Ravulizumab
(neuromyelitis optica spectrum disorders)

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

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Ravulizumab (Neuromyelitis-optica-Spektrum-Erkrankungen) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Patient and family involvement

The questionnaire on the disease and its treatment was answered by Herbert Temmes.

IQWiG thanks the respondent and the German Society of Multiple Sclerosis, Federal Association e. V., for participating in the written exchange about how they 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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AQP4	Aquaporin 4
BSG	Bundessozialgericht (Federal Social Court)
DCGMA	Drug Commission of the German Medical Association
EDSS	Expanded Disability Status Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NMO	neuromyelitis optica
NMOSD	neuromyelitis optica spectrum disorders
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
sIPTW	stabilized inverse probability of treatment weights
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

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 in accordance with § 35a Social Code Book (SGB) V. 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 5 June 2023.

Research question

The aim of the present report is to assess the added benefit of ravulizumab in comparison with the appropriate comparator therapy (ACT) in adult patients with neuromyelitis optica spectrum disorders (NMOSD) who are anti- aquaporin 4 (AQP4) 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 ravulizumab

Therapeutic indication	**ACT**[a]
Adults with NMOSD who are anti-AQP4 antibody-positive[b]	**Eculizumab** (from the 2nd relapse) or **satralizumab**[c]

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association (AkdÄ [Arzneimittelkommission der deutschen Ärzteschaft]) in accordance with §35a para. 7, sentence 4 SGB V list both approved and unapproved drug therapies for the treatment of NMOSD. According to the G-BA, drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).
b. According to the G-BA, it is assumed that the drug ravulizumab should be used for long-term treatment due to its drug properties and not as part of a relapse therapy.
c. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. For the proof of added benefit for the overall population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets. b. In contrast, the sole comparison against a treatment option which represents a comparator therapy for only part of the patient population is usually not sufficient to demonstrate added benefit for the overall population.

AQP4: aquaporin 4; BSG: Federal Social Court; DCGMA: Drug Commission of the German Medical Association; G-BA: Federal Joint Committee; NMOSD: neuromyelitis optica spectrum disorders; SGB: Social Code Book

In connection with the specification of the ACT, the G-BA pointed out that present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association (DCGMA) in accordance with §35a (para. 7, sentence 4) SGB V list both approved

and unapproved drug therapies for the treatment of NMOSD. According to the G-BA, drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

The company deviated from the company's ACT according to Table 2 by designating treatment of physician's choice taking into account the drugs eculizumab, satralizumab and inebilizumab as ACT. The company's deviation from the ACT specified by the G-BA will not be further commented on below, as the company did not present any suitable data for the benefit assessment – neither compared with a comparator therapy designated by the company (including inebilizumab) nor compared with the ACT specified by the G-BA. The present assessment is carried out in comparison with the G-BA's ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 24 weeks were used for the derivation of added benefit. This corresponds to the inclusion criteria of the company insofar as it considers studies with a slightly different minimum duration of 26 weeks.

Results

The company's information retrieval is unsuitable for ensuring the completeness of the search results. There are considerable deficiencies. Overall, it cannot be ensured that the company's information retrieval is suitable to identify all relevant studies in the therapeutic indication.

The check identified no study for the direct comparison of ravulizumab with the ACT in the present therapeutic indication. The company also did not present any direct comparative study with ravulizumab.

Due to the lack of directly comparative data, the company presented a comparison of individual arms from different studies using the propensity score method for the assessment of the added benefit of ravulizumab versus eculizumab. In addition, the company presented a comparison of ravulizumab with eculizumab and satralizumab via a network meta-analysis. It identified the ALXN1210-NMO-307 study for the comparisons on the intervention side, the ECU-NMO-301 study for eculizumab on the comparator side and the two studies SAkuraSky and SAkuraStar for satralizumab.

Irrespective of the deficiencies in information retrieval and the potential incompleteness of the study pool considered by the company, the comparisons presented are not suitable for the benefit assessment of ravulizumab versus the ACT. This is explained below.

Evidence provided by the company

Study ALXN1210-NMO-307

The ALXN1210-NMO-307 study is an ongoing external placebo-controlled, open-label study whose recruitment is completed. This study is a single-arm ravulizumab treatment design in which the placebo arm of the ECU-NMO-301 study, for which the company was also a sponsor, was used as an external placebo control. The following remarks initially refer exclusively to the ravulizumab arm.

58 adult patients with NMOSD, diagnosed according to the 2015 international consensus criteria for NMOSD, were included. Patients had to be AQP4 antibody seropositive and have had at least 1 relapse in the 12 months prior to study inclusion. Moreover, the patients had to have an Expanded Disability Status Scale (EDSS) ≤ 7. 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.

Treatment with ravulizumab was in compliance with the Summary of Product Characteristics (SPC).

Patients who were receiving background therapy with immunosuppressants and/or oral corticosteroids at baseline had to have been on this treatment on a stable dose for a certain period before the start of the study depending on the drug and had to maintain it on stable dosing in the study. The dosage or regimen should not be adjusted in the first 106 weeks. The treatment of relapses was permitted in the study at the investigator's discretion. At the start of the study, almost half of all patients were receiving background therapy with immunosuppressants.

The study is divided into an already completed primary treatment phase and a subsequent extension phase (up to 2 years or until approval). The end of the primary treatment period was set at 26 weeks or 50 weeks, depending on the occurrence of 2 confirmed relapses in the ravulizumab arm. As no patient was diagnosed with a confirmed relapse during the study, the primary treatment phase ended when all patients included had completed the 50th week of the study or had discontinued treatment before. The data presented by the company for the benefit assessment were based on the prespecified data cut-off at the end for this primary treatment phase.

