Ravulizumab (generalized myasthenia gravis)

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

EXTRACT

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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

- Markus Ebke, Clinic for Neurology and Clinical Neurophysiology, DIAKOVERE Krankenhaus gGmbH, Henriettenstift site, Germany

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Patient and family involvement

The questionnaire on the disease and its treatment was answered by Claudia Schlemminger.

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

IQWiG employees involved in the dossier assessment

- Marina Woeste
- Merlin Bittlinger
- Katharina Frangen
- Tatjana Hermanns
- Kirsten Janke
- Daniela Preukschat
- Dominik Schierbaum
- Christoph Schürmann

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
AChR	acetylcholine receptor
ACT	appropriate comparator therapy
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IPW	inverse probability weighting
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAIC	matching-adjusted indirect comparison
MG-ADL	Myasthenia Gravis-Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ravulizumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 21 October 2022.

Research question

The aim of the present report is to assess the added benefit of ravulizumab as an add-on to standard therapy for the treatment of adult patients with generalized myasthenia gravis who are anti-acetylcholine receptor (AChR) antibody-positive.

The research questions shown in Table 2 result from the appropriate comparator therapy (ACT) specified by the G-BA.

Table 2: Research questions of the benefit assessment of ravulizumab

Research question	Therapeutic indication	ACT[a]
1	Adults with anti-AChR antibody-positive generalized myasthenia gravis who are still eligible for standard treatment	Treatment of physician's choice[b, c, d]
2	Adults with anti-AChR antibody-positive refractory generalized myasthenia gravis	Eculizumab[d, e, f]

a. Presented is the respective ACT specified by the G-BA.
b. Various treatment options are mentioned in the present guidelines. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended in the guideline and used in practice. In accordance with the G-BA, the following therapies are considered suitable comparators for the treatment of physician's choice within the framework of a clinical study: cholinesterase inhibitors and immunosuppressants such as glucocorticoids, azathioprine, mycophenolate mofetil, ciclosporin A, methotrexate, and tacrolimus. In a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision (multicomparator study). The choice and, if necessary, limitation of treatment options must be justified.
c. Unchanged continuation of an inadequate (standard) therapy does not constitute implementation of the ACT if at the time of enrolment, treatment adjustments are still available to optimize treatment.
d. It must be ensured for all patients that any myasthenic crisis and/or critical deterioration is optimally treated. In accordance with the G-BA, it is assumed that the patients are not candidates for thymectomy at the time of therapy or that they have already had one.
e. In accordance with the G-BA, it is assumed that the patients are not candidates for escalation therapy and that cyclophosphamide is not a basic therapeutic agent in the present therapeutic indication.
f. It is assumed that patients in both study arms receive guideline-compliant symptomatic therapy with cholinesterase inhibitors as well as basic immunosuppressive therapy, if required. Comparable treatment regimens should be used in the intervention and comparator arms.

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

The company followed the G-BA's specification of the ACT by designating treatment of physician's choice as ACT for research question 1, and eculizumab as ACT for research question 2.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks are used for the derivation of added benefit.

If necessary for better readability, the present benefit assessment uses the following terms for the patient populations of the research questions presented in Table 2:

- Research question 1: patients who are still eligible for standard treatment
- Research question 2: patients with refractory disease

Research question 1: patients who are still eligible for standard treatment

Results

The company identified the RCT ALXN1210-MG-306 (hereafter referred to as CHAMPION) for the direct comparison of ravulizumab with the ACT. The analyses of this study presented by the company are unsuitable for the present benefit assessment, however. This is justified below.

The check for completeness of the study pool identified no additional relevant RCT for the direct comparison of ravulizumab versus the ACT for research question 1.

Evidence presented by the company – CHAMPION study

The CHAMPION study is a randomized, controlled, double-blind phase 3 study of treatment with ravulizumab. The study is divided into a 26-week randomized controlled study phase, followed by an open-label extension phase (up to 2 years).

The study included adult patients with generalized myasthenia gravis who had a Myasthenia Gravis Foundation of America (MGFA) classification II to IV at screening and a Myasthenia Gravis-Activities of Daily Living (MG-ADL) score of ≥ 6 at study start. The diagnosis had to be made at least 6 months before screening and be confirmed by a positive serologic test for anti-AChR antibodies at screening, among other things.

The CHAMPION study included a total of 175 patients who were randomly allocated in a 1:1 ratio to either treatment with ravulizumab ± background therapy or placebo ± background therapy.

In the intervention arm, administration of ravulizumab was as a weight-based initial dosing on day 1, followed by weight-based maintenance doses every 8 weeks from day 15. To maintain

blinding, patients in the comparator arm received placebo. Treatment with ravulizumab is in compliance with the dosing regimen specified in the Summary of Product Characteristics (SPC). However, the administration of ravulizumab as an add-on to standard therapy for generalized myasthenia gravis was not mandatory according to the planning of the study.

Patients who were receiving treatment with cholinesterase inhibitors, immunosuppressants (azathioprine, mycophenolate mofetil, methotrexate, ciclosporin, tacrolimus, cyclophosphamide) and/or oral corticosteroids before study start, had to maintain this treatment as stable background therapy in the study. Drug-specific specifications for the duration of pretreatment and the duration of stable dosing of the prior therapy before the start of the study had to be adhered to. For cholinesterase inhibitors, adjustments to the dose or schedule were only possible if there was compelling medical need, but dosing had to be returned to stable dosing levels from before study entry as soon as feasible. For immunosuppressants including oral corticosteroids, adjustments to the dose or schedule were not allowed during the randomized controlled study phase. Addition of drugs that were not administered at the start of the study or a change of drugs was not permitted during the randomized controlled study phase.

The primary outcome was the change from baseline in MG-ADL total score at week 26.

