Efgartigimod alfa (generalized myasthenia gravis)

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

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

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

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Part I: Benefit assessment

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I List of abbreviations

Abbreviation	Meaning
AChR	anti-acetylcholine receptor
ACT	appropriate comparator therapy
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MG-ADL	Myasthenia Gravis - Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
RCT	randomized controlled trial
RCT	randomized controlled trial
SAE	serious adverse event
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) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug efgartigimod alfa. 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 02 April 2024.

Research question

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

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of efgartigimod alfa

Therapeutic indication	**ACT**[a]
Adults with anti-AChR antibody-positive generalized myasthenia gravis for whom add-on therapy to standard treatment is an option	Eculizumab (for refractory patients) or ravulizumab[b, c]

a. Presented is the ACT specified by the G-BA.
b. In accordance with the G-BA, it is assumed that patients in both study arms receive guideline-compliant therapy with cholinesterase inhibitors as well as basic immunosuppressive therapy, if indicated. It is also assumed that all patients will be provided with supportive measures.
c. It must be ensured that all patients receive optimal treatment in case of any myasthenic crisis and/or critical deterioration. In accordance with the G-BA, it is assumed that the patients are no candidates for thymectomy at the time of therapy or that they have already had one.

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

The company followed the G-BA's specification of the ACT and designated eculizumab (for refractory patients) or ravulizumab as ACT.

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 were used for deriving the added benefit.

Results

Concurring with the company, no studies on the direct comparison of efgartigimod alfa versus the ACT were identified from the check of the completeness of the study pool.

The company therefore presented 2 separate adjusted indirect comparisons according to Bucher for the assessment of efgartigimod alfa versus ravulizumab or eculizumab. It identified the ARGX-113-1704 study (hereinafter referred to as ADAPT for short) for both indirect comparisons on the intervention side. For the indirect comparison with ravulizumab, the company identified the ALXN1210-MG-306 study (hereinafter referred to as CHAMPION for short) on the comparator side and the ECU-MG-301 study (hereinafter referred to as REGAIN for short) for the indirect comparison with eculizumab.

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

Evidence provided by the company

ADAPT study

The ADAPT study is a double-blind, randomized, multicentre study on the treatment with efgartigimod alfa over 26 weeks. The study investigated the comparison of efgartigimod alfa versus placebo, each in addition to standard therapy.

The ADAPT study included adult patients with generalized myasthenia gravis who had a Myasthenia Gravis Foundation of America (MGFA) classification of II to IV. In addition, patients had to have a Myasthenia Gravis - Activities of Daily Living (MG-ADL) score ≥ 5 at screening and at baseline, with more than 50% of the total score being attributable to non-ocular symptoms.

The study included a total of 167 patients who were randomly assigned in a 1:1 ratio to treatment with efgartigimod alfa + standard therapy (or placebo + standard therapy. Patients without anti-AChR antibodies are not covered by the present therapeutic indication. In the dossier, the company presents analyses on the subpopulation of patients with positive anti-AChR antibody status, which comprised 65 patients in the efgartigimod alfa arm and 64 patients in the placebo arm.

Treatment with efgartigimod alfa was largely in compliance with the Summary of Product Characteristics (SPC). Patients included in the study had to receive a standard therapy before the screening and continue to receive it in a stable manner during the study. Standard therapy was limited to cholinesterase inhibitors, corticosteroids and non-steroidal immunosuppressants (e.g. azathioprine, methotrexate, ciclosporin, tacrolimus, mycophenolate mofetil and cyclophosphamide). Adjustment of the dosage or the regimen during the course of the study was not permitted and led to discontinuation of the study medication. If the patients experienced a clinical deterioration as defined in the study protocol during the course of the study, the administration of rescue therapy was possible, but also led to discontinuation of the study medication.

The primary outcome of the ADAPT study was the reduction in the MG-ADL score after the first treatment cycle compared to the start of the cycle.

Individualized treatment cycles in the ADAPT study

The patients in the ADAPT study were treated in treatment cycles, each consisting of a 3-week treatment phase and a subsequent 5-week follow-up phase with close weekly recording of the outcomes.

All patients received an initial treatment cycle with efgartigimod alfa or placebo in addition to the ongoing standard therapy. Further cycles were possible on an individual basis under certain conditions, e.g. with regard to disease activity. In addition, a new treatment cycle had to be started on Day 127 (Week 18) at the latest in order to be completed within the 26-week study phase. Patients who required further treatment after day 127 and were therefore unable to complete the treatment cycle within the 26-week study phase therefore had to enter the ARGX-113-1705 extension study (hereinafter referred to as ADAPT+ for short) early in order to receive a further cycle. All patients in the ADAPT+ study received efgartigimod alfa in individualized treatment cycles.

In both the ADAPT study and the ADAPT+ study, the analyses on the response to therapy planned in accordance with the study design were primarily based on treatment cycles. The focus here was on the assessment of the response at the end of a cycle compared to the start of the cycle, and not on the assessment of the response primarily at the end of the study (Week 26). The primary aim of the ADAPT study was to assess the efficacy of efgartigimod alfa compared to placebo based on the response in the MG-ADL score to the first treatment cycle.

CHAMPION study

The CHAMPION study is a randomized, controlled, double-blind phase 3 study on the treatment with ravulizumab. In the 26-week randomized controlled phase of the study, the comparison of ravulizumab versus placebo was investigated, if applicable each in addition to the existing standard therapy.

The study included adult patients with generalized myasthenia gravis who had a II to IV MGFA classification at the time of screening and an MG-ADL score of ≥ 6 at baseline. For inclusion in the study, a positive serological test for anti-AChR antibodies had to be available at the time of screening.

