Benralizumab (eosinophilic granulomatosis with polyangiitis)

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 *Benralizumab (eosinophile Granulomatose mit Polyangiitis) – 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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Keywords

Benralizumab, Churg-Strauss Syndrome, Benefit Assessment, NCT04157348

Medical and scientific advice

- Thomas O. F. Wagner

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 2 people.

IQWiG thanks the respondents and the German patient organization 'Deutsche Rheuma-Liga Bundesverband e.V.' for participating in the written exchange and for their support. The respondents and the Deutsche Rheuma-Liga Bundesverband 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
ACQ	Asthma Control Questionnaire
ACR	American College of Rheumatology
ACT	appropriate comparator therapy
AE	adverse event
ANCA	anti-neutrophil cytoplasmic antibodies
BVAS	Birmingham Vasculitis Activity Score
CHCC	Chapel Hill Consensus Conference
EGPA	eosinophilic granulomatosis with polyangiitis
EULAR	European League Against Rheumatism
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
OCS	oral corticosteroid
PGIS	Patient Global Impression of Severity
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SC	subcutaneous
SF-36v2	Short Form 36-version 2 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SNOT-22	22-item Sino-Nasal Outcome Test
SPC	Summary of Product Characteristics
VDI	Vasculitis Damage Index
WPAI	Work Productivity and Activity Impairment

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug benralizumab. 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 25 November 2024.

Research question

The aim of the present report is to assess the added benefit of benralizumab as add-on treatment in comparison with the appropriate comparator therapy (ACT) for adult patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA).

The research questions presented in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of benralizumab

Research question	Therapeutic indication	ACT[a]
1	Add-on treatment for adult patients with relapsing or refractory EGPA with organ-threatening or life-threatening manifestations	Treatment of physician's choice, selecting from cyclophosphamide and rituximab to induce remission, followed by mepolizumab to maintain remission, each in combination with corticosteroids[b]
2	Add-on treatment for adult patients with relapsing or refractory EGPA without organ-threatening or life-threatening manifestations	Mepolizumab[c]

a. Presented is the respective ACT specified by the G-BA.

b. According to the G-BA, the treatment of severe EGPA is divided into 2 treatment phases: remission induction and remission maintenance.

- Remission induction: Current guidelines recommend the use of either cyclophosphamide or rituximab together with high-dose corticosteroid treatment to induce remission in the event of a relapse with organ-threatening or life-threatening manifestations. There is very limited evidence base for this specific situation in this generally rare disease. Corticosteroids and mepolizumab (as add-on treatment for relapsing-remitting or refractory EGPA) are approved for patients with EGPA. Even though the approved therapeutic indication for mepolizumab generally covers all degrees of severity, the Summary of Product Characteristics (SPC) points out that mepolizumab has not been studied in patients with organ-threatening or life-threatening manifestations of EGPA. Since guidelines also do not recommend mepolizumab for inducing remission in this severe form of the disease, mepolizumab is not considered standard therapy for this patient population. Corticosteroids are used in combination with other drugs, but are not an option as the sole therapy for patients with organ-threatening or life-threatening manifestations of EGPA. According to the G-BA, the off-label use of cyclophosphamide and rituximab as add-on treatment to corticosteroids is medically necessary and, according to generally accepted medical knowledge, is considered standard treatment in adults with relapsing or refractory EGPA with organ-threatening or life-threatening manifestations, and is generally preferable to the drug mepolizumab, which is currently approved in the therapeutic indication, §6 (2), sentence 3, number 2, AM-NutzenV.
- Remission maintenance: According to the G-BA and pursuant to §35a (7) sentence 4 SGB V, treatment with conventional nonsteroidal immunosuppressants (EULAR: methotrexate, azathioprine; EU expert panel: general nonsteroidal immunosuppressants; United States: azathioprine/methotrexate/mycophenolate mofetil), mepolizumab and rituximab should be considered to maintain remission in patients with organ-threatening or life-threatening manifestations (after new-onset or relapse), in accordance with the above-mentioned guidelines and the scientific and medical societies. The EULAR guideline refers to a prospective study on methotrexate in comparison with cyclophosphamide, as well as to observational studies on azathioprine, mepolizumab and rituximab. Overall, according to the G-BA, it cannot be clearly inferred from the available evidence that the use of the mentioned off-label treatment options is medically imperative, as mepolizumab, an approved drug recommended by guidelines and German medical societies, is an ACT option for remission maintenance in organ-threatening or life-threatening manifestations of EGPA.

c. According to the G-BA, it is assumed that patients in both study arms are offered guideline-compliant basic therapy with corticosteroids. It is also assumed that for patients who are eligible for treatment with benralizumab, treatment with corticosteroids alone is not suitable.

ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; EGPA: eosinophilic granulomatosis with polyangiitis; EULAR: European League Against Rheumatism; G-BA: Federal Joint Committee; SGB V: Social Code Book V

For better readability, the research questions defined by the G-BA are abbreviated below as follows:

- adult patients with organ-threatening or life-threatening manifestations
- adult patients without organ-threatening or life-threatening manifestations

Research questions 1 and 2 of the present benefit assessment correspond to the company's subpopulations 1 and 2.

In research question 1, the ACT presented by the company in Module 4 A deviates from the ACT specified by the G-BA. For research question 1, the company only cited "treatment of physician's choice, selecting from cyclophosphamide and rituximab in combination with corticosteroids" as the ACT, and thus only part (remission induction) of the ACT specified by the G-BA. The approach of the company is not appropriate. The assessment is conducted in comparison with the ACT specified by the G-BA. For research question 2, the company followed 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. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks are used for the derivation of added benefit.

Research question 1: adult patients with organ-threatening or life-threatening manifestations

Results

The check of completeness of the study pool did not identify any relevant studies comparing benralizumab with the ACT for research question 1 (adult patients with organ-threatening or life-threatening manifestations). Overall, no data on the comparison of benralizumab as add-on treatment versus the ACT are available for research question 1.

Results on added benefit

Since no data are available for the assessment of the added benefit of benralizumab in comparison with the ACT, there is no hint of an added benefit of benralizumab in comparison with the ACT; an added benefit is therefore not proven for this research question.

Research question 2: adult patients without organ-threatening or life-threatening manifestations

Study pool and study design

The MANDARA study was used for the benefit assessment for research question 2 (adult patients without organ-threatening or life-threatening manifestations).

The MANDARA study is a double-blind RCT comparing benralizumab with mepolizumab, each as an add-on to an oral corticosteroid (OCS) and, if necessary, an immunosuppressant in adult patients with EGPA. Patients who had an organ-threatening EGPA (organ failure due to active vasculitis, creatinine > 5.8 mg/dL) or life-threatening EGPA within 3 months prior to screening were excluded from participation in the study.