Approach of the company

The company used a subpopulation of the CHAMPION study, which the company considered to include patients with non-refractory disease (hereinafter referred to as non-refractory subpopulation) for the derivation of the added benefit of ravulizumab in comparison with the ACT for patients with anti-AChR antibody-positive generalized myasthenia gravis who are still eligible for standard treatment. In the non-refractory subpopulation, the company considered patients who were treated with only one immunosuppressant and did not receive chronic treatment (at least every 3 months) with intravenous immunoglobulins or plasmapheresis/plasma exchange, or who did not receive an immunosuppressant within the last 12 months before screening. Immunosuppressants included corticosteroids, azathioprine, mycophenolate mofetil, ciclosporin, tacrolimus, methotrexate, and cyclophosphamide or rituximab in pretreatment. Based on this definition, the company assigned a total of 66 patients to the non-refractory subpopulation (38% of the study population; intervention arm: n = 37; comparator arm: n = 29).

Data presented by the company are unsuitable for the benefit assessment

Implementation of the appropriate comparator therapy is unclear

The G-BA designated treatment of physician's choice as ACT for patients with anti-AChR antibody-positive generalized myasthenia gravis who are still eligible for standard treatment. Cholinesterase inhibitors and immunosuppressants such as glucocorticoids, azathioprine,

mycophenolate mofetil, ciclosporin A, methotrexate and tacrolimus are considered suitable comparators. According to the G-BA, in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision (multicomparator study). The choice and, if necessary, limitation of treatment options must be justified. According to the G-BA, unchanged continuation of an inadequate (standard) therapy does not constitute implementation of the ACT if at the time of enrolment, treatment adjustments are still available to optimize treatment.

Patient-specific treatment optimization is not provided for in the study

Although treatment with cholinesterase inhibitors and immunosuppressants (including oral corticosteroids) was a possible background therapy in the CHAMPION study, this was only possible if the patients had already received the drug(s) before the start of the study and in stable dosing. Addition of drugs that were not administered at the start of the study or a change of drugs was not permitted during the randomized controlled study phase. According to the planning of the study, optimization of background therapy was not planned at the start of the study either. Thus, a selection of several treatment options to permit an individualized treatment decision of physician's choice in the sense of the ACT was therefore not available in the study. Dose adjustments to optimize treatment was also not provided for in the study.

Available data call into question the adequate implementation of the appropriate comparator therapy

The company presented information on the patients' pretreatment, on background therapy at study start and on treatment adjustments during the course of the study only for the study population, but not for the subpopulation used for research question 1 (intervention arm: n = 37; comparator arm: n = 29). This means that the implementation of the ACT cannot be assessed for the subpopulation submitted by the company. However, the data available for the study population (intervention arm: n = 86; comparator arm: n = 89) of the CHAMPION study call into question the adequate implementation of the ACT for the subpopulation used by the company.

Against the background of the available information on the study population, it can be assumed that a relevant proportion either did not receive any of the drugs comprised by the ACT of the G-BA or only received symptomatic treatment with cholinesterase inhibitors. The company did not discuss in the dossier to what extent this can be considered an adequate implementation of the ACT for the subpopulation of patients with non-refractory disease in the study. Independent of symptomatic treatment with cholinesterase inhibitors, the administration of glucocorticoids in combination with steroid-sparing azathioprine is a common treatment in the present therapeutic indication. It is not clear from the available data why a certain treatment (e.g. with immunosuppressants) or an optimization of the

administered drugs (e.g. due to a lack of response or intolerance) was possibly not an option for the patients in the study population or the non-refractory subpopulation.

However, as described above and taking into account the average MG-ADL scores of about 9 to 10 points at baseline, patients with non-refractory disease who, according to the company, were considered in the subpopulation used by the company, can be assumed to still have options for further treatment optimization. It can therefore be assumed for the present benefit assessment that further treatment optimization might have achieved better symptomatic control at least in part of the population presented by the company. Overall, however, treatment adjustments by means of dose adjustments or addition of new drugs were only performed in individual cases in the course of the randomized controlled study phase.

In summary, on the basis of the information submitted by the company, it is questionable whether the patients in the non-refractory subpopulation continued an inadequate therapy or whether at the time of enrolment, it would have been possible to adjust treatment to achieve treatment optimization. Thus, it remains unclear whether the background therapy administered to these patients in the comparator arm was an implementation of a treatment of physician's choice according to the ACT specified by the G-BA. Overall, the available data suggest potential undertreatment in the comparator arm of the CHAMPION study. Thus, the results presented by the company for research question 1 on outcomes in the morbidity category have a risk of bias in favour of ravulizumab. For example, the observed effects for the morbidity outcome of MG-ADL (in the relevant operationalization: improvement by ≥ 4 points corresponding to 15% of the scale range) are not of a clear order of magnitude and could thus potentially have resulted solely from undertreatment in the comparator arm.

Results on added benefit

As no suitable data are available for the benefit assessment for adult patients with anti-AChR antibody-positive generalized myasthenia gravis who are still eligible for standard treatment, there is no hint of an added benefit of ravulizumab in comparison with the ACT; an added benefit is therefore not proven for this research question.

Research question 2: patients with refractory disease

Results

Concurring with the company, no study with a direct comparison of ravulizumab versus eculizumab for research question 2 was identified from the check of completeness of the study pool.

In the dossier, the company therefore presented an indirect comparison for the assessment of ravulizumab versus eculizumab based on the CHAMPION study on ravulizumab identified by the company and the ECU-MG-301 study (hereafter referred to as REGAIN) on eculizumab.

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

The data presented by the company are unsuitable for assessing the added benefit of ravulizumab in comparison with the ACT. This is justified below.

Evidence presented by the company – indirect comparison based on the studies CHAMPION and REGAIN

CHAMPION study

The CHAMPION study was also used by the company to assess the added benefit for research question 1 and was already described in the previous section of this benefit assessment.

Study REGAIN

The REGAIN study is a randomized, controlled, double-blind phase 3 study of treatment with eculizumab for 26 weeks.

The study included adult patients with refractory generalized myasthenia gravis who had an MGFA classification II to IV at screening and an MG-ADL score of ≥ 6 at study start. The diagnosis had to be confirmed by a positive serologic test for anti-AChR antibodies at screening, among other things.