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

In the intervention arm, treatment with ravulizumab was carried out by administering a weight-dependent initial dose on Day 1, followed by a weight-dependent maintenance dose

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. 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 and/or oral corticosteroids before the start of the study had to continue this treatment in a stable manner during the study. During the study, adjustments of these therapies were only possible under certain conditions, whereby the stable dosage prior to the start of the study was to be returned to as soon as possible. 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.

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

Study REGAIN

The REGAIN study is a randomized, controlled, double-blind phase 3 study comparing eculizumab with placebo, if applicable each in addition to ongoing standard therapy, for 26 weeks.

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

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 chronic plasmapheresis/chronic plasma exchange or chronic intravenous immunoglobulin was required to control muscle weakness, i.e. regular treatment at least every 3 months over the previous 12 months.

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

In the intervention arm, treatment with eculizumab was by administration of an initial dose followed by a maintenance dose 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. The administration of eculizumab as an add-on to standard therapy for generalized myasthenia gravis was not mandatory according to the study planning. Patients who were receiving treatment with cholinesterase inhibitors, immunosuppressants and/or oral corticosteroids before the start of the study had to continue this treatment in a stable manner during the study. During the study, adjustments of these therapies were only possible under certain conditions, whereby the stable dosage prior to the start of the study was to be returned to as soon as possible. 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.

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

Approach of the company

The company presented results from 2 separate indirect comparisons and derived an added benefit from these in an overall assessment. Both comparisons are adjusted indirect comparisons according to Bucher via the common comparator placebo. For the indirect comparison of efgartigimod alfa with ravulizumab, the company used the subpopulation of anti-AChR antibody-positive patients from the ADAPT study on the intervention side and the study population from the CHAMPION study on the comparator side. For the indirect comparison of efgartigimod alfa with eculizumab, the company used the study population of the REGAIN study on the comparator side, which included patients with refractory, anti-AChR antibody-positive generalized myasthenia gravis. In Module 4 A of the dossier, the company stated that it had formed a subpopulation of refractory patients of the ADAPT study based on the inclusion criteria of the REGAIN study in order to establish comparability of the populations.

Data presented by the company are unsuitable for the benefit assessment

Treatment/observation duration in the ADAPT study not sufficient for the present therapeutic indication

In the ADAPT study, treatment with the study medication was carried out in treatment cycles, each comprising a 3-week treatment phase (4 infusions) and a 5-week follow-up phase. The interval between successive treatment cycles varied from patient to patient. At first, the patients included in the study all received an initial treatment cycle. Although further cycles were possible on an individualized basis under certain conditions, including disease activity, patients who required further treatment after Day 127 (Week 18) and were therefore unable to complete the 8-week treatment cycle within the 26-week study phase had to enter the ADAPT+ extension study early in order to receive a further cycle. Overall, in the anti-AChR antibody-positive subpopulation, 62/65 of the patients in the intervention arm (95%) and 54/64 of the patients in the comparator arm (84%) switched to the ADAPT+ extension study.

Based on the available data, it remains unclear what proportion of patients entered the extension study prematurely due to the need for a new treatment cycle after Day 127 and what proportion only entered after completion of the maximum planned treatment and observation period of 26 weeks. However, the information on the observation period shows that a large proportion of patients must have entered the extension study before the end of the maximum planned treatment and observation period. For instance, the median observation period in both study arms of the ADAPT study is only 142 days (20.3 weeks). This is also reflected in the response rates for the outcomes of morbidity and health-related quality of life. While the response rates at the documentation time Week 20 were still ≥ 75% for all outcomes in both study arms, the response rates at the subsequent documentation time Week 22 were consistently ≤ 36%.

Generalized myasthenia gravis is a chronic condition with a typically fluctuating course of disease, requiring long-term therapy. The present therapeutic indication requires an observation period of at least 24 weeks. Although the ADAPT study was planned for a duration of 26 weeks, data are only available up to Week 20 for the majority of patients due to the cyclical treatment regimen combined with the premature switch of patients to the ADAPT+ extension study. The observation period in the ADAPT study is therefore not sufficient to derive statements on the added benefit in this therapeutic indication. For its derivation of the added benefit for outcomes of morbidity and health-related quality of life, the company primarily considered analyses of indirect comparisons at early documentation time points (particularly at Week 4) as well as analyses on the 'best response rate', in which, for example, analyses at Week 4 for treatment with efgartigimod alfa were compared with analyses at Week 26 for treatment with ravulizumab. This approach is not appropriate. Even if treatment with efgartigimod alfa is administered in cycles depending on the need for re-treatment, continuous monitoring of the response at least until Week 24 would be possible and necessary in the present therapeutic indication, in which long-term therapy is required. Moreover, the consideration of different time points per arm is generally not appropriate, and comparisons at early documentation time points (e.g. Week 4) is not meaningful.

In addition, the ADAPT study is not comparable with the studies CHAMPION and REGAIN, which were designed for continuous treatment with fixed dosing intervals and observation of response at Week 26, due to the individualized, cyclical treatment regimen combined with the early switch of patients to the ADAPT+ extension study. The median observation period on the comparator side was 26 weeks in both studies. Particularly against the background of the differences in the study design - treatment in cycles and, as a result, a strongly fluctuating response in the course of the ADAPT study compared with continuous treatment in the studies CHAMPION and REGAIN - and the need for continuous treatment, it cannot be concluded that there is sufficient similarity between the studies in the two indirect comparisons with a difference of 6 weeks (23%) in the median observation period between the studies.

Lack of similarity between the included patient populations

Irrespective of the differences in the study design and the resulting differences in the treatment and observation duration, both indirect comparisons show differences between the respective patient populations included.