A total of 140 patients were randomly allocated in a 1:1 ratio to 52 weeks of treatment with either benralizumab (N = 70) or mepolizumab (N = 70), each as an add-on to OCS and an immunosuppressant if necessary. The MANDARA's patient population is heterogeneous since it included both patients with active disease and those with a history of relapsing or refractory disease. Based on the Birmingham Vasculitis Activity Score (BVAS), 49% of patients in the intervention arm and 47% in the comparator arm had active disease (BVAS > 0) at baseline.

In the MANDARA study, benralizumab and mepolizumab were administered in compliance with the respective SPCs. To maintain blinding, patients both in the intervention and in the comparator arm received placebo. The patients received OCS and possibly immunosuppressants as concomitant treatment.

The primary outcome was the proportion of patients achieving remission at both Week 36 and Week 48. In the MANDARA study, remission was defined as BVAS = 0 and OCS dose ≤ 4 mg/day in the main analysis; and as BVAS = 0 and OCS dose ≤ 7.5 mg/day in the supportive analysis. Further patient-relevant outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

Risk of bias

The risk of bias across outcomes for the MANDARA study is rated as low. The risk of bias for the results on all outcomes for which usable data are available is rated as low.

Results

Mortality

All-cause mortality

No deaths occurred during the double-blind phase of the study. There is no hint of added benefit of benralizumab in comparison with mepolizumab, each as add-on treatment; an added benefit is therefore not proven.

Morbidity

Remission

For the outcome of remission with the 7.5 mg/day OCS threshold, no statistically significant difference between treatment groups was found. There is no hint of added benefit of

benralizumab in comparison with mepolizumab, each as add-on treatment; an added benefit is therefore not proven.

Severe EGPA symptoms

No suitable data are available for the outcome of severe EGPA symptoms. There is no hint of added benefit of benralizumab in comparison with mepolizumab, each as add-on treatment; an added benefit is therefore not proven.

Asthma symptoms (recorded using ACQ-6)

For the outcome of asthma symptoms (recorded using the Asthma Control Questionnaire [ACQ]-6), no statistically significant difference between treatment groups was found. There is no hint of added benefit of benralizumab in comparison with mepolizumab, each as add-on treatment; an added benefit is therefore not proven.

Sinonasal symptoms (recorded using SNOT-22)

For the outcome of sinonasal symptoms (recorded using the 22-item Sino-Nasal Outcome Test [SNOT-22]), no statistically significant difference between treatment groups was found. There is no hint of added benefit of benralizumab in comparison with mepolizumab, each as add-on treatment; an added benefit is therefore not proven.

Activity impairment (recorded using WPAI question 6)

For the outcome of activity impairment (recorded using the Work Productivity and Activity Impairment [WPAI] question 6), no statistically significant difference between treatment groups was found. There is no hint of added benefit of benralizumab in comparison with mepolizumab, each as add-on treatment; an added benefit is therefore not proven.

Symptoms (recorded using PGIS)

No suitable data are available for the outcome of symptoms (recorded using the Patient Global Impression of Severity [PGIS]). There is no hint of added benefit of benralizumab in comparison with mepolizumab, each as add-on treatment; an added benefit is therefore not proven.

Health-related quality of life (recorded using SF-36v2)

For the outcome of health-related quality of life (recorded using the Short Form 36-version 2 Health Survey [SF-36v2]), no statistically significant difference between treatment groups was found. There is no hint of added benefit of benralizumab in comparison with mepolizumab, each as add-on treatment; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of serious adverse events (SAEs) or discontinuation due to adverse events (AEs). In each case, there is no hint of greater or lesser harm from benralizumab in comparison with mepolizumab, each as add-on treatment; greater or lesser harm 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 benralizumab.

Table 3: Benralizumab – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Add-on treatment for adult patients with relapsing or refractory EGPA with organ-threatening or life-threatening manifestations	Treatment of physician's choice, selecting from cyclophosphamide and rituximab to induce remission, followed by mepolizumab to maintain remission, each in combination with corticosteroids[b]	Added benefit not proven
2	Add-on treatment for adult patients with relapsing or refractory EGPA without organ-threatening or life-threatening manifestations	Mepolizumab[c]	Added benefit not proven

[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].

Table 3: Benralizumab – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, the treatment of severe EGPA is divided into 2 treatment phases: remission induction and remission maintenance.
- Remission induction: Current guidelines recommend the use of either cyclophosphamide or rituximab together with high-dose corticosteroid treatment to induce remission in the event of a relapse with organ-threatening or life-threatening manifestations. There is very limited evidence base for this specific situation in this generally rare disease. Corticosteroids and mepolizumab (as add-on treatment for relapsing-remitting or refractory EGPA) are approved for patients with EGPA. Even though the approved therapeutic indication for mepolizumab generally covers all degrees of severity, the Summary of Product Characteristics (SPC) points out that mepolizumab has not been studied in patients with organ-threatening or life-threatening manifestations of EGPA. Since guidelines also do not recommend mepolizumab for inducing remission in this severe form of the disease, mepolizumab is not considered standard therapy for this patient population. Corticosteroids are used in combination with other drugs, but are not an option as the sole therapy for patients with organ-threatening or life-threatening manifestations of EGPA. According to the G-BA, the off-label use of cyclophosphamide and rituximab as add-on treatment to corticosteroids is medically necessary and, according to generally accepted medical knowledge, is considered standard treatment in adults with relapsing or refractory EGPA with organ-threatening or life-threatening manifestations, and is generally preferable to the drug mepolizumab, which is currently approved in the therapeutic indication, §6 (2), sentence 3, number 2, AM-NutzenV.
- Remission maintenance: According to the G-BA and pursuant to §35a (7) sentence 4 SGB V, treatment with conventional nonsteroidal immunosuppressants (EULAR: methotrexate, azathioprine; EU expert panel: general nonsteroidal immunosuppressants; United States: azathioprine/methotrexate/mycophenolate mofetil), mepolizumab and rituximab should be considered to maintain remission in patients with organ-threatening or life-threatening manifestations (after new-onset or relapse), in accordance with the above-mentioned guidelines and the scientific and medical societies. The EULAR guideline refers to a prospective study on methotrexate in comparison with cyclophosphamide, as well as to observational studies on azathioprine, mepolizumab and rituximab. Overall, according to the G-BA, it cannot be clearly inferred from the available evidence that the use of the mentioned off-label treatment options is medically imperative, as mepolizumab, an approved drug recommended by guidelines and German medical societies, is an ACT option for remission maintenance in organ-threatening or life-threatening manifestations of EGPA.

c. According to the G-BA, it is assumed that patients in both study arms are offered guideline-compliant basic therapy with corticosteroids. It is also assumed that for patients who are eligible for treatment with benralizumab, treatment with corticosteroids alone is not suitable.

ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; EGPA: eosinophilic granulomatosis with polyangiitis; EULAR: European League Against Rheumatism; G-BA: Federal Joint Committee; SGB V: Social Code Book V

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of benralizumab as add-on treatment in comparison with the ACT for adult patients with relapsing or refractory EGPA.

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

Table 4: Research questions of the benefit assessment of benralizumab

Research question	Therapeutic indication	ACT[a]
1	Add-on treatment for adult patients with relapsing or refractory EGPA with organ-threatening or life-threatening manifestations	Treatment of physician's choice, selecting from cyclophosphamide and rituximab to induce remission, followed by mepolizumab to maintain remission, each in combination with corticosteroids[b]
2	Add-on treatment for adult patients with relapsing or refractory EGPA without organ-threatening or life-threatening manifestations	Mepolizumab[c]

a. Presented is the respective ACT specified by the G-BA.

b. According to the G-BA, the treatment of severe EGPA is divided into 2 treatment phases: remission induction and remission maintenance.

- Remission induction: Current guidelines [3-5] recommend the use of either cyclophosphamide or rituximab together with high-dose corticosteroid treatment to induce remission in the event of a relapse with organ-threatening or life-threatening manifestations. There is very limited evidence base for this specific situation in this generally rare disease. Corticosteroids and mepolizumab (as add-on treatment for relapsing-remitting or refractory EGPA) are approved for patients with EGPA. Even though the approved therapeutic indication for mepolizumab generally covers all degrees of severity, the SPC [6] points out that mepolizumab has not been studied in patients with organ-threatening or life-threatening manifestations of EGPA. Since guidelines also do not recommend mepolizumab for inducing remission in this severe form of the disease, mepolizumab is not considered standard therapy for this patient population. Corticosteroids are used in combination with other drugs, but are not an option as the sole therapy for patients with organ-threatening or life-threatening manifestations of EGPA. According to the G-BA, the off-label use of cyclophosphamide and rituximab as add-on treatment to corticosteroids is medically necessary and, according to generally accepted medical knowledge, is considered standard treatment in adults with relapsing or refractory EGPA with organ-threatening or life-threatening manifestations, and is generally preferable to the drug mepolizumab, which is currently approved in the therapeutic indication, §6 (2), sentence 3, number 2, AM-NutzenV.
- Remission maintenance: According to the G-BA and pursuant to §35a (7) sentence 4 SGB V, treatment with conventional nonsteroidal immunosuppressants (EULAR: methotrexate, azathioprine; EU expert panel: general nonsteroidal immunosuppressants; United States: azathioprine/methotrexate/mycophenolate mofetil), mepolizumab and rituximab should be considered to maintain remission in patients with organ-threatening or life-threatening manifestations (after new-onset or relapse), in accordance with the above-mentioned guidelines and the scientific and medical societies. The EULAR guideline refers to a prospective study on methotrexate in comparison with cyclophosphamide, as well as to observational studies on azathioprine, mepolizumab and rituximab. Overall, according to the G-BA, it cannot be clearly inferred from the available evidence that the use of the mentioned off-label treatment options is medically imperative, as mepolizumab, an approved drug recommended by guidelines and German medical societies, is an ACT option for remission maintenance in organ-threatening or life-threatening manifestations of EGPA.

c. According to the G-BA, it is assumed that patients in both study arms are offered guideline-compliant basic therapy with corticosteroids. It is also assumed that for patients who are eligible for treatment with benralizumab, treatment with corticosteroids alone is not suitable.

ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; EGPA: eosinophilic granulomatosis with polyangiitis; EULAR: European League Against Rheumatism; G-BA: Federal Joint Committee; SGB V: Social Code Book V

For better readability, the research questions defined by the G-BA are abbreviated below as follows:

- adult patients with organ-threatening or life-threatening manifestations
- adult patients without organ-threatening or life-threatening manifestations

Research questions 1 and 2 of the present benefit assessment correspond to the company's subpopulations 1 and 2.

In research question 1, the ACT presented by the company in Module 4 A deviates from the ACT specified by the G-BA. For research question 1, the company only cited "treatment of physician's choice, selecting from cyclophosphamide and rituximab in combination with corticosteroids" as the ACT, and thus only part (remission induction) of the ACT specified by the G-BA. The company justified its deviating specification of the ACT for research question 1 by claiming that patients in remission maintenance under mepolizumab no longer have an active organ-threatening or life-threatening manifestation. For this reason, the company assigned this patient group to research question 2 (patients without active organ-threatening or life-threatening manifestations). The approach of the company is not appropriate. Maintaining remission is part of the therapeutic strategy also for patients with initial organ-threatening or life-threatening manifestations. The decisive factor for assigning patients to research question 1 or 2 is therefore the initial manifestation of disease (with [research question 1] or without [research question 2] organ-threatening or life-threatening manifestations). The assessment is conducted in comparison with the ACT specified by the G-BA. For research question 2, the company followed 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. RCTs with a minimum duration of 24 weeks are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 3 Research question 1: adult patients with organ-threatening or life-threatening manifestations

I 3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on benralizumab (status: 23 September 2024)
- bibliographical literature search on benralizumab (last search on 23 September 2024)
- search in trial registries/trial results databases for studies on benralizumab (last search on 23 September 2024)
- search on the G-BA website for benralizumab (last search on 23 September 2024)

To check the completeness of the study pool:

- search in trial registries for studies on benralizumab (last search on 10 December 2024); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check identified no relevant study.

I 3.2 Results on added benefit

There are no data available to assess the added benefit of benralizumab compared with the ACT for adult patients with relapsing or refractory EGPA with organ-threatening or life-threatening manifestations. There is no hint of an added benefit of benralizumab in comparison with the ACT; an added benefit is therefore not proven for this research question.

I 3.3 Probability and extent of added benefit

In its dossier, the company presented no data to assess the added benefit of benralizumab compared with the ACT for patients with relapsing or refractory EGPA with organ-threatening or life-threatening manifestations. An added benefit of benralizumab versus the ACT is therefore not proven for research question 1.

This assessment concurs with that of the company.