Patients had to have refractory disease, defined as follows according to the study protocol:

- failed treatment over ≥ 1 year with ≥ 2 immunosuppressants (either in combination or as monotherapy), i.e. continued impairment of activities of daily living (persistent weakness, experienced crisis, or unable to tolerate immunosuppressive therapies) despite immunosuppressants

  or

- ≥ 1 failed treatment with immunosuppressants and required chronic plasmapheresis/chronic plasma exchange or chronic intravenous immunoglobulin to control muscle weakness, i.e. regular treatment at least every 3 months over the previous 12 months

Immunosuppressants included, but were not limited to, corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, ciclosporin, tacrolimus or cyclophosphamide.

The REGAIN study included a total of 126 patients who were randomly allocated in a 1:1 ratio to either treatment with eculizumab ± background therapy or placebo ± background therapy.

In the intervention arm, treatment with eculizumab was by administration of an initial dose followed by a maintenance dose. To maintain blinding, patients in the comparator arm received placebo. Treatment with eculizumab is in compliance with the requirements of the SPC.

Patients who were receiving treatment with cholinesterase inhibitors, immunosuppressants (azathioprine, mycophenolate mofetil, methotrexate, ciclosporin, tacrolimus, cyclophosphamide) and/or oral corticosteroids before study start, had to maintain this treatment as stable background therapy in the study. Drug-specific specifications for the duration of pretreatment and the duration of stable dosing of the prior therapy before the start of the study had to be adhered to. For cholinesterase inhibitors, adjustments to the dose or schedule were only possible if there was compelling medical need, but dosing had to be returned to stable dosing levels from before study entry as soon as feasible. For immunosuppressants including oral corticosteroids, adjustments to the dose or schedule were not allowed during the randomized controlled study phase. Addition of drugs that were not administered at the start of the study or a change of drugs was not permitted during the randomized controlled study phase.

The primary outcome was the change from baseline in MG-ADL total score at week 26.

Approach of the company

In Module 4 A of the dossier, the company presented results from an indirect comparison of ravulizumab with eculizumab. For this comparison, the underlying effects in the studies on intervention and comparator therapy were calculated based on weighted individual patient data using the propensity score-based inverse probability weighting (IPW) method, before calculating the treatment effect. Subsequently, an indirect comparison was carried out using placebo as common comparator. In addition, Module 5 of the dossier contains 2 further analyses on the indirect comparison using placebo as common comparator: In one analysis, the underlying effects in the study with the intervention were calculated based on weighted individual patient data using the matching-adjusted indirect comparison (MAIC) method, before calculating the treatment effect. In the other analysis, the individual patient data were not weighted (referred to as “unadjusted” by the company) before calculating the treatment effect. For all analyses presented, the company used the study populations of the studies CHAMPION and REGAIN on the side of the intervention and the comparator therapy.

Data presented by the company are unsuitable for the benefit assessment

The analyses presented by the company are not suitable for deriving conclusions on the added benefit of ravulizumab in comparison with eculizumab for research question 2 of the present

benefit assessment. This is due to the fact that on the intervention side, in contrast to the comparator side, a relevant number of patients with non-refractory disease, who are not comprised by the present research question 2, were also included. This results in differences between the study populations in terms of refractoriness, as will be explained in more detail below. However, this characteristic is not taken into account in any of the analyses of the company.

Indirect comparison includes a relevant number of patients with non-refractory disease on the side of the intervention

For the indirect comparison of ravulizumab versus eculizumab using placebo as common comparator, the company used the study population of the studies CHAMPION or REGAIN on both sides of the comparison for its analyses. According to the inclusion criteria, the study population of the REGAIN study on treatment with eculizumab includes only patients with anti-AChR antibody-positive refractory generalized myasthenia gravis. In the CHAMPION study, however, there was no restriction regarding the refractoriness of the disease according to the inclusion and exclusion criteria. The study population of the CHAMPION study – in accordance with the procedure of the company for research question 1 – includes a relevant number of patients (38%) with non-refractory generalized myasthenia gravis. Thus, on the one hand, the study population does not represent the patient population according to research question 2. On the other, it cannot be assumed that there is sufficient similarity between the patients in the 2 studies of the indirect comparison. Irrespective of whether the methodological approach of the company in calculating the indirect comparisons is appropriate, the differences in the populations with regard to refractoriness were not taken into account in any of the analyses presented.

Results on added benefit

As no suitable data are available for the benefit assessment for adult patients with anti-AChR antibody-positive refractory generalized myasthenia gravis, there is no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven for this research question.

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

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

Table 3: Ravulizumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with anti-AChR antibody-positive generalized myasthenia gravis who are still eligible for standard treatment	Treatment of physician's choice[b, c, d]	Added benefit not proven
2	Adults with anti-AChR antibody-positive refractory generalized myasthenia gravis	Eculizumab[d, e, f]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. Various treatment options are mentioned in the present guidelines. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended in the guideline and used in practice. In accordance with the G-BA, the following therapies are considered suitable comparators for the treatment of physician's choice within the framework of a clinical study: cholinesterase inhibitors and immunosuppressants such as glucocorticoids, azathioprine, mycophenolate mofetil, ciclosporin A, methotrexate, and tacrolimus. In a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision (multicomparator study). The choice and, if necessary, limitation of treatment options must be justified.
c. Unchanged continuation of an inadequate (standard) therapy does not constitute implementation of the ACT if at the time of enrolment, treatment adjustments are still available to optimize treatment.
d. It must be ensured for all patients that any myasthenic crisis and/or critical deterioration is optimally treated. In accordance with the G-BA, it is assumed that the patients are not candidates for thymectomy at the time of therapy or that they have already had one.
e. In accordance with the G-BA, it is assumed that the patients are not candidates for escalation therapy and that cyclophosphamide is not a basic therapeutic agent in the present therapeutic indication.
f. It is assumed that patients in both study arms receive guideline-compliant symptomatic therapy with cholinesterase inhibitors as well as basic immunosuppressive therapy, if required. Comparable treatment regimens should be used in the intervention and comparator arms.

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

The G-BA decides on the added benefit.

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

I 2 Research question

The aim of the present report is to assess the added benefit of ravulizumab as an add-on to standard therapy for the treatment of adult patients with generalized myasthenia gravis who are anti-AChR antibody-positive.