Indirect comparison with eculizumab

For the indirect comparison of efgartigimod alfa versus eculizumab, the company used the study population of the REGAIN study on the comparator side. According to the inclusion criteria, the study population of the REGAIN study exclusively comprised patients with refractory, anti-AChR antibody-positive generalized myasthenia gravis. In Module 4 A of the dossier, the company stated that it would form a subpopulation of refractory patients of the ADAPT study based on the inclusion criteria of the REGAIN study in order to establish comparability with the study population of the REGAIN study on the intervention side. The criteria used by the company to form the subpopulation of the ADAPT study (N = 40 in the efgartigimod alfa arm and N = 41 in the placebo arm) differ from the inclusion criteria of the REGAIN study in particular in that no criteria regarding the duration of immunosuppressive pre-treatment were applied.

The discrepancy with regard to the definition of treatment-refractory patients is reflected in the prior and concomitant treatments of the patients included in the studies on the intervention and the comparator side. Relevant differences between the populations can primarily be seen in the treatment of exacerbations and myasthenic crises both before and during the course of the studies. For example, in the subpopulation of the ADAPT study formed by the company, only 5% or 12% of patients received treatment with intravenous immunoglobulins before the start of the study, while 82% of patients in the eculizumab arm and 76% of patients in the placebo arm of the REGAIN study were pretreated with intravenous immunoglobulins. In contrast to the REGAIN study, the administration of rescue therapy led to treatment discontinuation in the ADAPT study. For the subpopulation of refractory patients, no data on treatment discontinuations are available for the ADAPT study, but based on the data on the anti-AChR antibody-positive subpopulation, it can be assumed that rescue therapies were only used in isolated cases. For instance, in the anti-AChR antibody-positive subpopulation, the administration of rescue therapy was only occasionally the reason for discontinuation of treatment (2% vs. 3%). During the course of the REGAIN study, however, 6 of the patients in the intervention arm (10%) and 11 of the patients in the comparator arm (18%) experienced a clinical deterioration that required rescue treatment.

Overall, the differences in the prior and concomitant therapies make clear that the company's approach in forming the refractory subpopulation means that the populations under consideration are not sufficiently similar for an indirect comparison.

Indirect comparison with ravulizumab

The indirect comparison of efgartigimod alfa with ravulizumab also shows differences in the prior and concomitant treatments of the patients included in the studies on the intervention and the comparator side.

In addition, it should be noted also for this indirect comparison that the administration of rescue therapy in the ADAPT study led to discontinuation of the study medication, whereas this was the case neither in the CHAMPION nor the REGAIN study. During the course of the ADAPT study, one patient in the intervention arm (2%) and two patients in the comparator arm (3%) discontinued treatment due to the administration of rescue therapy. In the CHAMPION study, In contrast, 8 (9%) and 15 (17%) of the patients in the two study arms experienced a clinical deterioration of myasthenia gravis that required rescue therapy.

Based on the differences in the prior and concomitant therapies, it can therefore be assumed also for the indirect comparison with ravulizumab that the populations under consideration are not sufficiently similar for an indirect comparison.

Conclusion

Due to the individualized, cyclical treatment regimen in the ADAPT study combined with the possibility of a premature switch to the ADAPT+ extension study, the duration of treatment and observation in the ADAPT study is not sufficient for a derivation of conclusions on the added benefit in this therapeutic indication. Secondly, due to the differences in the observation periods between the studies, it cannot be assumed that there is sufficient similarity between the studies in the indirect comparisons - particularly in view of the differences in the study design (treatment in cycles followed by highly fluctuating response in the course of the ADAPT study compared to continuous treatment in the CHAMPION or REGAIN study) and the need for long-term treatment. In addition, in both indirect comparisons, the patient populations included in the studies on the intervention and comparator side are not sufficiently similar with regard to prior and concomitant therapy for the treatment of exacerbations and myasthenic crises. Therefore, the data presented by the company are unsuitable for the assessment of the added benefit of efgartigimod alfa in comparison with the ACT.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of efgartigimod alfa in comparison with the ACT; an added benefit is therefore not proven.

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

Table 3 shows a summary of probability and extent of added benefit of efgartigimod alfa.

Table 3: Efgartigimod alfa – extent and probability of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with anti-AChR antibody-positive generalized myasthenia gravis for whom add-on therapy to standard treatment is an option	Eculizumab (for refractory patients) or ravulizumab[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. In accordance with the G-BA, it is assumed that patients in both study arms receive guideline-compliant therapy with cholinesterase inhibitors as well as basic immunosuppressive therapy, if indicated. It is also assumed that all patients will be provided with supportive measures.
c. It must be ensured that all patients receive optimal treatment in case of any myasthenic crisis and/or critical deterioration. In accordance with the G-BA, it is assumed that the patients are no candidates for thymectomy at the time of therapy or that they have already had one.

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

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the context of the market launch in 2022. There, the G-BA had determined a considerable added benefit of efgartigimod alfa. However, in said assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

[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 efgartigimod alfa as an add-on therapy to the standard treatment in comparison with the ACT in adult patients with generalized myasthenia gravis who are AChR antibody-positive.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of efgartigimod alfa

Therapeutic indication	**ACT[a]**
Adults with anti-AChR antibody-positive generalized myasthenia gravis for whom add-on therapy to standard treatment is an option	Eculizumab (for refractory patients) or ravulizumab[b, c]
a. Presented is the ACT specified by the G-BA. b. In accordance with the G-BA, it is assumed that patients in both study arms receive guideline-compliant therapy with cholinesterase inhibitors as well as basic immunosuppressive therapy, if indicated. It is also assumed that all patients will be provided with supportive measures. c. It must be ensured that all patients receive optimal treatment in case of any myasthenic crisis and/or critical deterioration. In accordance with the G-BA, it is assumed that the patients are no candidates for thymectomy at the time of therapy or that they have already had one. AChR: acetylcholine receptor; ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT and designated eculizumab (for refractory patients) or ravulizumab as ACT.

