IQWiG Reports – Commission No. A19-63

Galcanezumab (migraine) –

Addendum to Commission A19-28[1]

Addendum

Commission: A19-63
Version: 1.0
Status: 21 August 2019

[1] Translation of addendum A19-63 *Galcanezumab (Migräne) – Addendum zum Auftrag A19-28* (Version 1.0; Status: 21 August 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Galcanezumab (migraine) – Addendum to Commission A19-28

Commissioning agency:
Federal Joint Committee

Commission awarded on:
5 August 2019

Internal Commission No.:
A19-63

Address of publisher:
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Keywords: galcanezumab, migraine disorders, benefit assessment, NCT02614183, NCT02614196, NCT02614261

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BSC	best supportive care
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
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

1 Background

On 5 August 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-28 (Galcanezumab – Benefit assessment according to §35a Social Code Book V) [1].

For the benefit assessment of galcanezumab, the pharmaceutical company (hereinafter referred to as "the company") presented in its dossier [2] data for the present research question: adult patients who do not respond to any of the following therapies (drug classes), are unsuitable for them or do not tolerate them: metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid, clostridium botulinum toxin type A (the latter, in compliance with the approval, only for chronic migraine). The appropriate comparator therapy (ACT) for this population is best supportive care (BSC) ("research question 3" of dossier assessment A19-28).

The G-BA commissioned IQWiG to assess the following analyses:

- reduction of migraine days/month by ≥ 75% from baseline
- reduction of migraine days/month by 100% from baseline
- reduction of headache days/month (total headache days, and – if possible – differentiated by migraine headache, probable migraine headache, non-migraine headache)

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

2 Assessment

For research question 3 of dossier assessment A19-28 (adult patients for whom BSC is the only remaining treatment option), the company presented results based on subpopulations of the approval studies EVOLVE-1, EVOLVE-2 (both episodic migraine) and REGAIN (chronic migraine) on the comparison of galcanezumab + BSC with placebo + BSC. The subpopulations comprised 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. The studies were used for the benefit assessment on commission A19-28.

For the outcome "symptoms", analyses of the operationalization reduction of migraine days/month by ≥ 50% from the baseline phase were included in the benefit assessment. This was due to the fact that the reduction of migraine days/month by ≥ 50% already represents an appropriate response criterion for the patient population for which BSC is the only remaining treatment option, irrespective of whether an episodic migraine or a chronic migraine is present. The studies presented by the company defined a migraine day as a calendar day on which a patient documented a migraine headache or a probable migraine headache.

Headache days/month were not included in the dossier assessment as the patient's burden of disease is more accurately reflected in the migraine days/month, which are also included in the headache days/month. The studies EVOLVE-1, EVOLVE-2 and REGAIN defined headache days as calendar days on which a patient documented any type of headache (migraine headache, probable migraine headache, non-migraine headache).

Data presented by the company

Migraine days/month

In its dossier, the company presented prospectively planned analyses for the reduction of migraine days/month. In addition to the operationalization for the reduction by 50% from the baseline phase, it also presented analyses for the reductions of ≥ 75% and 100%.

Headache days/month

In its dossier, the company presented analyses on the reduction of headache days/month by ≥ 50% from the baseline phase. Since this analysis was not prespecified in any of the 3 studies presented by the company, the prospectively planned analysis of the change in headache days/month compared with the baseline phase is also presented below. There are no analyses on the reduction of headache days/month by ≥ 75% or by 100% from the baseline phase. In addition, the dossier only contained analyses for headache days as a whole, but not differentiated by migraine headache, probable headache and non-migraine headache.

Risk of bias

The risk of bias of the results on the reduction of migraine days/month by ≥ 75% or 100% was rated as high for each study. As already described in the dossier assessment, this was due to the

unprespecified analysis using a grouped logit model for binomially distributed data and the high proportion of last observation carried forward (LOCF)-imputed monthly data in the results of the studies EVOLVE-1 and EVOLVE-2. Due to the size of the observed effects in the reduction of migraine days/month by ≥ 75%, the certainty of results for each study result was not downgraded despite the high risk of bias.

The risk of bias of the results on the reduction of headache days/month by ≥ 50% was also rated as high for each study. The reasons are the same as those described above for the reduction of migraine days/month. Due to the size of the observed effects, the certainty of results was also not downgraded for the reduction of headache days/month by ≥ 50% despite the high risk of bias. The risk of bias of the results on the change in headache days/month from the baseline phase resulting from the mixed-effects model repeated measures (MMRM) analyses was rated as high in both EVOLVE-1 and EVOLVE-2 due to the high proportion of missing values. The risk of bias of the result from the REGAIN study from the corresponding analysis was low.