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

Table 4: Research questions of the benefit assessment of ravulizumab

Research question	Therapeutic indication	ACT[a]
1	Adults with anti-AChR antibody-positive generalized myasthenia gravis who are still eligible for standard treatment	Treatment of physician's choice[b, c, d]
2	Adults with anti-AChR antibody-positive refractory generalized myasthenia gravis	Eculizumab[d, e, f]

a. Presented is the respective ACT specified by the G-BA.
b. Various treatment options are mentioned in the present guidelines. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended in the guideline and used in practice. In accordance with the G-BA, the following therapies are considered suitable comparators for the treatment of physician's choice within the framework of a clinical study: cholinesterase inhibitors and immunosuppressants such as glucocorticoids, azathioprine, mycophenolate mofetil, ciclosporin A, methotrexate, and tacrolimus. In a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision (multicomparator study). The choice and, if necessary, limitation of treatment options must be justified.
c. Unchanged continuation of an inadequate (standard) therapy does not constitute implementation of the ACT if at the time of enrolment, treatment adjustments are still available to optimize treatment.
d. It must be ensured for all patients that any myasthenic crisis and/or critical deterioration is optimally treated. In accordance with the G-BA, it is assumed that the patients are not candidates for thymectomy at the time of therapy or that they have already had one.
e. In accordance with the G-BA, it is assumed that the patients are not candidates for escalation therapy and that cyclophosphamide is not a basic therapeutic agent in the present therapeutic indication.
f. It is assumed that patients in both study arms receive guideline-compliant symptomatic therapy with cholinesterase inhibitors as well as basic immunosuppressive therapy, if required. Comparable treatment regimens should be used in the intervention and comparator arms.

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

The company followed the G-BA's specification of the ACT by designating treatment of physician's choice as ACT for research question 1, and eculizumab as ACT for research question 2.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks are used for the derivation of added benefit. This corresponds to the inclusion criteria of the company, which also considered RCTs in its information retrieval (with a slightly different minimum duration of 26 weeks). Although the company also searched for other study types for the

intervention, this remains without consequence, as the company only identified RCTs, which it considered for its assessment.

If necessary for better readability, the present benefit assessment uses the following terms for the patient populations of the research questions presented in Table 4:

- Research question 1: patients who are still eligible for standard treatment
- Research question 2: patients with refractory disease

I 3 Research question 1: patients who are still eligible for standard treatment

I 3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on ravulizumab (status: 2 September 2022)
- bibliographical literature search on ravulizumab (last search on 25 August 2022)
- search in trial registries/trial results databases for studies on ravulizumab (last search on 2 September 2022)
- search on the G-BA website for ravulizumab (last search on 2 September 2022)

To check the completeness of the study pool:

- search in trial registries for studies on ravulizumab (last search on 18 November 2022); for search strategies, see I Appendix A of the full dossier assessment

The company identified the RCT ALXN1210-MG-306 [3-7] (hereafter referred to as CHAMPION) for the direct comparison of ravulizumab with the ACT. The analyses of this study presented by the company are unsuitable for the present benefit assessment, however. This is particularly due to the fact that the information submitted by the company fails to show that the background therapy administered in the study's comparator arm was an implementation of the G-BA's specified ACT of treatment of physician's choice (for a detailed justification, see sections below).

The check for completeness of the study pool identified no additional relevant RCT for the direct comparison of ravulizumab versus the ACT for research question 1.

I 3.1.1 Evidence provided by the company

CHAMPION study

The CHAMPION study is a randomized, controlled, double-blind phase 3 study of treatment with ravulizumab (see Table 6 in I Appendix B of the full dossier assessment). The study is divided into a 26-week randomized controlled study phase, followed by an open-label extension phase (up to 2 years).

The study included adult patients with generalized myasthenia gravis who had an MGFA classification II to IV at screening and an MG-ADL score of ≥ 6 at study start. The diagnosis had to be made at least 6 months before screening and be confirmed by a positive serologic test for anti-AChR antibodies at screening. In addition, one of the following criteria had to be met:

- abnormal neuromuscular transmission test (demonstrated by single-fibre electromyography or repetitive electromyography),
- positive anticholinesterase test (e.g. edrophonium test), or
- demonstrated improvement in symptoms on oral cholinesterase inhibitors, as assessed by the treating physician.

Vaccination against meningococcal infections within the 3 years prior to, or at the time of, initiating study drug was required. If the vaccination was within 2 weeks before the first administration of the study drug, adequate antibiotic prophylaxis had to be given up to 2 weeks after vaccination. Patients were not allowed to have a history of thymectomy, thymomectomy, or any thymic surgery within the 12 months prior to screening. Patients who were receiving background therapy with immunosuppressants, oral corticosteroids or cholinesterase inhibitors at study start had be on this treatment on a stable dose for a certain period depending on the drug and to maintain it on stable dosing in the study.

The CHAMPION study included a total of 175 patients who were randomly allocated in a 1:1 ratio to either treatment with ravulizumab ± background therapy (N = 86) or placebo ± background therapy (N = 89). Randomization was stratified by region (North America, Europe, Asia-Pacific and Japan).

In the intervention arm, administration of ravulizumab was as a weight-based initial dosing on day 1, followed by weight-based maintenance doses every 8 weeks from day 15. To maintain blinding, patients in the comparator arm received placebo. Treatment with ravulizumab is in compliance with the dosing regimen specified in the SPC [8]. However, the administration of ravulizumab as an add-on to standard therapy for generalized myasthenia gravis was not mandatory according to the planning of the study.