Primary outcome was the time until the first confirmed relapse and the reduction of the relapse risk. Further patient-relevant outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

External placebo arm

The ALXN1210-NMO-307 study is a single-arm study design in which the placebo arm of the randomized double-blind eculizumab study ECU-NMO-301 was used as an external placebo control. A randomized controlled trial (RCT) against eculizumab was not considered feasible by the company because, in the company's view, a very large sample would be required for this.

Study ECU-NMO-301

ECU-NMO-301 is a completed, double-blind, randomized, placebo-controlled study.

It included 143 adult patients with NMOSD diagnosed according to the 2006 international consensus criteria for neuromyelitis optica (NMO) or the 2007 NMOSD criteria.

Patients had to be AQP4 antibody seropositive and have experienced at least 2 relapses in the 12 months prior to study inclusion or at least 3 relapses within 24 months prior to study inclusion with at least 1 relapse in the 12 months prior to study inclusion. Moreover, patients had to have an EDSS score ≤ 7. All patients had to have been vaccinated against meningococci at least 14 days before the first dose of the study drug. 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.

The 143 patients included in the ECU-NMO-301 study were randomly allocated in a 2:1 ratio to either treatment with eculizumab ± background therapy (N = 96) or placebo ± background therapy (N = 47). Randomization was stratified by the EDSS score (≤ 2.0, vs. ≥ 2.5 to ≤ 7) at the time of randomization and by the previous immunosuppressive background therapy - used for relapse prevention - or background therapy status (treatment-naive vs. continued background therapy since the last relapse vs. changes in background therapy since the last relapse).

Treatment with eculizumab in the intervention arm was in compliance with the SPC.

Patients who were receiving background therapy with immunosuppressants and/or oral corticosteroids at baseline had to have been on this treatment on a stable dose before the start of the study and had to maintain it on stable dosing in the study. The dosage or regimen should not be adjusted. The treatment of relapses was permitted in the study at the investigator's discretion. At the start of the study, a good three quarters of all patients were receiving background therapy with immunosuppressants.

The patients terminated the study when they experienced a relapse as determined by the investigator. The study was to be terminated as soon as a confirmed relapse had occurred in 24 patients.

Primary outcome was the time until the first confirmed NMOSD relapse. Further patient-relevant outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

Studies SAkuraSky and SAkuraStar

The studies SAkuraSky and SAkuraStar are both completed, double-blind RCTs comparing satralizumab with placebo in patients with NMOSD. In both studies, NMOSD was diagnosed according to the 2006 international consensus criteria for NMO or the 2007 NMOSD criteria. Further information on the study design of the studies SAkuraSky and SAkuraStar can be found in the G-BA's benefit assessment of satralizumab.

In both studies, patients could be both AQP4 antibody seropositive and seronegative. For the comparison, the company used the subpopulation of AQP4 antibody seropositive patients. In the SAkuraSky study, this corresponds to 41 patients in the intervention arm and 23 patients in the placebo arm. 27 or 28 patients in the SAkuraStar study are AQP4 antibody seropositive. In both studies, this corresponds to about 2 thirds of the respective total population.

In the SAkuraSky study, patients had to have experienced at least 2 relapses in the 24 months prior to study inclusion, 1 of which had to have occurred within 12 months prior to study inclusion. In the SAkuraStar study, patients had to have experienced 1 relapse within 12 months prior to study inclusion.

Treatment with satralizumab in the intervention arm of both studies was in compliance with the SPC.

In the SAkuraSky study, patients also had to receive a stable dose of immunosuppressive background therapy at the start of the study. The corresponding dose could not be changed during the course of the study and was to be continued throughout the entire course of the study. In the SAkuraStar study, background therapy with immunosuppressants was not permitted at the start of the study.

Primary outcome of both studies was the time to occurrence of a confirmed relapse.

Approach of the company

The company presented two different comparisons to derive the added benefit of ravulizumab in comparison with the ACT:

Comparison using a propensity score procedure

The company presents this comparison for the comparison of ravulizumab (study ALXN1210-NMO-307) and eculizumab (study ECU-NMO-301) due to the availability of individual data from both studies.

The company conducted 2 different analyses using the propensity score procedure. On the one hand, this is an analysis in which the patients are stratified into 2 groups (≤ median or > median) based on the propensity score, and on the other hand, it is a weighted analysis after a stabilized inverse probability of treatment weights (sIPTW) adjustment. According to the company, 6 confounders are included as variables in the propensity score calculation.

Comparison using Bayesian network meta-analysis

The company presented this comparison for the comparison of ravulizumab (study ALXN1210-NMO-307) versus eculizumab (study ECU-NMO-301) and satralizumab (studies SAKuraStar and SAkuraSky).

For the network meta-analysis, the company first forms a 3-arm study from the individual patient data of the ravulizumab group (study ALXN1210-NMO-307) as well as the eculizumab and placebo group of the RCT ECU-NMO-301. In this 3-arm study, the placebo arm of the eculizumab study acts as an external placebo arm for the ravulizumab treatment group. Via the placebo arm of this 3-arm study, the company enables a network connection to the drug satralizumab, for which 2 placebo-controlled RCTs are available (SAkuraStar and SAkuraSky).