I 4 Research question 2: adult patients without organ-threatening or life-threatening manifestations

I 4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on benralizumab (status: 23 September 2024)
- bibliographical literature search on benralizumab (last search on 23 September 2024)
- search in trial registries/trial results databases for studies on benralizumab (last search on 23 September 2024)
- search on the G-BA website for benralizumab (last search on 23 September 2024)

To check the completeness of the study pool:

- search in trial registries for studies on benralizumab (last search on 10 December 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 4.1.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: benralizumab vs. mepolizumab

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
D3253C00001 (MANDARA[c])	Yes	Yes	No	Yes [7-9]	Yes [10-12]	Yes [13]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.
CSR: clinical study report; RCT: randomized controlled trial

The MANDARA study was used for the benefit assessment for research question 2 (adult patients without organ-threatening or life-threatening manifestations). The study pool is consistent with the study pool of the company.

I 4.1.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: benralizumab + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MANDARA	RCT, double-blind[b], parallel	Adults (≥ 18 years) with relapsing[c] or refractory[d] EGPA[e], based on the history or presence of asthma + eosinophilia[f] + at least 2 additional features of EGPA[g]	▪ Benralizumab + OCS ± immunosuppressant (N = 70) ▪ Mepolizumab + OCS ± immunosuppressant (N = 70)	▪ Screening: up to 4 weeks ▪ Treatment[h]: 52 weeks ▪ Observation[i]: 4 weeks	50 centres in Belgium, Canada, France, Germany, Israel, Italy, Japan, United Kingdom, USA 10/2019–ongoing[j] ▪ Data cut-off after the end of the double-blind phase: 10 August 2023	Primary: proportion of patients in remission[k] Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: benralizumab + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. The study consists of 2 study phases: 52-week double-blind phase and subsequent open-label extension phase with benralizumab 30 mg (SC every 4 weeks) for at least 1 year; the open-label extension phase is not relevant for the present benefit assessment and is therefore not shown in the tables below.
c. ≥ 1 confirmed EGPA relapse (i.e. requiring increase in OCS dose, initiation or increased dose of immunosuppressive therapy or hospitalization) within the past 2 years which occurred ≥ 12 weeks prior to screening (Visit 1) while receiving an OCS dose of ≥ 7.5 mg/day;
different definition of relapsing disease in Japan: ≥ 1 confirmed EGPA relapse (increase in OCS dose, initiation of IV prednisolone [or equivalent], initiation/increased dose of immunosuppressive therapy, or initiation/increased dose of IV immunoglobulin, or hospitalization) within the past 2 years which occurred ≥ 12 weeks prior to screening (Visit 1) while receiving a dose of prednisolone (or equivalent) of ≥ 7.5 mg/day.
d. Failure to attain remission (BVAS = 0 and OCS dose ≤ 7.5 mg/day) within the 6 months following induction treatment with a standard regimen, administered for at least 3 months, or recurrence of symptoms of EGPA (not necessarily meeting the protocol definition of relapse) while tapering OCS (dose of ≥ 7.5 mg/day) within 6 months prior to screening (Visit 1). Patients who had received an induction regimen comprising corticosteroids alone could be included only if they have failed to attain remission after 3 months of treatment and the corticosteroids dose was ≥ 15 mg/day prednisolone for the 4 weeks prior to baseline (Visit 2).
e. Diagnosed with EGPA for ≥ 6 months before screening (Visit 1); patients with organ-threatening or life-threatening EGPA were excluded from study participation.
f. < 1 x 10^9/L and/or > 10% of leucocytes.
g. A biopsy showing histopathological evidence of eosinophilic vasculitis, or perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation; neuropathy, mono or poly (motor deficit or nerve conduction abnormality); pulmonary infiltrates, non-fixed; sinonasal abnormality; cardiomyopathy (established by echocardiography or magnetic resonance imaging); glomerulonephritis (haematuria, red cell casts, proteinuria); alveolar haemorrhage (by bronchoalveolar lavage); palpable purpura; ANCA-positive (MPO and/or PR3).
h. Last dose of the double-blind phase at Week 48.
i. For patients who prematurely discontinued the study medication, efficacy outcomes and side effects were recorded within 4 weeks (± 7 days) after the last dose (replacing the scheduled visit).
j. The double-blind phase of the study has been completed; the open-label extension phase is ongoing.
k. Main analysis defined as BVAS = 0 and OCS dose ≤ 4 mg/day, supportive analysis defined as BVAS = 0 and OCS dose ≤ 7.5 mg/day; both at Week 36 and Week 48.

AE: adverse event; ANCA: anti-neutrophil cytoplasmic antibodies; BVAS: Birmingham Vasculitis Activity Score; EGPA: eosinophilic granulomatosis with polyangiitis; IV: intravenous; MPO: myeloperoxidase; N: number of randomized patients; OCS: oral corticosteroids; PR3: proteinase-3; RCT: randomized controlled trial; SC: subcutaneous

Table 7: Characteristics of the intervention – RCT, direct comparison: benralizumab + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant (multipage table)

Study	Intervention	Comparison
MANDARA	▪ Benralizumab 30 mg SC every 4 weeks ▪ Placebo to mepolizumab SC every 4 weeks	▪ Mepolizumab 300 mg (3 times 100 mg) SC every 4 weeks ▪ Placebo to benralizumab SC every 4 weeks
	Dose adjustments for benralizumab and mepolizumab were not permitted. Dose delays/interruptions were permitted.	
	Concomitant treatment ▪ Oral corticosteroids: prednisolone or prednisone[a] at a stable dose ≥ 7.5 mg/day (≤ 50 mg/day) for ≥ 4 weeks before baseline (Visit 2) ▫ Dose reduction from Week 4, if possible[b] ▫ If clinically indicated, dose increase permitted from baseline until Week 4 and to treat relapses[c] ▪ Immunosuppressive therapy: ▫ e.g. azathioprine, methotrexate, or mycophenolate mofetil at a stable dose ≥ 4 weeks prior to baseline (Visit 2) and during the entire course of the study[d] **Prohibited prior and concomitant treatment** ▪ Corticosteroid therapy[e] (IV, IM or SC) from 4 weeks prior to baseline (Visit 2) ▪ Omalizumab from 130 days prior to screening (Visit 1) ▪ Cyclophosphamide from 2 or 3 weeks prior to baseline (Visit 2)[f] ▪ Rituximab from 6 months prior to screening (Visit 1) ▪ Immunoglobulins (IV or SC) from 30 days prior to screening (Visit 1) ▪ Interferon-α from 6 months prior to screening (Visit 1) ▪ Anti-TNF drugs from 12 weeks prior to screening (Visit 1) ▪ Anti-CD52 antibodies (alemtuzumab) from 6 months prior to screening (Visit 1) ▪ Any prior or current treatment with benralizumab, mepolizumab, reslizumab, or dupilumab ▪ Other biologic products[g] ▪ Other investigational products[h] ▪ Live attenuated vaccines from 30 days prior to screening (Visit 1) up to 12 weeks after the last dose of study medication	