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 were used for deriving the added benefit. This concurs with the company's inclusion criteria.

I 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 efgartigimod alfa (status: 16 January 2024)
- bibliographical literature search on efgartigimod alfa (last search on 16 January 2024)
- search in trial registries/trial results databases for studies on efgartigimod alfa (last search on 18 January 2024)
- search on the G-BA website for efgartigimod alfa (last search on 29 January 2024)
- bibliographical literature search on the ACT (last search on 16 January 2024)
- search in trial registries/trial results databases for studies on the ACT (last search on 18 January 2024)
- search on the G-BA website for the ACT (last search on 16 January 2024)

To check the completeness of the study pool:

- bibliographic literature search on eculizumab (last search on 18 April 2024); for search strategies, see Appendix A of the full dossier assessment
- search in trial registries for studies on efgartigimod alfa (last search on 11 April 2024); for search strategies, see I Appendix A of the full dossier assessment
- search in trial registries for studies on the ACT (last search on 16 April 2024); for search strategies, see Appendix A of the full dossier assessment

Concurring with the company, no studies on the direct comparison of efgartigimod alfa versus the ACT were identified from the check of the completeness of the study pool.

The company therefore presented 2 separate adjusted indirect comparisons according to Bucher [3] for the assessment of efgartigimod alfa versus ravulizumab or eculizumab. It identified the ARGX-113-1704 study (hereinafter referred to as ADAPT for short) [4-9] on the intervention side for both indirect comparisons. For the indirect comparison with ravulizumab, the company identified the ALXN1210-MG-306 study (hereinafter referred to as CHAMPION for short) on the comparator side [10-13] and for the indirect comparison with eculizumab, it identified the ECU-MG-301 study (hereinafter referred to as REGAIN for short) [13-18].

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

I 3.1 Evidence provided by the company

For a characterization of the studies described below, the interventions used in each case and the patients included, see also I Appendix B.

I 3.1.1 Evidence on efgartigimod alfa

ADAPT study

The ADAPT study is a double-blind, randomized, multicentre study on the 26-week treatment with efgartigimod alfa (see Table 7 in I Appendix B of the full dossier assessment). The study investigated the comparison of efgartigimod alfa versus placebo, each in addition to standard therapy.

The ADAPT study included adult patients with generalized myasthenia gravis who had a MGFA classification of II to IV. In addition, patients had to have a MG-ADL score ≥ 5 at screening and at baseline, with more than 50% of the total score being attributable to non-ocular symptoms. To be included in the study, patients had to have received a standard therapy for the treatment of myasthenia gravis at a stable dose over a certain period of time prior to screening, which varied depending on the drug.

The study included a total of 167 patients who were randomly assigned in a 1:1 ratio to treatment with efgartigimod alfa + standard therapy (N = 84) or placebo + standard therapy (N = 83). Randomization was stratified by family origin (Japanese vs. non-Japanese), anti-AChR antibody status (seropositive vs. seronegative) and type of standard therapy (non-steroidal immunosuppressants vs. no non-steroidal immunosuppressants).

Participation in the study was not restricted to anti-AChR antibody-positive patients. However, patients without anti-AChR antibodies were not covered by the present therapeutic indication. In the dossier, the company presents analyses on the subpopulation of patients with positive anti-AChR antibody status, which comprised 65 patients in the efgartigimod alfa arm and 64 patients in the placebo arm.

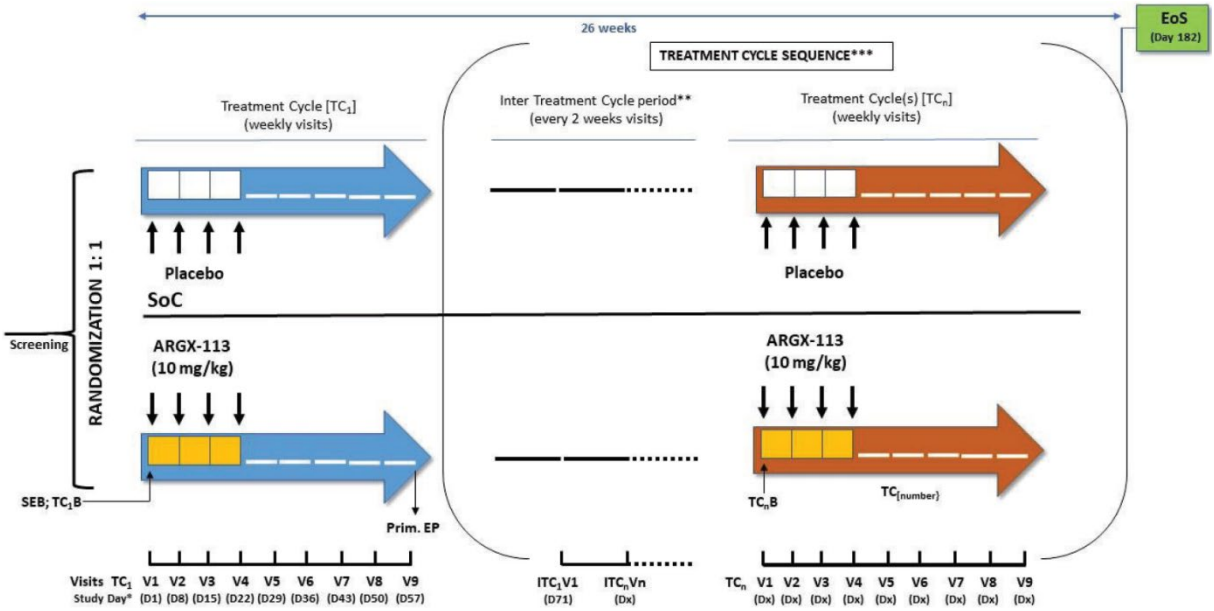
The study medication was administered as an intravenous infusion in both study arms. In doing so, treatment with efgartigimod alfa was largely carried out in accordance with the SPC, although subcutaneous injection was also possible, which was not investigated in the study [19,20]. Patients included in the study had to receive a standard therapy before the screening and continue to receive it in a stable manner during the study. Drug-specific specifications for the duration of pretreatment and the duration of stable dosing of the prior therapy before screening had to be adhered to (for details, see Table 8 in I Appendix B of the full dossier assessment). Standard therapy was limited to cholinesterase inhibitors, corticosteroids and non-steroidal immunosuppressants (e.g. azathioprine, methotrexate, ciclosporin, tacrolimus, mycophenolate mofetil and cyclophosphamide). Adjustment of the dosage or the regimen