Assessment of the evidence presented by the company

Comparison of individual arms using the propensity score procedure (ravulizumab vs. eculizumab)

Overall, the methods and the procedure of the company (positivity, selection of confounders, the decision structure for the selection of the propensity score procedures and the presentation of the results) are inadequate:

- Lack of positivity: According to the decision of the G-BA, eculizumab only represents an ACT for patients from the 2nd relapse onwards. However, patients with only 1 relapse were also included in the ravulizumab treatment group of the ALXN1210-NMO-307 study, which the company used for the propensity score procedure. Administration of eculizumab is not an option for this patient population and they should therefore have been excluded from the comparison of ravulizumab with eculizumab. However, all patients in the ravulizumab study are included in the company's propensity score analyses.
- Failure to address differences between the ravulizumab study and the eculizumab study: The ravulizumab study (ALXN1210-NMO-307) and the eculizumab study (ECU-NMO-301) used different diagnostic criteria for NMOSD diagnosis and different inclusion criteria for the number of previous relapses. For the non-randomized comparison based on individual patient data, the company did not apply uniform inclusion and exclusion criteria to the populations of the individual studies and did not discuss possible biases due to these differences. Accordingly, there are clear differences between the patient

populations of the studies considered by the company (e.g. a higher annual relapse rate in the eculizumab arm at the start of the study). Clear differences between the ravulizumab study (ALXN1210-NMO-307) and the eculizumab study (ECU-NMO-301) were also shown for the type of previous relapses within 24 months before study inclusion. Furthermore, the proportion of patients who received background therapy with immunosuppressants at the start of the study was lower in the ravulizumab study than in the eculizumab study. In summary, patients in the ECU-NMO-301 study (both the eculizumab arm and the placebo arm) had a higher disease burden than patients in the ravulizumab treatment group.

- A study protocol prepared in advance including analysis plan and predefinition of a decision structure for the analyses presented in the benefit assessment using the propensity score procedure is missing.
- Missing data on the procedure for the selection of the 6 confounders that, according to the company, were included as variables in the propensity score calculation.
- The confounder selection appears incomplete. For example, the company did not consider the type of relapses, the severity of previous relapses or existing concomitant diseases as confounders.
- In Module 4 A, results are only available for one of the two propensity score analyses mentioned by the company.

Overall, the data presented by the company are therefore not interpretable and are not used for the present benefit assessment.

Comparison using network meta-analysis

For the comparison by means of network meta-analysis, the company used a study on ravulizumab side (study ALXN1210-NMO-307) that compared ravulizumab with an external placebo arm from the eculizumab approval study (ECU-NMO-301). The company did not fully adjust the inclusion criteria for the ravulizumab treatment group of the ALXN1210-NMO-307 study to the eculizumab ECU-NMO-301 study. As a result, patients in the external placebo arm had a higher disease burden compared to the ravulizumab arm.

The company's analyses include the patients' data without taking into account the deviations in the baseline patient characteristics of the respective studies. As different patient populations are therefore considered, the effect resulting from the comparison of the ravulizumab treatment arm with the external placebo arm is not informative. This inconclusive comparison of the ravulizumab treatment group with the external placebo arm is the only evidence on ravulizumab presented by the company for the network meta-analysis.

The comparability of the patient populations of the satralizumab studies (SAkuraSky and SAkuraStar) to those of the ravulizumab and eculizumab studies cannot be assessed with sufficient certainty due to missing or insufficient data for the satralizumab studies.

In summary, the results from this network for the comparisons (ravulizumab vs. eculizumab; ravulizumab vs. satralizumab) cannot be interpreted for the benefit assessment.

Results on added benefit

No suitable data are available for assessing the added benefit of ravulizumab in comparison with the ACT in the treatment of adult patients with NMOSD who are AQP4-IgG seropositive. 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.

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

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with NMOSD who are anti-AQP4 antibody-positive[b]	**Eculizumab** (from the 2nd relapse) or **satralizumab**[c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association (AkdÄ [Arzneimittelkommission der deutschen Ärzteschaft]) in accordance with §35a para. 7, sentence 4 SGB V list both approved and unapproved drug therapies for the treatment of NMOSD. According to the G-BA, drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).
b. It is assumed that the drug ravulizumab should be used for long-term treatment due to its drug properties and not as part of a relapse therapy.
c. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. For the proof of added benefit for the overall population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets. b. In contrast, the sole comparison against a treatment option which represents a comparator therapy for only part of the patient population is usually not sufficient to demonstrate added benefit for the overall population.

AQP4: aquaporin 4; BSG: Federal Social Court; DCGMA: Drug Commission of the German Medical Association; G-BA: Federal Joint Committee; NMOSD: neuromyelitis optica spectrum disorders; SGB: Social Code Book

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 in comparison with the ACT in adult patients with NMOSD who are anti-AQP4 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 ravulizumab

Therapeutic indication	ACT[a]
Adults with NMOSD who are anti-AQP4 antibody-positive[b]	**Eculizumab** (from the 2nd relapse) or **satralizumab**[c]

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association (AkdÄ [Arzneimittelkommission der deutschen Ärzteschaft]) in accordance with §35a para. 7, sentence 4 SGB V list both approved and unapproved drug therapies for the treatment of NMOSD. According to the G-BA, drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).
b. According to the G-BA, it is assumed that the drug ravulizumab should be used for long-term treatment due to its drug properties and not as part of a relapse therapy.
c. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. For the proof of added benefit for the overall population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets. b. In contrast, the sole comparison against a treatment option which represents a comparator therapy for only part of the patient population is usually not sufficient to demonstrate added benefit for the overall population.