Table 7: Characteristics of the intervention – RCT, direct comparison: benralizumab + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant (multipage table)

Study	Intervention	Comparison
a. Stable OCS doses other than prednisone or prednisolone could be permitted, but had to be discussed with the study physician. b. From Week 4 post-baseline (Visit 4) onwards if the patient's BVAS = 0, their OCS dose was to be tapered downwards according to standard of care practice. If the BVAS > 0, the investigator could taper the patient's OCS downwards at his/her clinical discretion. The study protocol recommended a reduction in OCS dose every 2 weeks, with the intention of achieving a prednisone/prednisolone dose of ≤ 4 mg/day. Once a patient achieved a dose of 4 mg/day prednisone/prednisolone, the investigator was to continue tapering downwards, if clinically warranted, at dose steps of 0.5 to 1 mg every 2 weeks. c. An increase in the OCS dose was permitted within the 0 to 4 mg/day range without necessarily being defined as a relapse. d. Reduction in the dose was only permitted for safety reasons, with a return to the original dose, where possible. In the event immunosuppressive therapy was initiated or the dose increased, patients were excluded from further study treatment. e. Use of inhaled and topical steroids was permitted both as concomitant treatment and as pretreatment. Hydrocortisone (IV or IM) for the treatment of acute adrenal insufficiency was permitted throughout the study. f. Patients who had received cyclophosphamide induction regimen could be randomized a minimum of 2 weeks after the last oral dose, or 3 weeks after the last infusion if their total white blood cell count was ≥ 4×10^9/L. g. Biologic products within 4 months or 5 half-lives prior to screening (Visit 1), whichever was longer. h. Non-biologic products within 30 days or 5 half-lives prior to screening (Visit 1), whichever was longer. BVAS: Birmingham Vasculitis Activity Score; CD52: cluster of differentiation 52; IM: intramuscular; IV: intravenous; OCS: oral corticosteroids; RCT: randomized controlled trial; SC: subcutaneous; TNF: tumour necrosis factor		

Study design

The MANDARA study is a double-blind RCT comparing benralizumab with mepolizumab, each as an add-on to an OCS and, if necessary, an immunosuppressant in adult patients with EGPA. The diagnosis had to have been established at least 6 months prior to screening.

No consensus exists on the diagnostic criteria for EGPA. The literature lists the Lanham criteria [14], the Chapel Hill Consensus Conference (CHCC) nomenclature [15] as well as the American College of Rheumatology (ACR) criteria [16] or an updated version of the ACR/European League Against Rheumatism (EULAR) for a definition of EGPA [17].

The MANDARA study used modified ACR criteria, and the EGPA diagnosis was based on patient history or the presence of asthma and eosinophilia as well as at least 2 additional features of EGPA (see Table 6), which are, however, not all of the same diagnostic value.

Patients who had an organ-threatening EGPA (organ failure due to active vasculitis, creatinine > 5.8 mg/dL) or life-threatening EGPA within 3 months prior to screening were excluded from participation in the study.

A total of 140 patients were randomly allocated in a 1:1 ratio to 52 weeks of treatment with either benralizumab (N = 70) or mepolizumab (N = 70), each as an add-on to OCS and an immunosuppressant if necessary. Randomization was stratified by region of patient recruitment in North America, Japan and rest of the world (Western Europe and Israel).

In the MANDARA study, benralizumab and mepolizumab were administered in compliance with the respective SPCs [6,18]. To maintain blinding, patients in the intervention arm and in the comparator arm each received placebo, as dosing of mepolizumab (300 mg) was in the form of 3 subcutaneous (SC) applications of 100 mg. The concomitant treatment, consisting of OCS (prednisolone or equivalent) at a dosage ≥ 7.5 mg/day (up to a maximum of 50 mg/day) and, if necessary, an immunosuppressant, had to be stable for at least 4 weeks prior to randomization. OCS was taken daily or every 2 days, and the daily dose was recorded in an electronic diary. OCS dose adjustments were permitted (see Table 7). The use of immunosuppressants (e.g. azathioprine,, methotrexate, mycophenolate mofetil), in contrast, was allowed only if the dosage was kept stable from ≥ 4 weeks prior to baseline until the end of the study. Cyclophosphamide and rituximab treatment was disallowed during the study. At baseline, 26 of 70 patients (37%) in the intervention arm and 24 of 70 patients (34%) in the comparator arm received an immunosuppressant.

After completion of the 52-week double-blind phase, patients in both study arms could receive benralizumab as add-on treatment in an open-label extension phase.

The primary outcome was the proportion of patients achieving remission at both Week 36 and Week 48. In the MANDARA study, remission was defined as BVAS = 0 and OCS dose ≤ 4 mg/day in the main analysis; and as BVAS = 0 and OCS dose ≤ 7.5 mg/day in the supportive analysis. Further patient-relevant outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

The data cut-off from 10 August 2023 presented by the company was prespecified and took place at the end of the double-blind phase.

Patient characteristics

Table 8 shows the patient characteristics of the included study.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: benralizumab + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant (multipage table)

Study Characteristic Category	**Benralizumab + OCS ± immunosuppressant N[a] = 70**	**Mepolizumab + OCS ± immunosuppressant N[a] = 70**
MANDARA		
Age [years], mean (SD)	52 (14)	53 (14)
Sex [F/M], %	64/36	56/44
Family origin, n (%)		
White	53 (76[b])	57 (81[b])
Asian	9 (13[b])	8 (11[b])
Other	3 (4[b])	2 (3[b])
Missing data[c]	5 (7[b])	3 (4[b])
Duration of disease (years)		
Mean (SD)	5.4 (5.4)	4.9 (5.9)
Median [min; max]	3.0 [0.6; 24.0]	2.2 [0.1; 38.0]
EGPA disease history		
Relapsing EGPA, n (%)	45 (64)	48 (69)
Refractory EGPA, n (%)	42 (60)	42 (60)
Both relapsing and refractory EGPA, n (%)	18 (26)	20 (29)
Number of EGPA relapses[d] over past 2 years, n (%)		
0	12 (17)	13 (19)
1	24 (34)	20 (29)
2	17 (24)	17 (24)
3–5	12 (17)	16 (23)
> 5	2 (3)	2 (3)
Unknown	3 (4)	2 (3)
OCS[e] – daily dose (mg), median [min; max]	10.0 [5.0[f]; 30.0]	10.0 [7.5; 40.0]
OCS[e] – daily dose categories, n (%)		
< 12 mg/day	52 (74)	56 (80)
≥ 12 mg/day	18 (26)	14 (20)
Immunosuppressive therapy since diagnosis, n (%)	41 (59)	42 (60)
Immunosuppressants[g] at baseline, n (%)	26 (37)	24 (34)