Results

In accordance with the approach in dossier assessment A19-28, the results of the studies EVOLVE-1 and EVOLVE-2 (hereinafter referred to as "EVOLVE-1/-2"), summarized by the company in a meta-analysis on the basis of individual patient data, are used for the relevant subpopulations from the studies. If meaningful, the results on EVOLVE-1/-2 and the REGAIN study are additionally summarized in a meta-analysis. Table 1 and Table 2 show the results on the operationalizations of migraine days/month and headache days/month on the comparison of galcanezumab + BSC with placebo + BSC. Forest plots of the meta-analyses calculated by the Institute can be found in Appendix A.

Table 1: 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					
Migraine days/month[b], reduction by ≥ 75% from the baseline phase, averaged over the treatment period[c]					
EVOLVE-1	*7*	*26.19 [14.38; 42.85]*	*10*	*6.67 [2.32; 17.71]*	*3.93 [1.22; 12.64]; 0.025*
EVOLVE-2	*27*	*41.36 [33.87; 49.27]*	*28*	*2.98 [1.22; 7.09]*	*13.90 [5.63; 34.29]; < 0.001*
EVOLVE-1/-2[d]	34	38.16 [31.63; 45.16]	38	3.90 [2.02; 7.42]	9.78 [4.97; 19.24]; < 0.001
REGAIN	36	9.26 [6.03; 13.96]	110	2.42 [1.48; 3.94]	3.82 [2.00; 7.28]; < 0.001
Total[e]	Heterogeneity: Q = 3.88; df = 1; p = 0.049; I^2 = 74.2%				
Migraine days/month[b], reduction by 100% from the baseline phase, averaged over the treatment period[c]					
EVOLVE-1	*7*	*9.52 [3.32; 24.40]*	*10*	*6.67 [2.32; 17.71]*	*1.43 [0.34; 6.06]; 0.606*
EVOLVE-2	*27*	*19.75 [14.21; 26.78]*	*28*	*0.00 [ND[f]]*	*ND[f, g]*
EVOLVE-1/-2[d]	34	17.64 [12.93; 23.61]	38	1.75 [0.65; 4.65]	10.06 [3.58; 28.29]; < 0.001
REGAIN	36	0.00 [ND[f]]	110	0.30 [0.07; 1.26]	ND[f, h]
Total					-
Headache days/month[i], reduction by ≥ 50% from the baseline phase, averaged over the treatment period[c]					
EVOLVE-1	*7*	*38.10 [23.82; 54.78]*	*10*	*16.67 [8.72; 29.50]*	*2.29 [1.09; 4.81]; 0.032*
EVOLVE-2	*27*	*46.30 [38.59; 54.18]*	*28*	*13.10 [8.70; 19.25]*	*3.54 [2.29; 5.45]; < 0.001*
EVOLVE-1/-2[d]	34	44.61 [37.81; 51.61]	38	14.03 [10.04; 19.27]	3.18 [2.21; 4.57]; < 0.001
REGAIN	36	35.19 [29.06; 41.84]	110	8.79 [6.84; 11.22]	4.00 [2.94; 5.45]; < 0.001
Total[e]					3.63 [2.87; 4.60]; < 0.001
Headache days/month[i], reduction by ≥ 75% from the baseline phase, averaged over the treatment period					
No data					
Headache days/month[i], reduction by 100% from the baseline phase, averaged over the treatment period					
No data					

(continued)

Table 1: Results (morbidity, dichotomous) – RCT, direct comparison: galcanezumab + BSC vs. placebo + BSC (continued)

a: Mean proportion with 95% CI (per treatment group) and RR with 95% CI and p-value (group comparison): grouped logit model for binomially distributed data with a term for treatment; imputation of missing values using LOCF.
b: Defined as a calendar day on which a patient documented a migraine headache or a probable migraine headache.
c: Months 1–6 (EVOLVE-1/-2) or months 1–3 (REGAIN).
d: IPD meta-analysis; grouped logit model for binomially distributed data with terms for treatment and study; imputation of missing values using LOCF.
e: Institute's calculation; meta-analysis with fixed effect.
f: No presentation because not informative.
g: In the placebo + BSC arm, no patient had an event at any time point.
h: In the galcanezumab arm, no patient had an event at any time point; in the comparator arm, 1 patient had 1 event at a time point (month 3).
i: Defined as calendar days on which a patient documented any type of headache (migraine headache, probable migraine headache, non-migraine headache).