Patients who were receiving treatment with cholinesterase inhibitors, immunosuppressants (azathioprine, mycophenolate mofetil, methotrexate, ciclosporin, tacrolimus, cyclophosphamide) and/or oral corticosteroids before study start, had to maintain this treatment as stable background therapy in the study. Drug-specific specifications for the duration of pretreatment and the duration of stable dosing of the prior therapy before the start of the study had to be adhered to (for details, see Table 7 in I Appendix B of the full dossier assessment). For cholinesterase inhibitors, adjustments to the dose or schedule were only possible if there was compelling medical need, but dosing had to be returned to stable dosing levels from before study entry as soon as feasible. For immunosuppressants including oral corticosteroids, adjustments to the dose or schedule were not allowed during the randomized controlled study phase. However, if adjustments were to be made, for example due to toxicity, sponsor approval had to be obtained prior to the adjustment. Addition of drugs that were not administered at the start of the study or a change of drugs was not permitted

during the randomized controlled study phase. Treatment with rituximab, eculizumab (or other complement inhibitors) as well as chronic plasmapheresis/chronic plasma exchange or chronic administration of intravenous immunoglobulins were also not allowed. If patients experienced clinical deterioration as defined in the study protocol in the course of the study, however, rescue therapy (e.g. high-dose corticosteroids, plasma exchange/plasmapheresis or intravenous immunoglobulin) at the discretion of the investigator was allowed. In this case, additional administration of the study medication may have been necessary (for details see Table 7 in I Appendix B of the full dossier assessment).

After completion of the randomized controlled 26-week treatment phase, patients in the intervention and comparator arms could participate in the open-label extension phase of the study, where ravulizumab was administered to all patients.

The primary outcome was the change from baseline in MG-ADL total score at week 26. Further patient-relevant outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

Further information on the CHAMPION study characteristics, the intervention used, and the included patients are found in I Appendix B of the full benefit assessment.

Approach of the company

The company used a subpopulation of the CHAMPION study, which the company considered to include patients with non-refractory disease (hereinafter referred to as non-refractory subpopulation) for the derivation of the added benefit of ravulizumab in comparison with the ACT for patients with anti-AChR antibody-positive generalized myasthenia gravis who are still eligible for standard treatment. In the non-refractory subpopulation, the company considered patients who were treated with only one immunosuppressant and did not receive chronic treatment (at least every 3 months) with intravenous immunoglobulins or plasmapheresis/plasma exchange, or who did not receive an immunosuppressant within the last 12 months before screening. Immunosuppressants included corticosteroids, azathioprine, mycophenolate mofetil, ciclosporin, tacrolimus, methotrexate, and cyclophosphamide or rituximab in pretreatment. Based on this definition, the company assigned a total of 66 patients to the non-refractory subpopulation (38% of the study population; intervention arm: n = 37; comparator arm: n = 29).

Information on the characteristics of the patients in the non-refractory subpopulation of the CHAMPION study as well as information on the characteristics of the study population can be found in Table 8 in I Appendix B of the full benefit assessment.

I 3.1.2 Assessment of the evidence presented by the company

The analyses presented by the company for the non-refractory subpopulation of the CHAMPION study are not suitable for deriving conclusions on the added benefit of ravulizumab in comparison with the ACT for research question 1 of the present benefit assessment. This is particularly due to the fact that the information submitted by the company fails to show that the background therapy administered in the study's comparator arm was an implementation of the G-BA's specified ACT of treatment of physician's choice. This is further explained below.

Implementation of the appropriate comparator therapy is unclear

The G-BA designated treatment of physician's choice as ACT for patients with anti-AChR antibody-positive generalized myasthenia gravis who are still eligible for standard treatment. Cholinesterase inhibitors and immunosuppressants such as glucocorticoids, azathioprine, mycophenolate mofetil, ciclosporin A, methotrexate and tacrolimus are considered suitable comparators. According to the G-BA, in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision (multicomparator study). The choice and, if necessary, limitation of treatment options must be justified. According to the G-BA, unchanged continuation of an inadequate (standard) therapy does not constitute implementation of the ACT if at the time of enrolment, treatment adjustments are still available to optimize treatment.

Patient-specific treatment optimization is not provided for in the study

Although treatment with cholinesterase inhibitors and immunosuppressants (including oral corticosteroids) was a possible background therapy in the CHAMPION study, this was only possible if the patients had already received the drug(s) before the start of the study and in stable dosing (see Table 7 in I Appendix B of the full dossier assessment). As described in Section I 3.1.1, addition of drugs that were not administered at the start of the study or a change of drugs was not permitted during the randomized controlled study phase. According to the planning of the study, optimization of background therapy was not planned at the start of the study either. Thus, a selection of several treatment options to permit an individualized treatment decision of physician's choice in the sense of the ACT was therefore not available in the study. Dose adjustments to optimize treatment was also not provided for in the study.

Available data call into question the adequate implementation of the appropriate comparator therapy

The company presented information on the patients' pretreatment, on background therapy at study start and on treatment adjustments during the course of the study only for the study population, but not for the subpopulation used for research question 1 (intervention arm:

n = 37; comparator arm: n = 29; see Table 9 and Table 10 in I Appendix B of the full dossier assessment). This means that the implementation of the ACT cannot be assessed for the subpopulation submitted by the company. However, the data available for the study population (intervention arm: n = 86; comparator arm: n = 89) of the CHAMPION study call into question the adequate implementation of the ACT for the subpopulation used by the company. This is explained below.

At study start, 76 patients of the study population in the intervention arm and 81 patients in the comparator arm were receiving at least one immunosuppressant, with corticosteroids, mycophenolate mofetil and azathioprine being the most common. In contrast, 10 patients in the intervention arm and 8 patients of the study population in the comparator arm of the CHAMPION study were not receiving an immunosuppressant at study start (see Table 9 in I Appendix B of the full dossier assessment). According to the company's definition of non-refractory generalized myasthenia gravis (see Section I 3.1.1), it can be assumed that these patients are included in the subpopulation used for research question 1. Under this assumption, the patient group without immunosuppressive therapy would represent about 1 third of the non-refractory subpopulation (27% in the intervention arm and 28% in the comparator arm). 84% of patients in the intervention arm and 79% of patients in the comparator arm were receiving cholinesterase inhibitors, especially pyridostigmine (bromide), as concomitant medication at study start. The proportion of patients in the subpopulation who had concomitant treatment with cholinesterase inhibitors at study start remains unclear.