AQP4: aquaporin 4; BSG: Federal Social Court; DCGMA: Drug Commission of the German Medical Association; G-BA: Federal Joint Committee; NMOSD: neuromyelitis optica spectrum disorders; SGB: Social Code Book

In connection with the specification of the ACT, the G-BA pointed out that present guidelines and scientific-medical societies and/or the DCGMA in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the treatment of NMOSD. According to the G-BA, drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the Federal Social Court (BSG) comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

The company deviated from the company's ACT according to Table 4 by designating treatment of physician's choice taking into account the drugs eculizumab, satralizumab and inebilizumab as ACT. The company's deviation from the ACT specified by the G-BA will not be further commented on below, as the company did not present any suitable data for the benefit

assessment – neither compared with a comparator therapy designated by the company (including inebilizumab) nor compared with the ACT specified by the G-BA. The present assessment is carried out in comparison with the G-BA's ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 24 weeks were used for the derivation of added benefit. This corresponds to the inclusion criteria of the company insofar as it considers studies with a slightly different minimum duration of 26 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 ravulizumab and on the ACT (status: 12 May 2023)
- bibliographical literature search on ravulizumab (last search on 25 April 2023)
- search in trial registries/trial results databases for studies on ravulizumab (last search on 11 May 2023)
- search on the G-BA website for ravulizumab (last search on 12 May 2023)
- bibliographical literature search on the ACT (last search on 25 April 2023)
- search in trial registries/trial results databases for studies on the ACT (last search on 12 May 2023)
- search on the G-BA website for the ACT (last search on 12 May 2023)

The company's information retrieval is unsuitable for ensuring the completeness of the search results. This is due to the following reasons: For example, for the intervention side (ravulizumab), the company only presents the information retrieval for non-randomized comparative studies. It remains unclear whether the search results were also reviewed for RCTs on ravulizumab. The information retrieval on RCTs with ravulizumab is not presented.

However, the company limited its search for studies on the ACT in bibliographic databases to RCTs. In addition, the information on the included and excluded studies is contradictory. For example, when presenting the bibliographic search for the ACT in the flow chart (Module 4 A, Figure 4-11), the company stated that it had screened 48 publications in full text. Of these, 29 publications were excluded by the company after screening and 10 publications (on 9 studies) were included. It remains unclear which publications or studies are involved in the remaining 9 publications.

In addition, the company uses the Boolean operator "OR" in lower case in the ClinicalTrials.gov trial registry when searching in study registries (both for ravulizumab and for the ACT). This is not implemented as intended by the search interface. Correct use of the Boolean operator "OR" generates additional hits. This does not ensure that all potentially relevant studies in the therapeutic indication were identified by the company.

Overall, it is not ensured that the company's information retrieval identified all relevant studies in the therapeutic indication.

To check the completeness of the study pool:

- search in trial registries for studies on ravulizumab (last search on 27 June 2023); for search strategies, see I Appendix A of the full dossier assessment

The check identified no study for the direct comparison of ravulizumab with the ACT in the present therapeutic indication. The company also did not present any direct comparative study with ravulizumab.

For the assessment of the added benefit of ravulizumab versus eculizumab, the company therefore presented a comparison of individual arms from different studies using the propensity score procedure. In addition, the company presented a comparison of ravulizumab with eculizumab and satralizumab via a network meta-analysis. It identified the ALXN1210-NMO-307 study [3-6] for the comparisons on the intervention side, the ECU-NMO-301 study [7-10] on the comparator side for eculizumab and the two studies SAkuraSky [11] and SAkuraStar [11,12] for satralizumab.

Irrespective of the deficiencies in information retrieval described above and the potential incompleteness of the study pool considered by the company, the comparisons presented are not suitable for the benefit assessment of ravulizumab versus the ACT. This is explained below.

I 3.1 Evidence provided by the company

I 3.1.1 Evidence on ravulizumab

Study ALXN1210-NMO-307

The ALXN1210-NMO-307 study is an ongoing external placebo-controlled, open-label study whose recruitment is completed (see Table 6 in I Appendix B). This study is a single-arm ravulizumab treatment design in which the placebo arm of the ECU-NMO-301 study (see below and I 3.1.2.1 I 3.1.2.1), for which the company was also a sponsor, was used as an external placebo control. The following remarks initially refer exclusively to the ravulizumab arm.

It included 58 adult patients with NMOSD diagnosed according to the 2015 international consensus criteria for NMOSD [13]. Patients had to be AQP4 antibody seropositive and have had at least 1 relapse in the 12 months prior to study inclusion. Moreover, the patients had to have an EDSS ≤ 7. 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.

Treatment with ravulizumab was in compliance with the SPC [14].

Patients who were receiving background therapy with immunosuppressants and/or oral corticosteroids at baseline had to have been on this treatment on a stable dose for a certain

period before the start of the study depending on the drug and had to maintain it on stable dosing in the study. The dosage or regimen should not be adjusted in the first 106 weeks. The treatment of relapses was permitted in the study at the investigator's discretion. At the start of the study, almost half of all patients were receiving background therapy with immunosuppressants. For further details regarding permitted and non-permitted concomitant therapies, see Table 7 in I Appendix B of the full dossier assessment.

The study is divided into an already completed primary treatment phase and a subsequent extension phase (up to 2 years or until approval). The end of the primary treatment period was set at 26 weeks or 50 weeks, depending on the occurrence of 2 confirmed relapses in the ravulizumab arm. As no patient was diagnosed with a confirmed relapse during the study, the primary treatment phase ended when all patients included had completed the 50th week of the study or had discontinued treatment before. The data presented by the company for the benefit assessment were based on the prespecified data cut-off at the end for this primary treatment phase.

Primary outcome was the time until the first confirmed relapse and the reduction of the relapse risk. Further patient-relevant outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

External placebo arm

The ALXN1210-NMO-307 study is a single-arm study design in which the placebo arm of the randomized double-blind eculizumab study ECU-NMO-301 was used as an external placebo control.