during the course of the study was not permitted and led to discontinuation of the study medication. If the patients experienced a clinical deterioration as defined in the study protocol during the course of the study, the administration of rescue therapy was possible, but also led to discontinuation of the study medication (see Table 8 in I Appendix B of the full dossier assessment for details).

The primary outcome of the ADAPT study was the reduction in the MG-ADL score after the first treatment cycle compared to the start of the cycle. Further patient-relevant outcomes were recorded in the categories of morbidity and health-related quality of life as well as in the framework of adverse events (AEs).

Individualized treatment cycles in the ADAPT study

The patients in the ADAPT study were treated in treatment cycles, each consisting of a 3-week treatment phase and a subsequent 5-week follow-up phase with close weekly recording of the outcomes (see Figure 1).



* ± 1 day for treatment cycle visits and ± 2 days for inter treatment cycle visits

** interval time may vary from patient to patient

*** may be repeated as many times as needed during the time frame of the trial. last Treatment Cycle should not start later than on Day 127 of the trial

EoS = end of study; Prim. EP = primary endpoint; ITC = inter treatment cycle; SEB = study entry baseline; SoC = standard of care; TC = treatment cycle; TC_nB = treatment cycle [number] baseline

Figure 1: Design of the ADAPT study

All patients received an initial treatment cycle with efgartigimod alfa or placebo in addition to the ongoing standard therapy. Further cycles were possible on an individual patient basis, provided that all of the following requirements were met:

- Completion of the previous treatment cycle (i.e. completion of the 8-week period after the first dose in the cycle)
- MG-ADL score ≥ 5, where more than 50% of the total score had to be due to non-ocular symptoms
- Patients who had showed a response to the therapy in a previous treatment cycle had to have lost this response for a new treatment (a loss of response was defined as a reduction of < 2 points in the MG-ADL compared to the baseline value of the corresponding treatment cycle)

In addition, a new treatment cycle had to be started on Day 127 (Week 18) at the latest in order to be completed within the 26-week study phase. Patients who required further treatment after Day 127 and were therefore unable to complete the treatment cycle within the 26-week study phase therefore had to switch to the ARGX-113-1705 extension study [21]prematurely (hereinafter referred to as ADAPT+ for short) early in order to receive a further cycle. In addition, all patients who completed the observation period within the study could also switch to the ADAPT+ study, provided they had not discontinued treatment with the study medication due to rescue therapy, pregnancy or life-threatening serious adverse events (SAEs) or SAEs that pose a safety risk. All patients in the ADAPT+ study received efgartigimod alfa in individualized treatment cycles.

In both the ADAPT study and the ADAPT+ study, the analyses on the response to therapy planned in accordance with the study design were primarily based on treatment cycles. The focus here was on the assessment of the response at the end of a cycle compared to the start of the cycle, and not on the assessment of the response primarily at the end of the study (Week 26). The primary aim of the ADAPT study was to assess the efficacy of efgartigimod alfa compared to placebo based on the response in the MG-ADL score to the first treatment cycle.

I 3.1.2 Evidence on the ACT

I 3.1.2.1 Evidence on ravulizumab

CHAMPION study

As already described in dossier assessment A22-115 [22], the CHAMPION study is a randomized, controlled, double-blind phase 3 study on the treatment with ravulizumab (see Table 7 in I Appendix B). In the 26-week randomized controlled phase of the study, the comparison of ravulizumab versus placebo was investigated, if applicable each in addition to the existing standard therapy. This phase was followed by an open extension phase (up to 2 years) in which all patients could receive ravulizumab.

The study included adult patients with generalized myasthenia gravis who had a II to IV MGFA classification at the time of screening and an MG-ADL score of ≥ 6 at baseline. For inclusion

in the study, a positive serological test for anti-AChR antibodies had to be available at the time of screening. Patients who were receiving standard therapy with immunosuppressants, oral corticosteroids or cholinesterase inhibitors at study start had to have received these on a stable dose for a certain period of time before the study start depending on the drug, and had to continue to receive these at a stable dose during 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 ± standard therapy (N = 86) or placebo ± standard therapy (N = 89). Randomization was stratified by region (North America, Europe, Asia-Pacific and Japan).

In the intervention arm, treatment with ravulizumab was carried out by administering a weight-dependent initial dose on Day 1, followed by a weight-dependent maintenance dose 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 [23]. 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. However, based on the available information on concomitant therapies, it can be assumed that the vast majority of patients received standard therapy for myasthenia gravis consisting of cholinesterase inhibitors, immunosuppressants and/or oral corticosteroids at the start of the study (see Table 12 in I Appendix B).

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 continue this treatment in a stable manner 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 8 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. 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 8 in I Appendix B of the full dossier

assessment). Chronic treatment with plasma exchange/plasmapheresis or intravenous immunoglobulins was not permitted as concomitant medication in the study, in contrast to acute therapy as part of rescue medication.

