galcanezumab in the prevention of chronic migraine (REGAIN): study details [online]. In: ClinicalTrials.gov. 07.01.2019 [Accessed: 10.04.2019]. URL: https://clinicaltrials.gov/ct2/show/NCT02614261.

Eli Lilly. Evaluation of galcanezumab in the prevention of chronic migraine (REGAIN): study results [online]. In: ClinicalTrials.gov. 07.01.2019 [Accessed: 10.04.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02614261.

Eli Lilly. A phase 3, randomized, double-blind, placebo-controlled study of LY2951742 in patients with chronic migraine: the REGAIN study; study I5Q-MC-CGAI(a); clinical protocol [unpublished]. 2015.

Eli Lilly. A phase 3, randomized, double-blind, placebo-controlled study of LY2951742 in patients with chronic migraine: the REGAIN study; final results from the double-blind treatment phase and interim results from the open-label treatment phase; study I5Q-MC-CGAI; clinical study report [unpublished]. 2017.

Eli Lilly. A phase 3, randomized, double-blind, placebo-controlled study of LY2951742 in patients with chronic migraine: the REGAIN study; study I5Q-MC-CGAI; statistical analysis plan [unpublished]. 2017.

Eli Lilly. A phase 3, randomized, double-blind, placebo-controlled study of LY2951742 in patients with chronic migraine: the REGAIN study; study I5Q-MC-CGAI; Zusatzanalysen [unpublished]. 2019.

Förderreuther S, Zhang Q, Stauffer VL, Aurora SK, Lainez MJA. Preventive effects of galcanezumab in adult patients with episodic or chronic migraine are persistent: data from the phase 3, randomized, double-blind, placebo-controlled EVOLVE-1, EVOLVE-2, and REGAIN studies. J Headache Pain 2018; 19(1): 121.

2.7 Probability and extent of added benefit – summary

Table 17: Galcanezumab – probability and extent of added benefit

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

a: Presentation of the respective ACT specified by the G-BA.
b: All 4 drug classes specified as ACTs for research question 1 (beta-blockers, flunarizine, topiramate or amitriptyline) must have been considered before the patients fall under research question 2.
c: According to Appendix VI to Section K of the Pharmaceutical Directive: if treatment with all other drugs approved for this indication has been unsuccessful or is contraindicated.
d: In compliance with the approval only for chronic migraine.
e: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
f: Both for adults with episodic migraine and for adults with chronic migraine.
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

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

References 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.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58.

3. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults; report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012; 78(17): 1337-1345.

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

5. Lilly. Emgality: Fachinformation [online]. 11.2018 [Accessed: 03.05.2019]. URL: https://www.fachinfo.de.

6. Diener HC, Gaul C, Kropp P. Therapie der Migräneattacke und Prophylaxe der Migräne: S1-Leitlinie; AWMF-Registernummer: 030/057 [online]. 01.2018 [Accessed: 19.12.2018]. URL: https://www.awmf.org/uploads/tx_szleitlinien/030-057l_S1_Migraene-Therapie_2018-04_1.pdf.

7. Pringsheim T, Davenport W, Mackie G, Worthington I, Aube M, Christie SN et al. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci 2012; 39(Suppl 2): S1-S59.

8. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review); report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000; 55(6): 754-762.

9. Gemeinsamer Bundesausschuss. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie: Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (sog. Off-Label-Use) [online]. 26.03.2019 [Accessed: 21.05.2019]. URL: https://www.g-ba.de/downloads/83-691-524/AM-RL-VI-Off-label-2019-03-26.pdf.

10. Katsarava Z, Buse DC, Manack AN, Lipton RB. Defining the differences between episodic migraine and chronic migraine. Curr Pain Headache Rep 2012; 16(1): 86-92.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-28-galcanezumab-migraine-benefit-assessment-according-to-35a-social-code-book-v.12043.html.