BSC: best supportive care; CI: confidence interval; IPD: individual patient data; LOCF: last observation carried forward; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 2: Results (morbidity, 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 mean (SD)	Change[b] mean (SE)[c]	N[a]	Values at baseline mean (SD)	Change[b] mean (SE)[c]	MD [95% CI]; p-value[c]
Morbidity							
Headache days/month[d]							
EVOLVE-1	*7*	*10.2 (2.62)*	*−2.23 (1.64)*	*10*	*10.3 (3.29)*	*−1.30 (1.27)*	*−0.92 [−5.47; 3.63]; 0.673*
EVOLVE-2	*27*	*10.7 (3.42)*	*−3.35 (0.92)*	*28*	*10.3 (2.94)*	*−0.12 (1.02)*	*−3.23 [−5.63; −0.83]; 0.010*
EVOLVE-1/-2[e]	34	10.6 (3.25)	−3.63 (0.97)	38	10.3 (2.99)	−0.86 (0.85)	−2.77 [−4.82; −0.71]; 0.009
REGAIN	36	21.8 (4.85)	−6.41 (1.00)	109	21.8 (3.94)	−1.72 (0.69)	−4.69 [−6.67; −2.72]; < 0.001
Total[f]							−3.77 [−5.19; −2.34]; < 0.001

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: Averaged over months 1–6 (EVOLVE-1/-2) or months 1–3 (REGAIN).
c: MMRM with terms for treatment, geographical region, value at the start of treatment 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 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.
d: Defined as calendar days on which a patient documented any type of headache (migraine headache, probable migraine headache, non-migraine headache).
e: IPD meta-analysis; MMRM with terms for treatment, number of migraine days/month (< 8/≥ 8), geographical region, baseline 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.
BSC: best supportive care; CI: confidence interval; IPD: individual patient data; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

Migraine days/month

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

For the reduction of migraine days/month by ≥ 75% compared with the baseline phase, averaged over the treatment period, there was heterogeneity between the results from EVOLVE-1/-2 and the REGAIN study ($p < 0.05$). A meta-analysis is therefore not meaningful. However, a statistically significant advantage of galcanezumab + BSC in comparison with placebo + BSC was shown both for the results from EVOLVE-1/-2 and for the REGAIN study for the reduction of migraine days/month by ≥ 75% from the baseline phase.

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

For the reduction of migraine days/month by 100%, there was only 1 patient with a reduction of migraine days/month by 100% at 1 time point in the treatment period (month 3), so that the resulting effect estimation was not informative. A meta-analysis of EVOLVE-1/-2 and the REGAIN study for the reduction of migraine days/month by 100% is therefore not possible. A statistically significant advantage of galcanezumab + BSC in comparison with placebo + BSC was shown for EVOLVE-1/-2.

Summary on the reduction of migraine days/month

The overall consideration of the results on migraine days/month on the basis of the reduction by ≥ 50%, ≥ 75% and by 100% from the baseline phase showed overall consistent results in favour of galcanezumab + BSC versus placebo + BSC.

Headache days/month

For the reduction of headache days/month by ≥ 50% and for the change in headache days/month, each in comparison with the baseline phase, the meta-analysis of EVOLVE-1/-2 and the REGAIN study showed for both analysis a statistically significant advantage of galcanezumab + BSC in comparison with placebo + BSC.

Separate analyses on migraine headache, probable migraine headache and non-migraine headache, which comprise the headache days in the studies EVOLVE-1, EVOLVE-2 and REGAIN, are not available.

Subgroup analyses

In accordance with the methods described in dossier assessment A19-28, no effect modification for the operationalizations assessed in the present addendum were shown by the relevant subgroup characteristics (sex, region, disease severity at baseline; only for patients with chronic migraine: prophylaxis of migraine during the study, medication overuse at baseline).

2.1 Summary

The present addendum does not change the conclusion on the added benefit of galcanezumab from dossier assessment A19-28.

The G-BA decides on the added benefit.

3 References

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

2. Lilly Deutschland. Galcanezumab (Emgality): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 01.04.2019 [Accessed: 11.07.2019]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/450/#tab/dossier.