Overall, on the basis of the available data, it remains unclear how many patients in the subpopulation received drugs at study start that are considered suitable comparators in the context of treatment of physician's choice in accordance with the G-BA. Against the background of the available information on the study population, it can be assumed that a relevant proportion either did not receive any of the drugs comprised by the ACT of the G-BA or only received symptomatic treatment with cholinesterase inhibitors, however. The company did not discuss in the dossier to what extent this can be considered an adequate implementation of the ACT for the subpopulation of patients with non-refractory disease in the study. Independent of symptomatic treatment with cholinesterase inhibitors, the administration of glucocorticoids in combination with steroid-sparing azathioprine is a common treatment in the present therapeutic indication [9,10]. It is not clear from the available data why a certain treatment (e.g. with immunosuppressants) or an optimization of the administered drugs (e.g. due to a lack of response or intolerance) was possibly not an option for the patients in the study population or in the non-refractory subpopulation. The dossier also contains no subgroup analyses on patients with or without therapy with immunosuppressants, which could be considered as an approximation in the present benefit assessment. In the context of the approval procedure for ravulizumab, such analyses were

also requested by the European Medicines Agency (EMA) [11], but were not submitted by the company.

However, for patients with non-refractory disease who, according to the company, are considered in the subpopulation formed by the company, it can be assumed, as described above, that in principle there are still options for further treatment optimization, especially if this is based exclusively on symptomatic therapy with cholinesterase inhibitors without the use of immunosuppressive therapy. It also remains unclear for patients in the subpopulation who were receiving immunosuppressive therapy at study start, whether treatment in the comparator arm of the study could have been optimized further by treatment adjustments (e.g. the addition of a drug). The mean baseline MG-ADL score of about 9 to 10 points in the non-refractory subpopulation suggests that the majority of patients with non-refractory disease did not have mild symptoms. It can therefore be assumed for the present benefit assessment that further treatment optimization might have achieved better symptomatic control at least in part of the population presented by the company. Overall, however, only few patients in the study population had their treatment adjusted in the course of the randomized controlled study phase (see Table 10 in I Appendix B of the full dossier assessment). In accordance with the requirements of the planning of the study, the addition of new drugs or dose adjustments were performed only in individual cases. During the randomized controlled study phase, more patients in the comparator arm than in the intervention arm received rescue therapy for clinical deterioration as defined in the study protocol (intervention arm vs. comparator arm, non-refractory subpopulation presented by the company: 1 [3%] vs. 5 [17%], study population: 8 [9%] vs. 14 [16%]).

In summary, on the basis of the information submitted by the company, it is questionable whether the patients in the non-refractory subpopulation continued an inadequate therapy or whether at the time of enrolment, it would have been possible to adjust treatment to achieve treatment optimization. Thus, it remains unclear whether the background therapy administered to these patients in the comparator arm was an implementation of a treatment of physician's choice according to the ACT specified by the G-BA. In particular, the subpopulation used by the company for research question 1 could include a relevant number of patients who might have benefited from treatment optimization. For example, the addition of an immunosuppressant could have optimized treatment for patients who were not receiving an immunosuppressant at the start of the study. It remains unclear also for the group of patients who were already receiving one immunosuppressant to what extent optimization would have been possible by adding a second drug, for example. As described above, the administration of glucocorticoids in combination with steroid-sparing azathioprine, i.e. the administration of 2 immunosuppressants, is a common treatment in the present therapeutic indication [9,10]. Overall, the available data suggest potential undertreatment in the comparator arm of the CHAMPION study. Thus, the results presented by the company for

research question 1 on outcomes in the morbidity category have a risk of bias in favour of ravulizumab. For example, the observed effects for the morbidity outcome of MG-ADL (in the relevant operationalization: improvement by ≥ 4 points corresponding to 15% of the scale range [1]) are not of a clear order of magnitude and could thus potentially have resulted solely from undertreatment in the comparator arm.

Further limitations of the data presented by the company

Irrespective of the fact that the analyses of the CHAMPION study presented by the company are not suitable for the benefit assessment for the reasons described above, there is the following uncertainty regarding the patient population formed by the company:

Even though there is no uniform definition of a refractory disease in the literature on generalized myasthenia gravis, several publications [12-16], which are also partly referred to by the company in the dossier, cite a lack of response to prior therapies for the definition of refractory disease. Lack of response to immunosuppressive therapies was also part of the inclusion criteria in the REGAIN study (see Section I 4.1.1), on the basis of which eculizumab was approved for patients with refractory generalized myasthenia gravis [17,18].

According to the information provided by the company in Module 4 A, it excluded patients with refractory disease from the subpopulation for research question 1 on the basis of the inclusion criteria of the REGAIN study in order to define patients with non-refractory disease in the study population of the CHAMPION study. However, it is unclear to what extent information on the response to previous immunosuppressive therapies was actually taken into account by the company when forming the non-refractory subpopulation. According to information in the additional analyses for the dossier [7], the company applied a definition for the formation of the subpopulation for research question 1 that only takes into account whether or how many immunosuppressants the patients received and whether they had chronic treatment with intravenous immunoglobulins or plasmapheresis/plasma exchange (see also Section I 3.1.1). The company did not provide any information on prior and concomitant treatments for the non-refractory subpopulation of the CHAMPION study formed by the company, or on the patients excluded due to refractory disease.

Overall, it is therefore unclear whether the non-refractory subpopulation formed by the company represents the population according to research question 1.

I 3.2 Results on added benefit

The company presented no suitable data for the assessment of the added benefit in comparison with the ACT for adult patients with anti-AChR antibody-positive generalized myasthenia gravis who are still eligible for standard treatment. There is no hint of an added

benefit of ravulizumab in comparison with the ACT; an added benefit is therefore not proven for this research question.

I 3.3 Probability and extent of added benefit

As no suitable data are available for the assessment of the added benefit of ravulizumab compared with the ACT in adult patients with anti-AChR antibody-positive generalized myasthenia gravis who are still eligible for standard treatment, an added benefit of ravulizumab for research question 1 is not proven.

This deviates from the company's assessment, which derived an indication of a considerable added benefit of ravulizumab versus the ACT for research question 1.