The company justified this approach by stating that NMOSD is a very rare disease with irreversible damage as a result of relapses. For ethical reasons, an external placebo-controlled, open-label clinical trial had therefore been conducted in agreement with the regulatory authorities to assess the efficacy of ravulizumab. According to the company, the ravulizumab study was designed on the basis of the eculizumab study in order to enable a comparison of the ravulizumab arm with the placebo group of the eculizumab study. In addition, adjusted comparisons using the propensity score procedure should be carried out as sensitivity analyses. An RCT against eculizumab was not considered feasible by the company because, in the company's view, a very large sample would be required for this.

I 3.1.2 Evidence on the ACT

I 3.1.2.1 Evidence on eculizumab

Study ECU-NMO-301

The ECU-NMO-301 study is a completed, double-blind, randomized, placebo-controlled study (see Table 6 in I Appendix B of the full dossier assessment).

It included 143 adult patients with NMOSD diagnosed according to the 2006 international consensus criteria for NMO or the 2007 NMOSD criteria [15,16] (see also Section I 3.3.1).

Patients had to be AQP4 antibody seropositive and have experienced at least 2 relapses in the 12 months prior to study inclusion or at least 3 relapses within 24 months prior to study inclusion with at least 1 relapse in the 12 months prior to study inclusion. Moreover, patients had to have an EDSS score ≤ 7. All patients had to have been vaccinated against meningococci at least 14 days before the first dose of the study drug. 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.

The 143 patients included in the ECU-NMO-301 study were randomly allocated in a 2:1 ratio to either treatment with eculizumab ± background therapy (N = 96) or placebo ± background therapy (N = 47). Randomization was stratified by the EDSS score (≤ 2.0, vs. ≥ 2.5 to ≤ 7) at the time of randomization and by the previous immunosuppressive background therapy - used for relapse prevention - or background therapy status (treatment-naive vs. continued background therapy since the last relapse vs. changes in background therapy since the last relapse).

Treatment with eculizumab in the intervention arm was in compliance with the SPC [17].

Patients who were receiving background therapy with immunosuppressants and/or oral corticosteroids at baseline had to have been on this treatment on a stable dose before the start of the study and had to maintain it on stable dosing in the study. The dosage or regimen should not be adjusted. The treatment of relapses was permitted in the study at the investigator's discretion. At the start of the study, a good three quarters of all patients were receiving background therapy with immunosuppressants. For further details regarding permitted and non-permitted concomitant therapies, see Table 7 in I Appendix B of the full dossier assessment.

The patients terminated the study when they experienced a relapse as determined by the investigator. The study was to be terminated as soon as a confirmed relapse had occurred in 24 patients.

Primary outcome was the time until the first confirmed NMOSD relapse. Further patient-relevant outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

I 3.1.2.2 Evidence on satralizumab

Studies SAkuraSky and SAkuraStar

The studies SAkuraSky and SAkuraStar are both completed, double-blind RCTs comparing satralizumab with placebo in patients with NMOSD. In both studies, NMOSD was diagnosed according to the 2006 international consensus criteria for NMO or the 2007 NMOSD criteria [15,16] (see also Section I 3.3.2). Further information on the SAkuraSky and the SAkuraStar study design is available in the G-BA's benefit assessment of satralizumab [18].

In both studies, patients could be both AQP4 antibody seropositive and seronegative. For the comparison, the company used the subpopulation of AQP4 antibody seropositive patients. In the SAkuraSky study, this corresponds to 41 patients in the intervention arm and 23 patients in the placebo arm. 27 or 28 patients in the SAkuraStar study are AQP4 antibody seropositive. In both studies, this corresponds to about 2 thirds of the respective total population.

In the SAkuraSky study, patients had to have experienced at least 2 relapses in the 24 months prior to study inclusion, 1 of which had to have occurred within 12 months prior to study inclusion. In the SAkuraStar study, patients had to have experienced 1 relapse within 12 months prior to study inclusion.

Treatment with satralizumab in the intervention arm of both studies was in compliance with the SPC [19].

In the SAkuraSky study, patients also had to receive a stable dose of immunosuppressive background therapy at the start of the study. The corresponding dose could not be changed during the course of the study and was to be continued throughout the entire course of the study. In the SAkuraStar study, background therapy with immunosuppressants was not permitted at the start of the study.

Primary outcome of both studies was the time to occurrence of a confirmed relapse.

I 3.2 Approach of the company

The company presented two different comparisons to derive the added benefit of ravulizumab in comparison with the ACT:

- Comparison using a propensity score procedure; The company presents this comparison for the comparison of ravulizumab (study ALXN1210-NMO-307) and eculizumab (study ECU-NMO-301) due to the availability of individual data from both studies.
- Comparison using Bayesian network meta-analysis: The company presented this comparison for the comparison of ravulizumab (study ALXN1210-NMO-307) versus eculizumab (study ECU-NMO-301) and satralizumab (studies SAKuraStar and SAkuraSky).

I 3.2.1 Comparison of individual arms using the propensity score procedure (ravulizumab vs. eculizumab)

For the comparison of individual arms using the propensity score, the company used the ravulizumab treatment group of the ALXN1210-NMO-307 study and the eculizumab treatment group of the ECU-NMO-301 study (see Section I 3.1.1 and I 3.1.2.1). Patient-specific data were available to the company for both studies.

To account for potential bias resulting from differences in study designs and random differences in recruitment, the company stated that it conducted 2 different analyses using propensity score procedures.