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: benralizumab + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant (multipage table)

Study Characteristic Category	**Benralizumab + OCS ± immunosuppressant N[a] = 70**	**Mepolizumab + OCS ± immunosuppressant N[a] = 70**
BVAS		
Mean (SD)	2.3 (3.5)	1.9 (2.9)
Median [min; max]	0 [0; 18]	0 [0; 15]
BVAS > 0, n (%)	34 (49)	33 (47)
General	9 (13)[h]	10 (14)[h]
Skin	2 (3)[h]	4 (6)[h]
Mucous membrane/eyes	3 (4)[h]	3 (4)[h]
Ear, nose and throat	24 (34)[h]	18 (26)[h]
Chest	21 (30)[h]	14 (20)[h]
Cardiovascular	0 (0)[h]	0 (0)[h]
Abdominal	1 (1)[h]	1 (1)[h]
Renal	1 (1)[h]	1 (1)[h]
Nervous system	11 (16)[h]	8 (11)[h]
ACQ-6		
Mean (SD)	1.4 (1.2)	1.2 (1.1)
Median [min; max]	1.2 [0; 4.5]	1.0 [0; 5.3]
< 1.5, n (%)	39 (56)	42 (60)
≥ 1.5, n (%)	31 (44)	28 (40)
SNOT-22		
Mean (SD)	32.7 (21.8)	30.4 (21.3)
Median [min; max]	31.0 [0; 103]	25.0 [0; 89]
Treatment discontinuation, n (%)[i]	1 (1)	3 (4)
Study discontinuation, n (%)[j]	1 (1)	3 (4)

a. Number of randomized patients who received at least one dose of the respective treatment.
b. Institute's calculation.
c. "Missing data" on family origin originates from French study centres due to local requirements.
d. Based on the information on EGPA disease history, it is assumed that both patients with relapsing disease and patients with refractory disease were included.
e. Prednisone/prednisolone or equivalent.
f. One patient began reducing the prednisolone or prednisone dose to 5 mg/day on the day of Visit 2. The screening dose remained stable at 7.5 mg/day.
g. Azathioprine, methotrexate, methotrexate sodium, hydroxychloroquine and mycophenolate mofetil.
h. Institute's calculation.
i. Reasons for treatment discontinuation in the intervention arm vs. the control arm (percentages relate to the randomized patients) were withdrawal of patient consent (1% vs. 3%) and AEs (0% vs. 1%).
j. Reasons for study discontinuation in the intervention arm vs. the control arm (percentages relate to the randomized patients) were COVID-19 pandemic (1% vs. 0%), AEs (0% vs. 1%), withdrawal of patient consent (0% vs. 1%), and other (0% vs. 1%).

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: benralizumab + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant (multipage table)

Study Characteristic Category	Benralizumab + OCS ± immunosuppressant N[a] = 70	Mepolizumab + OCS ± immunosuppressant N[a] = 70
ACQ-6: Asthma Control Questionnaire (6-item version); AE: adverse event; BVAS: Birmingham Vasculitis Activity Score; EGPA: eosinophilic granulomatosis with polyangiitis; F: female; M: male; max: maximum; min. minimum; n: number of patients in the category; N: number of randomized patients; OCS: oral corticosteroids; RCT: randomized controlled trial; SD: standard deviation; SNOT-22: 22-item Sino-Nasal Outcome Test		

Patient characteristics were sufficiently balanced between the treatment arms. The mean patient age was approximately 52 years; most patients were women (64% and 56%), and most were of white family origin. About 79% of patients had at least one EGPA relapse in the past 2 years. The median daily OCS dose at baseline was 10 mg. 37% of patients in the intervention arm and 34% in the comparator arm received an immunosuppressant as additional concomitant therapy. Around 60% of the study population had already received an immunosuppressant at any time since their EGPA diagnosis.

The proportion of patients who discontinued treatment or the study by the end of the double-blind phase of the study was low at 1% in the intervention arm and 4% in the comparator arm.

Further comments on the included study population

The MANDARA study comprises a heterogeneous patient population because both patients with active disease and patients with a history of relapsing or refractory disease were eligible for inclusion (for the definition of relapsing and refractory, see Table 6). Based on the BVAS, 49% of patients in the intervention arm and 47% in the comparator arm had active disease (BVAS > 0) at baseline, with the majority of patients having symptoms in the ear, nose and throat area (34% vs. 26%) and in the chest area (30% vs. 20%). 44% versus 40% of patients had inadequately controlled asthma symptoms (ACQ-6 ≥ 1.5) [19]. In addition to the symptoms caused by vasculitis, asthma is part of the characteristic clinical picture of EGPA and is not necessarily associated with vasculitis (see also Section I 4.2.1). This explains the difference between the number of patients with chest symptoms according to BVAS and the number of patients with inadequate asthma control.

The present benefit assessment uses the remission definition according to the current S3 guideline [20] (see Section I 4.2.1). It is not clear from the available information how many patients were in remission at enrolment, based on this definition (BVAS = 0 and OCS ≤ 7.5 mg/day). In principle, patients were eligible if their daily OCS dose was at least 7.5 mg. Patients with a treatment of exactly 7.5 mg OCS per day at enrolment were already in

remission at this time if they also had a BVAS = 0. With regard to the aforementioned remission definition, it is unclear whether these patients required initiation of a new therapy with benralizumab or mepolizumab. However, besides achieving remission according to the above definition, a further reduction in the daily OCS dose (e.g. to 5 mg/day [20]) is also a recognized treatment goal in the therapeutic indication of EGPA. It is conceivable that long-term treatment with new treatment options such as benralizumab and mepolizumab can generally lead to a permanent reduction in the OCS dose. The mentioned uncertainty therefore remains without consequence for the present benefit assessment.

Furthermore, it is unclear how many patients had refractory or relapsing disease at enrolment, as the available information only refers to the history of refractory and relapsing disease. Since it is assumed that there was no deviating distribution of relevant extent at enrolment, this remains without consequence for the present benefit assessment.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: benralizumab + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
MANDARA	Yes	Yes	Yes	Yes	Yes	Yes	Low
OCS: oral corticosteroids; RCT: randomized controlled trial							

The risk of bias across outcomes for the MANDARA study is rated as low.

Transferability of the study results to the German health care context

The company described that more than 70% of patients in the MANDARA study were treated in European study centres and more than 80% had white skin colour. According to the company, there is no evidence of pharmacokinetic or pharmacodynamic differences between the different population groups.