I 4 Research question 2: patients with refractory disease

I 4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on ravulizumab (status: 2 September 2022)
- bibliographical literature search on ravulizumab (last search on 25 August 2022)
- search in trial registries/trial results databases for studies on ravulizumab (last search on 2 September 2022)
- search on the G-BA website for ravulizumab (last search on 2 September 2022)
- study list on the ACT (status: 2 September 2022)
- bibliographical literature search on the ACT (last search on 25 August 2022)
- search in trial registries/trial results databases for studies on the ACT (last search on 2 September 2022)
- search on the G-BA website for the ACT (last search on 2 September 2022)

To check the completeness of the study pool:

- search in trial registries for studies on ravulizumab (last search on 18 November 2022); for search strategies, see I Appendix A of the full dossier assessment
- search in trial registries for studies on eculizumab (last search on 18 November 2022); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, no study with a direct comparison of ravulizumab versus eculizumab for research question 2 was identified from the check of completeness of the study pool.

In the dossier, the company therefore presented an indirect comparison for the assessment of ravulizumab versus eculizumab based on the CHAMPION study on ravulizumab identified by the company (see also Section I 3) and the ECU-MG-301 study [19-23] (hereafter referred to as REGAIN) on eculizumab.

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

The data presented by the company are unsuitable for assessing the added benefit of ravulizumab in comparison with the ACT. This is due to the fact that on the intervention side,

in contrast to the comparator side, a relevant number of patients with non-refractory disease, who are not comprised by the present research question 2, were also included. This results in differences between the study populations in terms of refractoriness. However, this characteristic is not taken into account in any of the analyses of the company. This is explained in more detail in the following sections.

I 4.1.1 Evidence provided by the company

CHAMPION study

The CHAMPION study was also used by the company to assess the added benefit for research question 1 and was already described in Section I 3.1.1.

Further information on the CHAMPION study characteristics, the intervention used, and the included patients are found in I Appendix B of the full benefit assessment.

Study REGAIN

The REGAIN study is a randomized, controlled, double-blind phase 3 study of treatment with eculizumab for 26 weeks (see Table 6 in I Appendix B of the full dossier assessment).

The study included adult patients with refractory generalized myasthenia gravis who had an MGFA classification II to IV at screening and an MG-ADL score of ≥ 6 at study start. The diagnosis had to be confirmed by a positive serologic test for anti-AChR antibodies at screening. In addition, one of the following criteria had to be met:

- abnormal neuromuscular transmission test (demonstrated by single-fibre electromyography or repetitive electromyography),
- positive anticholinesterase test (e.g. edrophonium test), or
- demonstrated improvement in symptoms on oral cholinesterase inhibitors, as assessed by the treating physician.

Vaccination against meningococcal infections no later than 14 days prior to initiating study drug was required. If the vaccination was within 2 weeks before the first administration of the study drug, adequate antibiotic prophylaxis had to be given up to 2 weeks after vaccination. Patients were not allowed to have a history of thymectomy within the 12 months prior to screening. Patients who were receiving background therapy with immunosuppressants, oral corticosteroids or cholinesterase inhibitors at study start had be on this treatment on a stable dose for a certain period depending on the drug and to maintain it on stable dosing in the study.

Patients had to have refractory disease, defined as follows according to the study protocol:

- failed treatment over ≥ 1 year with ≥ 2 immunosuppressants (either in combination or as monotherapy), i.e. continued impairment of activities of daily living (persistent weakness, experienced crisis, or unable to tolerate immunosuppressive therapies) despite immunosuppressants

  or

- ≥ 1 failed treatment with immunosuppressants and required chronic plasmapheresis/chronic plasma exchange or chronic intravenous immunoglobulin to control muscle weakness, i.e. regular treatment at least every 3 months over the previous 12 months

Immunosuppressants included, but were not limited to, corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, ciclosporin, tacrolimus or cyclophosphamide.

The REGAIN study included a total of 126 patients who were randomly allocated in a 1:1 ratio to either treatment with eculizumab ± background therapy (N = 63) or placebo ± background therapy (N = 63). Randomization was stratified by MGFA group (IIa/IIIa, IVa, IIb/IIIb, IVb).

In the intervention arm, treatment with eculizumab was by administration of an initial dose (900 mg once weekly for 4 weeks, then 1200 mg in week 5), followed by maintenance doses (1200 mg every 2 weeks). To maintain blinding, patients in the comparator arm received placebo. Treatment with eculizumab is in compliance with the requirements of the SPC [18].

Patients who were receiving treatment with cholinesterase inhibitors, immunosuppressants (azathioprine, mycophenolate mofetil, methotrexate, ciclosporin, tacrolimus, cyclophosphamide) and/or oral corticosteroids before study start, had to maintain this treatment as stable background therapy in the study. Drug-specific specifications for the duration of pretreatment and the duration of stable dosing of the prior therapy before the start of the study had to be adhered to (for details, see Table 7 in I Appendix B of the full dossier assessment). For cholinesterase inhibitors, adjustments to the dose or schedule were only possible if there was compelling medical need, but dosing had to be returned to stable dosing levels from before study entry as soon as feasible. For immunosuppressants including oral corticosteroids, adjustments to the dose or schedule were not allowed during the randomized controlled study phase. However, if adjustments were to be made, for example due to toxicity, sponsor approval had to be obtained prior to the adjustment. Addition of drugs that were not administered at the start of the study or a change of drugs was not permitted during the randomized controlled study phase. Treatment with rituximab was also not allowed. If patients experienced clinical deterioration as defined in the study protocol in the course of the study, rescue therapy (e.g. high-dose corticosteroids, plasma exchange/plasmapheresis or intravenous immunoglobulin) at the discretion of the treating

physician was allowed. In this case, additional administration of the study medication may have been necessary (for details see Table 7 in I Appendix B of the full dossier assessment).

Following the 26-week treatment, patients had the option of participating in an open-label extension phase as part of the ECU-MG-302 study.

The primary outcome was the change from baseline in MG-ADL total score at week 26. Further patient-relevant outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

Further information on the REGAIN study characteristics and the intervention used in the study can be found in I Appendix B of the full benefit assessment.