On the one hand, this is an analysis in which the patients are stratified into 2 groups (≤ median or > median) based on the propensity score, and on the other hand, it is a weighted analysis after a sIPTW adjustment.

According to the company, the following 6 confounders are included as variables in the propensity score calculation:

- Geographical region
- Sex
- Age at first dose
- Intake of immunosuppressive therapy
- EDSS total score at baseline
- Confirmed annual relapse rate within 24 months before screening

For this comparison of individual arms, the company presented results on various outcomes in the categories of morbidity, health-related quality of life and side effects using the propensity score procedure.

I 3.2.2 Comparison using network meta-analysis

To assess the relative treatment effects between ravulizumab, eculizumab and satralizumab, the company conducted a comparison using a Bayesian network meta-analysis.

For the network meta-analysis, the company first forms a 3-arm study from the individual patient data of the ravulizumab group (study ALXN1210-NMO-307) as well as the eculizumab and placebo group of the RCT ECU-NMO-301. In this 3-arm study, the placebo arm of the eculizumab study acts as an external placebo arm for the ravulizumab treatment group. Via the placebo arm of this 3-arm study, the company enables a network connection to the drug satralizumab, for which 2 placebo-controlled RCTs are available (SAkuraStar and SAkuraSky;

see Section I 3.1.2.2). Since the two satralizumab studies included patients regardless of their AQP4 antibody serostatus, the company only considered the data of patients who were positive for AQP4 antibodies in the analyses it presented.

Thus, placebo served as common comparator in the network meta-analysis. For the analyses, the patients' data were included without adjustment, i.e. without taking into account the deviations in the baseline patient characteristics of the respective studies.

Overall, the company formed 3 networks on the basis of the aforementioned ravulizumab, eculizumab and satralizumab studies. These differ in that different patient populations of the studies were considered, depending on whether they received the respective intervention with or without concomitant immunosuppressive background therapy (without immunosuppressive therapy, with immunosuppressive therapy, with or without immunosuppressive therapy). The company did not present any justification for the consideration of these 3 networks. However, it can be assumed that this is due to the fact that in both studies on satralizumab, patients with concomitant immunosuppressive background therapy were excluded from the SAkuraStar study, but that concomitant immunosuppressive background therapy of the patients was an inclusion criterion for the SAkuraSky study. The ravulizumab and eculizumab study included patients both with and without immunosuppressive background therapy. Since the present therapeutic indication includes patients with and without concomitant immunosuppressive background therapy, the following sections refer to the corresponding network (without or with immunosuppressive therapy).

The company presented results from the network meta-analysis exclusively for the outcome "relapses" (time to 1st confirmed relapse; relapse rate).

I 3.3 Assessment of the evidence presented by the company

I 3.3.1 Comparison of individual arms using the propensity score procedure (ravulizumab vs. eculizumab)

The comparison of individual arms presented by the company using the propensity score procedure is not suitable for the assessment of the added benefit of ravulizumab versus eculizumab. This is justified below.

Lack of positivity

In order to achieve the goal of positivity in the present case, ravulizumab and eculizumab had to represent a potential treatment option for the patient groups of both studies considered at the time of the treatment decision.

According to the GB-A's specification, eculizumab only represents an ACT for patients from the 2nd relapse onwards (see Table 4). However, patients with only 1 relapse were also included in the ravulizumab treatment group of the ALXN1210-NMO-307 study, which the company used for the propensity score procedure. Administration of eculizumab is not an option for this patient population (lack of positivity).

Data on the exact proportion of the patients with only one relapse before study inclusion are not available. There is only the information that the patients in the ravulizumab study had a median of 2 relapses before inclusion in the study. This information only allows the estimation that a range of up to 50% of the patients in the ravulizumab study only had 1 relapse before inclusion in the study and therefore had to be excluded beforehand for the comparison of ravulizumab with eculizumab. However, all patients in the ravulizumab study are included in the company's propensity score analyses.

Overall, it is unclear whether treatment with eculizumab would basically have been an option for all patients of the ravulizumab arm considered in the propensity score analyses (positivity). The company did not explain to what extent the positivity is given from the company's point of view. This approach is not appropriate.

Failure to address differences between the ravulizumab study and the eculizumab study

The studies used by the company show relevant differences:

Inclusion criterion "NMOSD diagnostic criteria"

For the non-randomized comparison based on individual patient data presented by the company, uniform inclusion and exclusion criteria should initially be applied to the populations of the individual studies as far as possible. However, the company did not apply standardized inclusion and exclusion criteria and did not discuss possible bias due to these differences.

Thus, the ravulizumab treatment group (ALXN1210-NMO-307) was diagnosed with NMOSD according to the broader/more sensitive international consensus criteria for NMOSD from 2015 [13]. In contrast, the diagnosis in the eculizumab study (ECU-NMO-301) was made according to the (older) 2006 international consensus criteria for NMO [16] or according to the 2007 NMOSD criteria [15].

The revision of the diagnostic criteria carried out in 2015 led to an expansion of the clinical and imaging spectrum of NMOSD and allows an earlier and more accurate diagnosis of NMOSD; for example, involvement of the optic nerve and/or spinal cord is no longer a mandatory requirement for an NMOSD diagnosis according to the 2015 criteria. The patients in the eculizumab study were all seropositive for AQP4 antibodies and it can thus be assumed that they also fulfil the 2015 criteria. However, it remains open whether further/other patients

would have been included in the eculizumab study if the broader/more sensitive 2015 criteria had been used (e.g. patients without involvement of the optic nerve and/or spinal cord).

