# Zilucoplan
# (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 one person.

IQWiG thanks the respondent and the Deutsche Myasthenia Gesellschaft (DMG) e. V. for participating in the written exchange and their assistance. The respondent and the DMG e. V. were not involved in the actual preparation of the dossier assessment.

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# Part I: Benefit assessment

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

# I List of abbreviations

| Abbreviation | Meaning |
|---|---|
| AChR | acetylcholine receptor |
| ACT | appropriate comparator therapy |
| CTCAE | Common Terminology Criteria for Adverse Events |
| 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 |
| QMG | Quantitative Myasthenia Gravis |
| RCT | randomized controlled trial |
| SGB | Sozialgesetzbuch (Social Code Book) |

## 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 zilucoplan. 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 01 March 2024.

### Research question

The aim of the present report is to assess the added benefit of zilucoplan as an add-on therapy to the standard treatment in comparison with the appropriate comparator therapy (ACT) for the treatment of 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 for the benefit assessment of zilucoplan

| **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 efgartigimod alfa or ravulizumab[b, c] |
| a. Presented is the ACT specified by the G-BA.<br>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.<br>c. 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.<br>AChR: acetylcholine receptor; ACT: appropriate comparator therapy; G-BA: Federal Joint Committee | |

In the dossier, the company states that it follows the G-BA's definition of the ACT and names eculizumab (for refractory patients) or efgartigimod alfa or ravulizumab as the ACT. In its assessment, however, the company includes studies versus any comparator therapy and bases its assessment primarily on placebo-controlled studies. The approach of the company is not appropriate. The present assessment was conducted in comparison with the G-BA's ACT presented in Table 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 were used for the derivation of added benefit. This deviates from the company's inclusion criteria, which specified a minimum duration of 12 weeks.

**Results**

***Evidence provided by the company***

Concurring with the company, no RCT was identified for the benefit assessment that would allow a direct comparison of zilucoplan with the ACT.

As the company did not identify any RCTs for the direct comparison of zilucoplan with the ACT, it conducted an information retrieval on zilucoplan that included any comparator therapy and identified the placebo-controlled studies MG0009 and MG0010 (RAISE), which were decisive for the approval of zilucoplan. For its assessment, the company conducted meta-analyses of these studies and, according to its information, classified the added benefit of zilucoplan on the basis of the results of the meta-analyses compared to placebo.

In addition, in Appendix 4-J, in Module 4 A of the dossier, the company additionally presents an adjusted indirect comparison of zilucoplan versus ravulizumab via the common comparator placebo, which, according to the company, serves to classify the added benefit of zilucoplan in comparison with the ACT. The company presented this indirect comparison only as a supplement in Appendix 4-J of Module 4 A of the dossier (and not in the corresponding sections provided in Module 4 A). Moreover, it did not carry out information retrieval for indirect comparison. Both the comparison with placebo and the comparison with ravulizumab are based on a treatment duration of 12 weeks.

Based on the overall analysis of the available data (for comparison with placebo or ravulizumab over 12 weeks in each case), the company concludes that there is an overall added benefit of zilucoplan compared with the ACT, which cannot be quantified because the scientific data basis does not allow this.

***Evidence presented by the company is unsuitable for the benefit assessment***

Studies MG0009 and MG0010 as well as the meta-analyses on these studies presented by the company are not suitable for the present benefit assessment, as they do not allow a comparison with the ACT. In addition, with a comparison over 12 weeks, the study duration is too short in each case to be able to derive conclusions on the added benefit in the present therapeutic indication. Generalized myasthenia gravis is a chronic condition with a typically fluctuating course of disease, requiring long-term therapy. Therefore, a comparison over at least 24 weeks of treatment is necessary in the present therapeutic indication.

The indirect comparison additionally presented by the company was thus unsuitable to draw conclusions on the added benefit of zilucoplan versus the ACT. The company presented the indirect comparison only as a supplement in the appendix instead of in the corresponding sections of the dossier template and without information retrieval. The data were not evaluated in accordance with the requirements of the dossier template. Apart from the lack

of data evaluation, the indirect comparison fails to meet the minimum study duration of 24 weeks required in the present therapeutic indication – as was the case in studies MG0009 and MG0010 – and only examines the comparison over 12 weeks of treatment.