The company also stated that patients in the MANDARA study could continue treatment with nonsteroidal immunosuppressants (azathioprine, methotrexate, mycophenolic acid or mycophenolate mofetil) in addition to OCS, provided that they were already receiving these at a stable dose at enrolment. According to the company, no treatment was allowed to be

started or adjusted at the beginning or during the course of the study (toxicity-related dose reductions were permitted, however).

The company additionally stated that, according to guideline recommendations, patients who have achieved remission after a relapse should be treated with OCS and mepolizumab or nonsteroidal immunosuppressants or rituximab, while at the same time it should be intended to reduce the OCS dose to the lowest possible level [4,5,20]. Thus, in the company's view, the MANDARA study's background therapy with nonsteroidal immunosuppressants and OCS or OCS alone represents a therapeutic treatment that is compliant with guidelines and established in practice. According to the company, nonsteroidal immunosuppressants could be administered in both arms according to the above-mentioned criteria. According to the company, administration of these drugs was comparable in both study arms, making possible bias in the results due to these therapeutics very unlikely.

Taking the above aspects into account, the company presumed good transferability of the study results to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4.2 Results on added benefit

I 4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - remission
  - severe EGPA symptoms
  - asthma symptoms (recorded using the ACQ-6)
  - sinonasal symptoms (recorded using the SNOT-22)
  - activity impairment (recorded using the WPAI question 6)
  - symptoms (recorded using the PGIS)
- Health-related quality of life
  - recorded using the SF-36v2

- Side effects
  - SAEs
  - discontinuation due to AEs
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 A).

Table 10 shows the outcomes for which data were available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: benralizumab + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant

Study	Outcomes										
	All-cause mortality[a]	Remission[b]	Severe EGPA symptoms[c]	Asthma symptoms (ACQ-6)	Sinonasal symptoms (SNOT-22)	Activity impairment (WPAI question 6)	Symptoms (PGIS)	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Specific AEs
MANDARA	Yes	Yes	No[d]	Yes	No[d]	Yes	No[d]	Yes	Yes	Yes	No[e]

a. Deaths were recorded as AEs.
b. Operationalized as BVAS = 0 and OCS dose (prednisolone or prednisone) ≤ 7.5 mg/day.
c. Operationalized as hospitalization for EGPA symptoms.
d. No suitable data available; see body of text for reasons.
e. No specific AEs were identified based on the AEs that occurred in the relevant study.

ACQ: Asthma Control Questionnaire; AE: adverse event; BVAS: Birmingham Vasculitis Activity Score; EGPA: eosinophilic granulomatosis with polyangiitis; OCS: oral corticosteroids; PGIS: Patient Global Impression of Severity; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36 Health Survey Version 2; SNOT-22: 22-item Sino-Nasal Outcome Test; WPAI: Work Productivity and Activity Impairment

Remission

In Module 4 A, the company presented analyses on the proportion of patients in remission both at Week 36 and at Week 48, at Week 52 and within the first 24 weeks with maintenance until Week 52, each for 3 different definitions of remission:

- BVAS = 0 and OCS dose ≤ 7.5 mg/day

- BVAS = 0 and OCS dose ≤ 4 mg/day
- BVAS = 0 and OCS dose = 0 mg/day (steroid-free remission)

In the MANDARA study, the definition of remission with the threshold value of the OCS dose ≤ 7.5 mg/day was a supportive analysis for the primary outcome of remission (BVAS = 0 and OCS dose ≤ 4 mg/day). In addition, the company presented the individual components (BVAS = 0; OCS ≤ 7.5 mg/day; OCS ≤ 4 mg/day; OCS = 0 mg/day) at the respective time points mentioned above as supportive analyses.

BVAS is an instrument for the clinical assessment of disease activity in systemic vasculitis which is completed by the treating physician. The BVAS is divided into 9 organ-based systems, with each section containing items about signs or symptoms typical for the involvement of the respective organ in systemic vasculitis [21,22]. Several items of this instrument are rated on the basis of laboratory or imaging results, which, individually, are not necessarily patient-relevant. However, the definition of remission requires a BVAS of 0, i.e. no signs of disease activity in any item; the fact that the instrument for surveying disease activity includes laboratory and imaging results is therefore irrelevant in this case. The MANDARA study shows that in patients who relapsed during the course of the study, this relapse was predominantly caused by vasculitic manifestations (see Table 19 in I Appendix C of the full dossier assessment), so that the selected remission definition is sufficient. However, since the BVAS was not developed specifically for the therapeutic indication of EGPA, the EGPA symptoms of asthma and sinonasal symptoms, which are additional characteristic features besides vasculitis, but not necessarily caused by vasculitis, may not be adequately covered [4]. The development of an EGPA-specific instrument, which includes the other characteristic manifestations in addition to those caused by vasculitis, therefore appears desirable in principle. Emmi et al. explicitly recommend taking into account asthmatic and/or sinonasal manifestations when defining remission in the therapeutic indication of EGPA [4]. This remains of no consequence for the present benefit assessment.

The current S3 guideline, the EULAR and the ACR define remission as the absence of typical signs, symptoms or other features of active anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis with or without immunosuppressive therapy [5,20]. The current ACR and EULAR recommendations do not specify OCS thresholds from which the definition of remission is met. Referring to the older remission definition of the EULAR [23], the S3 guideline considers a maximum OCS dose of 7.5 mg prednisone or equivalent per day to be reasonable [4,20,23]. Besides this threshold value of the daily OCS dose, other threshold values can be found in the literature, such as ≤ 4 mg/day [4], or ≤ 5 mg/day or 0 mg/day [24].

The present benefit assessment uses the definition according to the recommendation of the current S3 guideline with the threshold value of 7.5 mg of the daily OCS dose. The individual component BVAS = 0 (no disease activity) is shown as supplementary information.

According to EULAR, the probability of relapse is particularly high within the first 6 months of remission [23]. Therefore, this benefit assessment uses the analysis of the percentage of patients who achieved remission as per S3 guideline within the first 24 weeks and remained in remission until study end (Week 52, i.e. for at least 28 weeks). The analyses of the percentage of patients who were in remission at both Week 36 and Week 48 show consistent results. The same applies to the remission definition with the OCS threshold value of 4 mg/day for both analyses mentioned.

The analyses of steroid-free remission (BVAS = 0 and OCS dose = 0 mg/day) in Module 4 A are post hoc analyses. The availability of new treatment options makes it conceivable in principle that the guideline recommendation on the definition of remission will be adjusted to lower OCS thresholds or towards steroid-free remission in the future; however, since steroid-free remission was not predefined in the present study, the remission definition with the threshold value of 7.5 mg (of the daily OCS dose) is used for the present benefit assessment.