These differences in diagnostic criteria may lead to different populations (e.g. a lower disease burden in patients in the ravulizumab study), which limits the interpretation of the results. This also corresponds to the assessment of the European Medicines Agency (EMA) [20].

Inclusion criterion "Number of previous relapses"

The ravulizumab study also included patients with only 1 relapse, while inclusion in the eculizumab study required at least 2 relapses within the 12 months prior to study inclusion or 3 relapses within 24 months prior to study inclusion with at least 1 relapse in the 12 months prior to study inclusion, resulting in a lack of positivity for the non-randomized comparison (see above).

According to these different specifications on the number of previous relapses, there are clear differences between the patient populations of the studies analysed by the company. Patients in the ravulizumab arm had a median annual relapse rate of 1.44 within 24 months before the start of the study, while the median relapse rate in the eculizumab arm of the ECU-NMO-301 study was 1.85 (1.92 in the placebo arm). The median number of relapses before the start of the study was also lower in the ravulizumab arm (2 previous relapses) than in the eculizumab arm of the ECU-NMO-301 study (5 previous relapses; in the placebo arm: 4 previous relapses; see also Table 8).

The different inclusion criteria with regard to previous relapses in the ravulizumab study and the eculizumab study therefore mean that the patients in the eculizumab arm have a higher disease burden compared to the ravulizumab arm.

Number of previous relapses

There are some clear differences between the ravulizumab study (ALXN1210-NMO-307) and the eculizumab study (ECU-NMO-301) with regard to the type of previous relapses within 24 months prior to study inclusion: transverse myelitis occurred in 59% of patients in the ravulizumab arm compared to 77% of patients in the eculizumab arm of the ECU-NMO-301 study (or 89% in the placebo arm; see Table 8).

In a comment submitted to the EMA during the approval procedure, the company itself states that, based on its own calculations, patients with transverse myelitis within the 24 months prior to screening have a 3-fold higher risk of a further relapse than patients without a relapse of this type [21].

Proportion of patients with immunosuppressive background therapy

At the start of the study, around half of the patients in the ravulizumab study received immunosuppressive background therapy, whereas in the eculizumab study around three quarters of the patients received background immunosuppressive therapy. This difference could be due to the fact that the patients in the ravulizumab study had a lower disease burden.

Conclusion on differences between studies

In summary, patients in the ECU-NMO-301 study (both the eculizumab arm and the placebo arm) had a higher disease burden than patients in the ravulizumab treatment group (ALXN1210-NMO-307 study; see also Table 8).

Inadequate confounder identification and questionable completeness

Since the necessary structural equality between the treatment groups is not guaranteed in non-randomized studies, group differences in possible confounders (confounding variables), i.e. factors that are related to both the treatment and outcomes and can thus alter a treatment effect, must be taken into account in the effect estimation. The first prerequisite for this is that relevant confounders are systematically identified. In addition, the underlying procedure for identifying the confounders must be sufficiently documented.

In Module 4 A, the company names the 6 variables listed in Section I 3.2.1, which it claims were included in the propensity score calculation. Information on the procedure for selecting these confounders is missing. Consequently, it is unclear whether the approach of the company is suitable for the systematic identification of important confounders.

Moreover, the confounder selection appears incomplete. For example, the company did not consider the type of relapses as confounders. It cannot be ruled out, for example, that a relapse event of transverse myelitis in the patient's history poses a higher risk of a further relapse than for patients without a relapse of this type (see above). Criteria that, according to the S2k guideline [22], should also be taken into account when deciding on treatment for patients with NMOSD - such as the severity of previous relapses or existing comorbidities - should at first be assessed as relevant confounders. Overall, it is questionable whether the company identified and considered all relevant confounders.

Inadequate predefinition and presentation of the results of the propensity score procedure

A study protocol prepared in advance including analysis plan for the analyses presented in the benefit assessment using the propensity score procedure is missing. However, it can be assumed that the company orientated itself on the statistical analysis plan (SAP) of the ALXN1210-NMO-307 study [23]. The company does not make any concrete statements in this regard. However, it is neither evident from the SAP of the ALXN1210-NMO-307 study nor from

Module 4 A of the company that a decision structure for the selection of the propensity score procedure was defined in advance and that the conduct of sensitivity analyses and a necessary minimum degree of overlap and balance for the comparisons using the propensity score method were predefined.

In Module 4 A, the company states that it used 2 different propensity score procedures for the comparison of ravulizumab with eculizumab (see Section I 3.2.1). Advantages of the respective procedures and the question why other procedures are less suitable in the present case are not discussed.

Moreover, in Module 4 A, the company eventually only presented results for one of the two propensity score analyses. The information provided does not make clear which propensity score procedure is involved in the results presented. However, based on the number of patients included in the corresponding analyses, it can be assumed that stratification was applied according to the propensity score median. There are therefore no results available using a further propensity score procedure (sensitivity analyses). However, such sensitivity analyses are necessary to demonstrate the best possible structural equality of the analysis populations for the chosen propensity score procedure.