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 and health-related quality of life as well as in the framework of AEs.

I 3.1.2.2 Evidence on eculizumab

Study REGAIN

As already described in dossier assessment A22-115 [22], the REGAIN study is a randomized, controlled, double-blind phase 3 study comparing eculizumab with placebo, each in addition to the ongoing standard therapy (if applicable) over 26 weeks (see Table 7 in I Appendix B).

The study included adult patients with refractory generalized myasthenia gravis who had a II to IV MGFA classification at screening and an MG-ADL score of ≥ 6 at baseline. The diagnosis had to be confirmed by a positive serologic test for anti-AChR antibodies at screening. Patients who were receiving standard therapy with immunosuppressants, oral corticosteroids or cholinesterase inhibitors at study start had to have received these on a stable dose for a certain period of time before the study start depending on the drug, and had to continue to receive these at a stable dose during 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 chronic plasmapheresis/chronic plasma exchange or chronic intravenous immunoglobulin was required 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 ± standard therapy (N = 63) or placebo ± standard 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 [24]. The administration of eculizumab as an add-on to standard therapy for generalized myasthenia gravis was not mandatory according to the study planning. However, based on the available information on concomitant therapies, it can be assumed that the vast majority of patients received standard therapy for myasthenia gravis consisting of cholinesterase inhibitors, immunosuppressants and/or oral corticosteroids at the start of the study (see Table 13 in I Appendix B).

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 continue this treatment in a stable manner 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 8 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. 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 8 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 and health-related quality of life as well as in the framework of AEs.

I 3.2 Approach of the company

The company presented results from 2 separate indirect comparisons and derived an added benefit from these in an overall assessment:

- indirect comparison of efgartigimod alfa (ADAPT study) with ravulizumab (CHAMPION study)
- indirect comparison of efgartigimod alfa (ADAPT study) with eculizumab (REGAIN study)

Both comparisons are adjusted indirect comparisons according to Bucher [3] via the common comparator placebo. For the indirect comparison of efgartigimod alfa with ravulizumab, the company used the subpopulation of anti-AChR antibody-positive patients from the ADAPT study on the intervention side and the study population from the CHAMPION study on the comparator side. For the indirect comparison of efgartigimod alfa with eculizumab, the company used the study population of the REGAIN study on the comparator side, which included patients with refractory, anti-AChR antibody-positive generalized myasthenia gravis. In Module 4 A of the dossier, the company stated that it had formed a subpopulation of refractory patients of the ADAPT study based on the inclusion criteria of the REGAIN study in order to establish comparability of the populations. In Module 4 A of the dossier, the company presented analyses on outcomes of morbidity, health-related quality of life and side effects up to Week 26 for both indirect comparisons.

In addition, the company presented results for the subpopulation of anti-AChR antibody-positive patients in the ADAPT study for the comparison of efgartigimod alfa with placebo and took these into account to support the derivation of the added benefit.

The company based its derivation of the added benefit in particular on what it considered to be the consistently early response to treatment with efgartigimod alfa. To this end, it considered analyses of the indirect comparisons for outcomes of morbidity and health-related quality of life at early documentation time points (particularly at Week 4). For the indirect comparison with ravulizumab, the company also based its derivation of the added benefit primarily on analyses of the so-called “best response rate”, in which it compared results on the response at Week 4 for treatment with efgartigimod alfa with results on the response at Week 18 and Week 26 for treatment with ravulizumab.

Overall, the company claimed an indication of considerable added benefit for efgartigimod alfa based on the overall assessment of the available evidence.

I 3.3 Assessment of the evidence presented by the company

The analyses presented by the company are unsuitable for drawing conclusions on the added benefit of efgartigimod alfa in comparison with the ACT. One reason for this is that patients in

the ADAPT study were not treated/observed for long enough to allow conclusions for the present therapeutic indication of generalized myasthenia gravis. Secondly, there are relevant differences between the patient populations included in both indirect comparisons, which is why it cannot be assumed that there is sufficient similarity between the patients in the two studies of indirect comparisons. This is further explained below.

Treatment/observation duration in the ADAPT study not sufficient for the present therapeutic indication

In the ADAPT study, treatment with the study medication was carried out in treatment cycles, each comprising a 3-week treatment phase (4 infusions) and a 5-week follow-up phase. The interval between successive treatment cycles varied from patient to patient. As described in Section I 3.1.1, the patients included in the study all received an initial treatment cycle. Although further cycles were possible on an individualized basis under certain conditions, including disease activity, patients who required further treatment after Day 127 (Week 18) and were therefore unable to complete the 8-week treatment cycle within the 26-week study phase had to enter the ADAPT+ extension study early in order to receive a further cycle. Overall, a maximum of 3 treatment cycles would have been possible in the ADAPT study. However, in the anti-AChR antibody-positive subpopulation of the ADAPT study, 22% of the patients in the intervention arm and 33% of the patients in the comparator arm only received the initial treatment cycle (see Table 5). A large proportion of these patients subsequently entered the ADAPT+ extension study. The vast majority of patients in both study arms received 2 treatment cycles (68% vs. 66%), with all but 3 patients being transferred to the ADAPT+ extension study. Only 11% and 2% of patients, respectively, all of whom transferred to the ADAPT+ extension study, received a third treatment cycle. Overall, 62/65 of the patients in the intervention arm (95%) and 54/64 of the patients in the comparator arm (84%) transferred to the ADAPT+ extension study.