Approach of the company

In Module 4 A of the dossier, the company presented results from an indirect comparison of ravulizumab with eculizumab. For this comparison, the underlying effects in the studies on intervention and comparator therapy were calculated based on weighted individual patient data using the propensity score-based IPW method, before calculating the treatment effect. Subsequently, an indirect comparison was carried out using placebo as common comparator. In addition, 2 further analyses are available in Module 5 of the dossier [23]: One analysis was an indirect comparison using placebo as common comparator, where the underlying effects in the study with the intervention were calculated based on weighted individual patient data using the MAIC method, before calculating the treatment effect. The other analysis is an indirect comparison using placebo as common comparator, where the individual patient data were not weighted (referred to as “unadjusted” by the company) before calculating the treatment effect. The company stated for all analyses that the indirect comparison was carried out according to the approach by Bucher [24]. For all analyses presented, the company used the study populations of the studies CHAMPION and REGAIN on the side of the intervention and the comparator therapy.

I 4.1.2 Assessment of the evidence presented by the company

The analyses presented by the company are not suitable for deriving conclusions on the added benefit of ravulizumab in comparison with eculizumab for research question 2 of the present benefit assessment. This is due to the fact that on the intervention side, in contrast to the comparator side, a relevant number of patients with non-refractory disease, who are not comprised by the present research question 2, were also included. This results in differences between the study populations in terms of refractoriness, as will be explained in more detail below. However, this characteristic is not taken into account in any of the analyses of the company.

Indirect comparison includes a relevant number of patients with non-refractory disease on the side of the intervention

For the indirect comparison of ravulizumab versus eculizumab using placebo as common comparator, the company used the study population of the studies CHAMPION or REGAIN on both sides of the comparison for its analyses. According to the inclusion criteria, the study population of the REGAIN study on treatment with eculizumab includes only patients with anti-AChR antibody-positive refractory generalized myasthenia gravis (see Section I 4.1.1). In the CHAMPION study, however, there was no restriction regarding the refractoriness of the disease according to the inclusion and exclusion criteria. The study population of the CHAMPION study – in accordance with the procedure of the company for research question 1 – includes a relevant number of patients (38%) with non-refractory generalized myasthenia gravis (see Section I 3.1.1). Thus, on the one hand, the study population does not represent the patient population according to research question 2. On the other, it cannot be assumed that there is sufficient similarity between the patients in the 2 studies of the indirect comparison. Irrespective of whether the methodological approach of the company in calculating the indirect comparisons is appropriate, the differences in the populations with regard to refractoriness were not taken into account in any of the analyses presented.

Overall, it is not appropriate that the company, unlike its approach in research question 1 (where it formed a subpopulation of patients with non-refractory disease), did not base its analyses in research question 2 on a subpopulation of patients with refractory disease.

Further deficiencies of the data presented by the company

Irrespective of the fact that the analyses presented by the company on the indirect comparison are not suitable for the benefit assessment for the reasons described above, the company did not adequately prepare the analyses in Module 4 A as well as in Module 5 of the dossier.

In none of the analyses described for the indirect comparison of ravulizumab versus eculizumab did the company conduct analyses on outcomes of the category of side effects. In Module 4 A, it only provided a descriptive presentation of the results for the outcomes of the side effects category in the CHAMPION study and the REGAIN study. This approach is not appropriate against the background that the company had individual patient data from both studies and in view of the fact that the studies CHAMPION and REGAIN had a comparable study duration of 26 weeks (for the randomized controlled study phase).

The results presented by the company for the indirect comparison in Module 4 A and in Module 5 of the dossier do not contain any information on the number of patients included in the analyses of the respective outcomes. Furthermore, information on the proportions of patients with events in the respective arms of the individual studies CHAMPION and REGAIN

is missing. The preparation of the results thus does not meet the requirements for the reporting of results according to the dossier template [25].

I 4.2 Results on added benefit

The company presented no suitable data for the assessment of the added benefit in comparison with the ACT for adult patients with anti-AChR antibody-positive refractory generalized myasthenia gravis. There is no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven for this research question.

I 4.3 Probability and extent of added benefit

As no suitable data are available for the assessment of the added benefit of ravulizumab compared with eculizumab in adult patients with anti-AChR antibody-positive refractory generalized myasthenia gravis, an added benefit of ravulizumab for research question 2 is not proven.

This concurs with the assessment of the company, which, based on the indirect comparison using placebo as common comparator presented in Module 4 A of the dossier, concluded for research question 2 that an added benefit of ravulizumab compared with eculizumab is not proven.

I 5 Probability and extent of added benefit – summary

Table 5 summarizes the result of the assessment of the added benefit of ravulizumab in comparison with the ACT.

Table 5 Ravulizumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with anti-AChR antibody-positive generalized myasthenia gravis who are still eligible for standard treatment	Treatment of physician's choice[b, c, d]	Added benefit not proven
2	Adults with anti-AChR antibody-positive refractory generalized myasthenia gravis	Eculizumab[d, e, f]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. Various treatment options are mentioned in the present guidelines. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended in the guideline and used in practice. In accordance with the G-BA, the following therapies are considered suitable comparators for the treatment of physician's choice within the framework of a clinical study: cholinesterase inhibitors and immunosuppressants such as glucocorticoids, azathioprine, mycophenolate mofetil, ciclosporin A, methotrexate, and tacrolimus. In a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision (multicomparator study). The choice and, if necessary, limitation of treatment options must be justified.
c. Unchanged continuation of an inadequate (standard) therapy does not constitute implementation of the ACT if at the time of enrolment, treatment adjustments are still available to optimize treatment.
d. It must be ensured for all patients that any myasthenic crisis and/or critical deterioration is optimally treated. In accordance with the G-BA, it is assumed that the patients are not candidates for thymectomy at the time of therapy or that they have already had one.
e. In accordance with the G-BA, it is assumed that the patients are not candidates for escalation therapy and that cyclophosphamide is not a basic therapeutic agent in the present therapeutic indication.
f. It is assumed that patients in both study arms receive guideline-compliant symptomatic therapy with cholinesterase inhibitors as well as basic immunosuppressive therapy, if required. Comparable treatment regimens should be used in the intervention and comparator arms.

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

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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