Appendix A – Figures of the meta-analyses

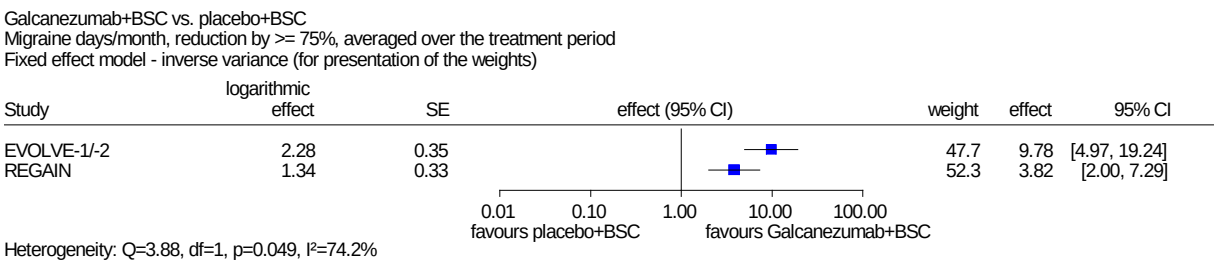

Figure 1: Meta-analysis with fixed effect (inverse variance method) for migraine days/month; ≥ 75% reduction from the baseline phase, averaged over the treatment period (EVOLVE-1/-2: months 1–6; REGAIN: months 1–3)

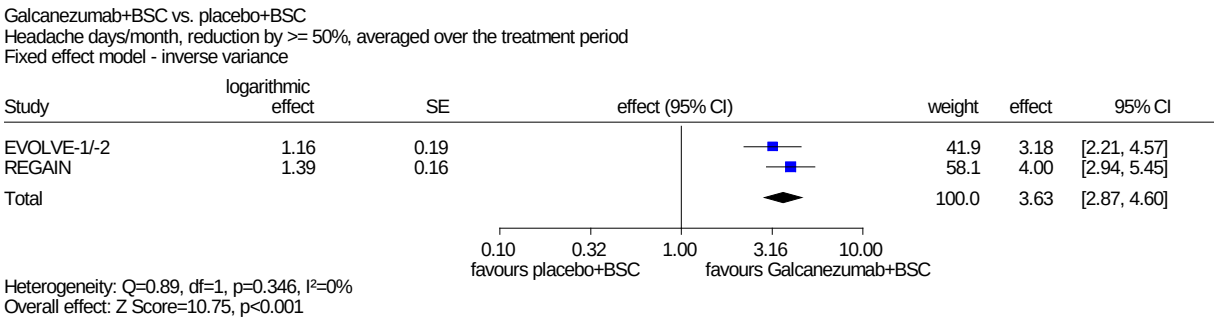

Figure 2: Meta-analysis with fixed effect (inverse variance method) for headache days/month; ≥ 50% reduction from the baseline phase, averaged over the treatment period (EVOLVE-1/-2: months 1–6; REGAIN: months 1–3)

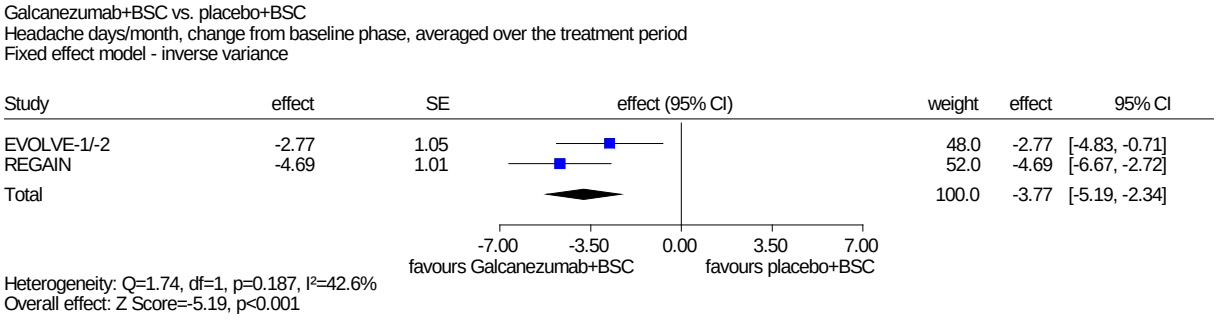

Figure 3: Meta-analysis with fixed effect (inverse variance method) for headache days/month; change from the baseline phase, averaged over the treatment period (EVOLVE-1/-2: months 1–6; REGAIN: months 1–3)