Table 5: Number of patients per treatment cycle in the ADAPT study

Study treatment cycle	Efgartigimod alfa + standard therapy N[a] = 65	Placebo + standard therapy N[a] = 64
ADAPT		
Treatment cycle 1		
Patients with one treatment cycle, n (%)	14 (22)	21 (33)
Transfer to extension study ADAPT+, n (%)	12 (18)	13 (20)
Treatment cycle 2		
Patients with two treatment cycles, n (%)	44 (68)	42 (66)
Transfer to extension study ADAPT+, n (%)	43 (66)	40 (63)
Treatment cycle 3		
Patients with three treatment cycles, n (%)	7 (11)	1 (2)
Transfer to extension study ADAPT+, n (%)	7 (11)	1 (2)

a. Number of randomized patients. The information corresponds to the subpopulation of AChR antibody-positive patients.

AChR: acetylcholine receptor; n: number of patients in the category; N: number of randomized patients

In particular for the groups of patients who only received one or two cycles, it remains unclear what proportion of patients entered the extension study prematurely due to the need for a new treatment cycle after Day 127 and what proportion only entered after completion of the maximum planned treatment and observation period of 26 weeks. However, the available information on the observation period shows that a large proportion of patients must have entered the extension study before the end of the maximum planned treatment and observation period. For instance, the median observation period in both study arms of the ADAPT study is only 142 days (20.3 weeks). This is also reflected in the response rates for the outcomes of morbidity and health-related quality of life. While the response rates at the documentation time Week 20 were still ≥ 75% for all outcomes in both study arms, the response rates at the subsequent documentation time Week 22 were consistently ≤ 36% see Table 11 in I Appendix B).

Generalized myasthenia gravis is a chronic condition with a typically fluctuating course of disease, requiring long-term therapy [25,26]. The present therapeutic indication requires an observation period of at least 24 weeks. Although the ADAPT study was planned for a duration of 26 weeks, data are only available up to Week 20 for the majority of patients due to the cyclical treatment regimen combined with the premature switch of patients to the ADAPT+ extension study. The observation period in the ADAPT study is therefore not sufficient to derive statements on the added benefit in this therapeutic indication. In Module 4 A of the dossier, the company also points out of that, due to the study design, there is a significant

decrease in the number of patients in both treatment arms from Week 20 onwards. As described in Section I 3.2, for its derivation of the added benefit for outcomes of morbidity and health-related quality of life, the company primarily considered analyses of indirect comparisons at early documentation time points (particularly at Week 4) as well as analyses on the 'best response rate', in which, for example, analyses at Week 4 for treatment with efgartigimod alfa were compared with analyses at Week 26 for treatment with ravulizumab. This approach is not appropriate. Even if treatment with efgartigimod alfa is administered in cycles depending on the need for re-treatment, continuous monitoring of the response at least until Week 24 would be possible and necessary in the present therapeutic indication, in which long-term therapy is required. Moreover, the consideration of different time points per arm is generally not appropriate, and comparisons at early documentation time points (e.g. Week 4) is not meaningful.

In addition, the ADAPT study is not comparable with the studies CHAMPION and REGAIN, which were designed for continuous treatment with fixed dosing intervals and observation of response at Week 26, due to the individualized, cyclical treatment regimen combined with the early switch of patients to the ADAPT+ extension study. In the CHAMPION study, 79/86 of the patients in the intervention arm (92%) and 83/89 of the patients in the comparator arm (93%) completed the randomized controlled study phase of 26 weeks. 57/62 (92%) and 61/63 (97%) patients completed the REGAIN study. Thus, the median observation period in both studies was 26 weeks. Particularly against the background of the differences in the study design - treatment in cycles and, as a result, a strongly fluctuating response in the course of the ADAPT study compared with continuous treatment in the studies CHAMPION and REGAIN - and the need for continuous treatment, it cannot be concluded that there is sufficient similarity between the studies in the two indirect comparisons with a difference of 6 weeks (23%) in the median observation period between the studies.

Lack of similarity between the included patient populations

Irrespective of the differences in the study design and the resulting differences in the treatment and observation duration, both indirect comparisons show differences between the respective patient populations included.

Indirect comparison with eculizumab

For the indirect comparison of efgartigimod alfa versus eculizumab, the company used the study population of the REGAIN study on the comparator side. According to the inclusion criteria, the study population of the REGAIN study exclusively comprised patients with refractory, anti-AChR antibody-positive generalized myasthenia gravis. In Module 4 A of the dossier, the company stated that it would form a subpopulation of refractory patients of the ADAPT study based on the inclusion criteria of the REGAIN study in order to establish

comparability with the study population of the REGAIN study on the intervention side. The company defines the refractory patients in the ADAPT study using the following criteria:

- prior exposure to ≥ 2 immunosuppressants, or
- treatment with ≥ 1 immunosuppressive therapy requiring several plasmaphereses (plasma exchange) or intravenous immunoglobulins within 1 year prior to enrolment

In addition, according to the company, selection was particularly based on the inclusion criterion of an MG-ADL score ≥ 6 points. The criteria used by the company to form the subpopulation of the ADAPT study (N = 40 in the efgartigimod alfa arm and N = 41 in the placebo arm) differ from the inclusion criteria of the REGAIN study in particular in that no criteria regarding the duration of immunosuppressive pre-treatment were determined (see Section I 3.1.2.2). For example, inclusion in the REGAIN study required, among other things, failed treatment with ≥ 2 immunosuppressants over a period of ≥ 1 year. In contrast, although the company also considered those patients who had received ≥ 2 immunosuppressants to form its subpopulation, this was done regardless of the duration of the previous immunosuppressive therapy. The exclusion criterion regarding plasmapheresis (plasma exchange) or intravenous immunoglobulins was also more strictly defined in the REGAIN study via regular treatment at least every 3 months within the last 12 months.