In addition, there are further specific aspects:

- The 2 propensity score procedures used by the company are based on the 6 confounders considered by the company. The prerequisite for the application of these 2 procedures is sufficient overlap, measured by the propensity score of the compared cohorts.
  The overlap of the propensity scores of the groups to be compared cannot be adequately assessed due to the insufficiently described confounder selection. Even the propensity score determined by the company on the basis of the 6 confounders selected by it, does not allow an adequate assessment of the overlap, as propensity score graphs such as histograms or boxplots are not shown. However, the data presented show that the lower quartile of propensity scores in the ravulizumab group is close to the upper quartile of the eculizumab group. This rather suggests a lack of overlap.
- There are differences between the ravulizumab and eculizumab arms in the patient characteristics before adjustment using propensity scores (see Table 8). Patients in the eculizumab arm have a higher disease burden at baseline than the patient population of the ravulizumab arm (see above in this section). Information on the baseline characteristics after adjustment is only available for the 6 confounders and for 2 further baseline characteristics (scale value of the Hauser Ambulation Index and scale value of the European Quality of Life 5 Dimensions visual analogue scale) (Table 4-20 in Module 4 A; only for the approach using sIPTW adjustment). Therefore, the balance for all patient

characteristics cannot be assessed. In principle, appropriate assessment of the balance is impossible due to the inadequate selection of confounders.

- In addition, the completeness of the study pool for the comparison of ravulizumab with eculizumab is questionable due to the deficiencies in the information retrieval described in Chapter I 3.

Conclusion

Overall, the methods and the procedure of the company for the presented comparisons of individual arms are inadequate. There are relevant shortcomings with regard to positivity, the uniformity of inclusion and exclusion criteria, the selection of confounders, the decision structure for the selection of propensity score procedures and with regard to the presentation of the results. The data presented by the company are therefore not interpretable and are not used for the present benefit assessment.

I 3.3.2 Comparison using network meta-analysis

The analyses of the network meta-analysis presented by the company are not suitable for deriving conclusions on the added benefit of ravulizumab versus the G-BA's ACT. This is justified below.

External placebo arm unsuitable as common comparator

For the comparison of ravulizumab versus eculizumab and satralizumab, the company conducted a Bayesian network meta-analysis (see Section I 3.2.2). The company's analyses include the patients' data without taking into account the deviations in the baseline patient characteristics of the respective studies.

On the ravulizumab side, the company used a study that compared ravulizumab with an external placebo arm from the eculizumab approval study.

The company did not fully adjust the inclusion criteria for the ravulizumab treatment group of the ALXN1210-NMO-307 study to the eculizumab ECU-NMO-301 study. As described in Section I 3.3.1 for the analyses presented by the company using the propensity score, there are clear differences between the ravulizumab treatment group and the external placebo arm of the eculizumab study, particularly in the number and type of previous relapses of the patients. Due to these differences, patients in the external placebo arm had a higher disease burden than those in the ravulizumab arm.

As different patient populations are therefore considered, the effect resulting from the comparison of the ravulizumab treatment arm with the external placebo arm is not informative. These differences in patient characteristics between the ravulizumab arm and the external placebo arm and the resulting potential impact on the primary and secondary

outcomes were also critically noted by the EMA in the approval procedure for ravulizumab [20].

This inconclusive comparison of the ravulizumab treatment group with the external placebo arm is the only evidence on the ravulizumab side presented by the company for the network meta-analysis and is therefore included in the comparison with both eculizumab and satralizumab. For the comparison with satralizumab, it should be noted that there are clear differences for the outcome of relapses (time to first confirmed relapse; relapse rate) - irrespective of a final assessment of the comparability of the operationalizations. However, it is unclear whether this effect would persist in an adequate comparison.

It should also be noted that the comparability of the patient population of the satralizumab studies with the patient population of the ravulizumab study cannot be assessed with sufficient certainty, as essential data are missing, particularly on the number and type of previous relapses.

In summary, the results from this network for the comparisons (ravulizumab vs. eculizumab; ravulizumab vs. satralizumab) cannot be interpreted for the benefit assessment.

Results only for the outcome of relapses

The company only presented results from the network meta-analysis for the outcome "relapses" (time to 1st confirmed relapse; relapse rate). Analyses of results on further morbidity outcomes, health-related quality of life and adverse events (AEs) are missing. The company did not present any justification for this. Irrespective of the overall lack of suitability of the data presented by the company for the comparison of ravulizumab with the ACT, balancing of the benefits and harms is thus not possible.

Furthermore, the completeness of the study pool for the comparison of ravulizumab with the ACT is questionable due to the deficiencies in the information retrieval described in Chapter I 3.

Conclusion

Patients in the external placebo arm have a higher disease burden compared to the ravulizumab arm. The company's analyses include the patients' data without taking into account the deviations in the baseline patient characteristics of the respective studies. Overall, the results of the network meta-analysis cannot be interpreted due to the unsuitable comparison of ravulizumab vs. external placebo arm and are therefore not used for the present benefit assessment.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of ravulizumab in comparison with the ACT in the treatment of adult patients with NMOSD who are AQP4-IgG seropositive. There is no hint of an added benefit of ravulizumab in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

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

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with NMOSD who are anti-AQP4 antibody-positive[b]	**Eculizumab** (from the 2nd relapse) or **satralizumab**[c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association (AkdÄ [Arzneimittelkommission der deutschen Ärzteschaft]) in accordance with §35a para. 7, sentence 4 SGB V list both approved and unapproved drug therapies for the treatment of NMOSD. According to the G-BA, drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).
b. It is assumed that the drug ravulizumab should be used for long-term treatment due to its drug properties and not as part of a relapse therapy.
c. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. For the proof of added benefit for the overall population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets. b. In contrast, the sole comparison against a treatment option which represents a comparator therapy for only part of the patient population is usually not sufficient to demonstrate added benefit for the overall population.

AQP4: aquaporin 4; BSG: Federal Social Court; DCGMA: Drug Commission of the German Medical Association; G-BA: Federal Joint Committee; NMOSD: neuromyelitis optica spectrum disorders; SGB: Social Code Book

The assessment described above deviates from that of the company, which derived a hint of a major added benefit on the basis of the data provided by it.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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