**Results on added benefit**

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of zilucoplan 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 the added benefit of zilucoplan.

Table 3: Zilucoplan – probability and extent 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 efgartigimod alfa 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 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.

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 zilucoplan as an add-on therapy to the standard treatment in comparison with the ACT for the treatment of adult patients with generalized myasthenia gravis who are anti-AChR antibody-positive.

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

Table 4: Research question for the benefit assessment of zilucoplan

| **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 efgartigimod alfa or ravulizumab[b, c] |
| a. Presented is the ACT specified by the G-BA.<br>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.<br>c. 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.<br>AChR: acetylcholine receptor; ACT: appropriate comparator therapy; G-BA: Federal Joint Committee | |

In the dossier, the company states that it follows the G-BA's definition of the ACT and names eculizumab (for refractory patients) or efgartigimod alfa or ravulizumab as the ACT. In its assessment, however, the company includes studies versus any comparator therapy and bases its assessment primarily on placebo-controlled studies (see Chapter I 3). The approach of the company is not appropriate. The present assessment was conducted in comparison with the G-BA’s ACT presented in Table 4.

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 the derivation of added benefit. This deviates from the company’s inclusion criteria, which specified a minimum duration of 12 weeks.

## 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 zilucoplan (status: 15 December 2023)
- bibliographical literature search on zilucoplan (last search on 15 December 2023)
- search in trial registries/trial results databases for studies on zilucoplan (last search on 15 December 2023)
- search on the G-BA website for zilucoplan (last search on 15 December 2023)

To check the completeness of the study pool:

- search in trial registries for studies on zilucoplan (last search on 18 March 2024); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of the completeness of the study pool identified no RCT that would allow a direct comparison of zilucoplan versus the ACT.

As the company did not identify any RCT for the direct comparison of zilucoplan in comparison with the ACT, it conducted an information retrieval for further investigations on zilucoplan including any comparator therapy. The company identified the placebo-controlled studies MG0009 [3] and MG0010 (RAISE) [4], which were decisive for the approval of zilucoplan. For its assessment, the company conducted a meta-analysis of these studies and, according to its information, classified the added benefit of zilucoplan on the basis of the results of the meta-analysis compared to placebo. In addition, in Appendix 4-J, in Module 4 A of the dossier, the company additionally presents an adjusted indirect comparison of zilucoplan versus ravulizumab via the common comparator placebo, which, according to the company, serves to classify the added benefit of zilucoplan in comparison with the ACT. The company presented this indirect comparison only as a supplement in Appendix 4-J of Module 4 A of the dossier (and not in the corresponding sections provided in Module 4 A). Moreover, it did not carry out information retrieval for indirect comparison. The Institute did therefore not check the completeness of the study pool for the indirect comparison.

The data presented by the company are unsuitable for drawing conclusions on the added benefit of zilucoplan in comparison with the ACT. This is justified below.

**Evidence provided by the company**

***Studies MG0009 and MG0010 comparing zilucoplan to placebo***

The MG0009 study is a triple-arm randomized, double-blind study comparing zilucoplan at doses of ~0.1 mg/kg body weight and ~0.3 mg/kg body weight with placebo, while the randomized, double-blind study MG0010 is comparing zilucoplan at a dose of ~0.3 mg/kg body weight with placebo. Both studies included adults with generalized myasthenia gravis and positive serology for AChR antibodies who at the time of screening had a Myasthenia Gravis Foundation of America (MGFA) classification II to IV, and at the time of screening and at baseline had a Quantitative Myasthenia Gravis (QMG) score of ≥ 12 points with a score of ≥ 2 points in ≥ 4 items. In the MG0009 study, inclusion was limited to patients up to MGFA classification IVa. In the MG0010 study, the patients additionally had to have a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 6 points.