The discrepancy with regard to the definition of treatment-refractory patients is reflected in the prior and concomitant treatments of the patients included in the studies on the intervention and the comparator side (see Table 13 in I Appendix B). Relevant differences between the populations can primarily be seen in the treatment of exacerbations and myasthenic crises both before and during the course of the studies. Although data on the chronic administration of intravenous immunoglobulins are not available for the subpopulation of the ADAPT study formed by the company, only a total of 5% or 12% of patients received treatment with intravenous immunoglobulins before the start of the study. In contrast, 82% of patients in the eculizumab arm and 76% of patients in the placebo arm of the REGAIN study received pretreatment with intravenous immunoglobulins. Chronic treatment with intravenous immunoglobulins was given to 29% and 27% of patients respectively before the start of the study. In addition, only 20% of patients of the subpopulation of the ADAPT study formed by the company in each of the two treatment arms had a history of plasma exchange/plasmapheresis, while this was the case in 50% and 46% of patients in the REGAIN study, respectively. None of the patients in the subpopulation of the ADAPT study formed by the company underwent treatment with intravenous immunoglobulins during the course of the study. No information is available on further rescue therapies. However, in contrast to the REGAIN study, the administration of rescue therapy in the ADAPT study led to treatment discontinuation (see Section I 3.1). For the subpopulation of refractory patients, no data on treatment discontinuations are available, but based on the

data on the anti-AChR antibody-positive subpopulation, it can be assumed that rescue therapies were only used in isolated cases. For instance, in the anti-AChR antibody-positive subpopulation, the administration of rescue therapy was only occasionally the reason for discontinuation of treatment (2% vs. 3%). During the course of the REGAIN study, however, 6 of the patients in the intervention arm (10%) and 11 of the patients in the comparator arm (18%) experienced a clinical deterioration that required rescue treatment. To treat exacerbations and myasthenic crises during the study, patients received intravenous immunoglobulins (6% vs. 10%), plasma exchange/plasmapheresis (5% vs. 6%) and high-dose corticosteroids (0% vs. 8%).

Overall, the differences in the prior and concomitant therapies described before make clear that the company's approach in forming the refractory subpopulation means that the populations under consideration are not sufficiently similar for an indirect comparison. However, the consideration of a sufficiently similar patient population is a key prerequisite for an adjusted indirect comparison.

Indirect comparison with ravulizumab

The indirect comparison of efgartigimod alfa with ravulizumab also shows differences in the prior and concomitant treatments of the patients included in the studies on the intervention and the comparator side (see Table 12 in I Appendix B). In relation to the anti-AChR antibody-positive patients, prior therapy with intravenous immunoglobulins was administered in 6% and 11% of patients in both study arms in the ADAPT study and thus clearly less frequently compared to the patients in the CHAMPION study (42% and 45% respectively). The same applies to the treatment of exacerbations and myasthenic crises during the course of the study. 2% of patients in each of the two study arms received intravenous immunoglobulins during the course of the ADAPT study, compared with 6% of patients in the intervention and 14% patients in the comparator arm of the CHAMPION study.

In addition, it should be noted that the administration of rescue therapy in the ADAPT study led to discontinuation of the study medication, whereas this was the case neither in the CHAMPION nor the REGAIN study (see Section I 3.1). During the course of the ADAPT study, one patient in the intervention arm (2%) and two patients in the comparator arm (3%) discontinued treatment due to the administration of rescue therapy. In the CHAMPION study, In contrast, 8 (9%) and 15 (17%) of the patients in the two study arms experienced a clinical deterioration of myasthenia gravis that required rescue therapy.

Based on the differences in the prior and concomitant therapies described before, it can therefore be assumed also for the indirect comparison with ravulizumab that the populations under consideration are not sufficiently similar for an indirect comparison.

Conclusion

Due to the individualized, cyclical treatment regimen in the ADAPT study combined with the possibility of a premature switch to the ADAPT+ extension study, the duration of treatment and observation in the ADAPT study is not sufficient for a derivation of conclusions on the added benefit in this therapeutic indication. Secondly, due to the differences in the observation periods between the studies, it cannot be assumed that there is sufficient similarity between the studies in the indirect comparisons - particularly in view of the differences in the study design (treatment in cycles followed by highly fluctuating response in the course of the ADAPT study compared to continuous treatment in the CHAMPION or REGAIN study) and the need for long-term treatment. In addition, in both indirect comparisons, the patient populations included in the studies on the intervention and comparator side are not sufficiently similar with regard to prior and concomitant therapy for the treatment of exacerbations and myasthenic crises. Therefore, the data presented by the company are unsuitable for the assessment of the added benefit of efgartigimod alfa in comparison with the ACT.

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of efgartigimod alfa as an add-on therapy to standard treatment in comparison with the ACT in adult patients with generalized myasthenia gravis who are anti-AChR antibody-positive. There is no hint of an added benefit of efgartigimod alfa in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 6 summarizes the result of the assessment of added benefit of efgartigimod alfa in comparison with the ACT.

Table 6: Efgartigimod alfa – extent and probability of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with anti-AChR antibody-positive generalized myasthenia gravis for whom add-on therapy to standard treatment is an option	Eculizumab (for refractory patients) or ravulizumab[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. In accordance with the G-BA, it is assumed that patients in both study arms receive guideline-compliant therapy with cholinesterase inhibitors as well as basic immunosuppressive therapy, if indicated. It is also assumed that all patients will be provided with supportive measures.
c. It must be ensured that all patients receive optimal treatment in case of any myasthenic crisis and/or critical deterioration. In accordance with the G-BA, it is assumed that the patients are no candidates for thymectomy at the time of therapy or that they have already had one.

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

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit on the basis of the data provided by it.

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the context of the market launch in 2022. There, the G-BA had determined a considerable added benefit of efgartigimod alfa. However, in said assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

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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