The treatment with the dosage ~0.3 mg/kg body weight was carried out in the studies according to the Summary of Product Characteristics (SPC) [5] of zilucoplan. In both studies, zilucoplan was compared with placebo over a treatment duration of 12 weeks. Subsequently, all patients in the unblinded extension study MG0011 [6] could continue treatment with zilucoplan at a dose of ~0.3 mg/kg body weight until approval, provided they met the inclusion criteria of this study.

The company uses the respective study arms from the two studies MG0009 and MG0010 for the comparison of zilucoplan at a dose of ~0.3 mg/kg body weight with placebo over 12 weeks for its assessment and states that it classifies the added benefit of zilucoplan over placebo on this basis. According to the company, it summarized the results of the studies by means of meta-analyses where possible.

***Supplementary indirect comparison of zilucoplan versus ravulizumab***

In addition, the company presented an adjusted indirect comparison according to Bucher for the comparison of zilucoplan with ravulizumab via the common comparator placebo. The company presented the evaluation of the indirect comparison exclusively in Appendix 4-J in Module 4 A of the dossier, instead of an evaluation in the corresponding sections provided in Module 4 A. The company did not provide an information retrieval for the indirect comparison. On the intervention side, it used results from the MG0009 and MG0010 studies, and on the comparison side, results from the ALXN1210-MG-306 study (also referred to as the CHAMPION study). For this study comparing ravulizumab versus placebo over 26 weeks, the company referred to the dossier on the early benefit assessment of ravulizumab in the present therapeutic indication [7]. For its adjusted indirect comparison, the company used results for the intervention and comparison side each from a comparison of zilucoplan or ravulizumab versus the common comparator placebo over 12 weeks (for the intervention possibly results of studies MG0009 and MG0010 summarized via meta-analyses).

The company aimed to classify the added benefit compared with the ACT via the additional indirect comparison and discussed that zilucoplan consistently showed numerical advantages over ravulizumab. In doing so, the company considered results on selected outcomes (the MG-ADL, the visual analogue scale of the EQ-5D and the MQ-QoL15r).

***Conclusion of the company***

Based on the overall analysis of the available data (for comparison with placebo or ravulizumab over 12 weeks in each case), the company concludes that there is an overall added benefit of zilucoplan compared with the ACT, which cannot be quantified because the scientific data basis does not allow this.

**Evidence presented by the company is unsuitable for the benefit assessment**

Studies MG0009 and MG0010 as well as the meta-analyses on these studies presented by the company are not suitable for the present benefit assessment, as they do not allow a comparison with the ACT. In addition, with a comparison over 12 weeks, the study duration is too short in each case to be able to derive conclusions on the added benefit in the present therapeutic indication. Generalized myasthenia gravis is a chronic condition with a typically fluctuating course of disease, requiring long-term therapy [8,9]. In the present therapeutic indication, a comparison over at least 24 weeks of treatment is necessary. Accordingly, the EMA, as part of the approval process, already pointed out several times during the consultation process on the study design (scientific advice) that at least a 24-week comparative study duration is recommended and is also common in the therapeutic indication [8].

The indirect comparison additionally presented by the company was thus unsuitable to draw conclusions on the added benefit of zilucoplan versus the ACT. The company presented the indirect comparison only as a supplement in the appendix instead of in the corresponding sections of the dossier template and without information retrieval. The data were not evaluated in accordance with the requirements of the dossier template [10]. In addition, the company considered results on selected outcomes for the indirect comparison. Apart from the lack of data evaluation, the indirect comparison fails to meet the minimum study duration of 24 weeks required in the present therapeutic indication – as was the case in studies MG0009 and MG0010 – and only examines the comparison over 12 weeks of treatment.

## I 4 Results on added benefit

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

## I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of zilucoplan in comparison with the ACT is summarized in Table 5.

Table 5: Zilucoplan – probability and extent 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 efgartigimod alfa 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 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.

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

The assessment described above deviates from that of the company, which derived a non-quantifiable added benefit of zilucoplan compared with the ACT on the basis of the overall assessment of the available data (for comparison with placebo or ravulizumab over 12 weeks in each case).

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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