Average OCS dose (reduction)

In Module 4 A, the company presented both continuous analyses for the comparison between baseline and various 4-week periods (from Week 21 to Week 52; e.g. averaged over Weeks 21 to 24) and analyses of the proportion of patients with an average daily OCS dose of 0 mg/day, ≤ 4 mg/day and ≤ 7.5 mg/day, each at Weeks 49 to 52. The average OCS dose (reduction) is not used for the present benefit assessment, as appropriate consideration of the OCS dose is already given in the remission definition.

Relapse

In Module 4 A, the company presented results on the time to the first relapse and the annualized relapse rate for relapse and severe relapse.

The MANDARA study defined the outcome of relapse as worsening or persistence of active disease since the last visit. Worsening or persistence of active disease was characterized by vasculitis (BVAS > 0), or asthma symptoms/signs with a corresponding worsening in ACQ-6 score (compared with the last visit), or nasal/sinus disease, with a corresponding worsening in at least one of the sinonasal symptom questions (compared with the last visit). In addition, one or more of the following measures had to be taken: an increased dose of OCS therapy to > 4 mg/day, or an increased dose or addition of immunosuppressive therapy, or hospitalization related to EGPA worsening. Severe relapse was defined as any organ- or life-threatening EGPA event, or BVAS ≥ 6 (involving at least 2 organ systems in addition to any general symptoms), or an asthma relapse requiring hospitalization, or sinonasal relapse

requiring hospitalization. For the questionnaire to assess sinonasal symptoms, the study documents indicate the symptoms queried, but there is no information on the wording of the individual items.

At baseline, 51% of patients in the intervention arm and 53% in the control arm had a BVAS = 0 (no disease activity). In accordance with the inclusion criteria, patients with a daily OCS dose of at least 7.5 mg were enrolled. It remains unclear how many patients at baseline were in remission according to the S3 guideline definition (BVAS = 0 and OCS dose ≤ 7.5 mg/day) (see Section I 4.2.1). In the present situation, however, it is assumed that achieving and maintaining remission is the primarily relevant analysis. In addition, if remission in accordance with the S3 guideline recommendation (see above) and relapse according to the operationalization described above were considered simultaneously, patients might be double counted in the analysis of a survey point, i.e. individual patients might be simultaneously classified as both being in remission and relapsed. Therefore, the outcome of relapse in the form of an annualized rate is presented only as supplementary information in I Appendix D of the full dossier assessment.

Severe EGPA symptoms

Severe EGPA symptoms (operationalized as EGPA-related hospitalization) are part of the outcome of relapse (see above). In Module 4 A, the company presented the proportion of patients with EGPA-related hospitalization and the annualized hospitalization rate until Week 52. The results for severe EGPA symptoms are not presented, as it is unclear whether the results presented are EGPA-related hospitalizations or hospitalizations due to AEs. Regardless of this, the results presented by the company in Module 4 A show no statistically significant difference between the study arms.

No information is available on overall hospitalization.

Vasculitic organ damage assessed using the Vasculitis Damage Index (VDI)

In Module 4 A, the company presented both continuous analyses comparing baseline with Weeks 24 and 52, and responder analyses at Week 52 (worsening by at least 15%) for the outcome of vasculitic organ damage assessed using the VDI. The VDI is an instrument to assess organ damage in patients with systemic vasculitides, which is completed by the investigator [25]. Organ damage is assessed on the basis of 64 items, divided into 11 organ system categories. Damage is defined as the existence of a medical event over a period of ≥ 3 months after the onset of vasculitis. One point is given for each item of the VDI if damage is detected, resulting in a total score of 0 points (no damage) to a maximum of 64 points. The VDI records organ damage cumulatively, so that the score can only remain stable or increase over time, but not decrease. A health impairment that has subsided over time is still included in the total score of subsequent assessments.

Organ damage is considered patient relevant. However, the recording of organ damage via the VDI is partly based on vital parameters, imaging techniques and laboratory parameters (e.g. absent pulse in one limb, thrombocytopenia, leukopenia, proteinuria, and hypertension), and not exclusively on patient-noticeable symptoms. Besides, the VDI records events of varying degrees of severity. For example, events such as alopecia, hypertension or the need for antihypertensives are mentioned, which can be categorized as less severe compared with other events such as blindness in both eyes and hearing loss.

For the assessment of organ damage using the VDI, it therefore remains unclear whether all included events are patient relevant and to what extent events of varying severity were included in the score. Furthermore, it remains unclear whether some of the included events are reversible and therefore do not represent permanent organ damage. For these reasons, the VDI is not used for the benefit assessment.

Symptoms, recorded using PGIS

In Module 4 A, the company presented both continuous analyses for the comparison between baseline and various time points (from Week 24 to Week 52) as well as responder analyses at Week 52 (improvement by at least 15%) of the patient-reported single-item scale PGIS. However, there is no information on the wording of the item in the study documents. For this reason, the results of the PGIS are not used for the benefit assessment. Regardless of this, the results of the generally relevant responder analyses for the PGIS in Module 4 A show no statistically significant difference between the study arms.

Adverse events

The company presented analyses of AEs and SAEs, each with and without disease-related events. In the analyses without disease-related events, it remains unclear from the available information which Preferred Terms (PTs) were not considered as disease-related events. The analyses without disease-related events are therefore not used for the benefit assessment. In the present data situation, however, the overall rates including the disease-related events can be used, as there is no evidence that events attributable to the underlying disease were included to a relevant extent.

No other specific AEs relevant to the benefit assessment were identified.

I 4.2.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: benralizumab + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant

Study		Outcomes										
	Study level	All-cause mortality[a]	Remission[b]	Severe EGPA symptoms	Asthma symptoms (ACQ-6)	Sinonasal symptoms (SNOT-22)	Activity impairment (WPAI question 6)	Symptoms (PGIS)	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Specific AEs
MANDARA	L	L	L	–[c]	L	L	L	–[c]	L	L	L	–

a. Deaths were recorded as AEs.
b. Operationalized as BVAS = 0 and OCS dose (prednisolone or prednisone) ≤ 7.5 mg/day.
c. No suitable data available; for the reasoning, see Section I 4.2.1 of the present dossier assessment.

ACQ: Asthma Control Questionnaire; AE: adverse event; BVAS: Birmingham Vasculitis Activity Score; EGPA: eosinophilic granulomatosis with polyangiitis; L: low; OCS: oral corticosteroids; PGIS: Patient Global Impression of Severity; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36-version 2 Health Survey; SNOT-22: 22-item Sino-Nasal Outcome Test; WPAI: Work Productivity and Activity Impairment

The risk of bias for the results on all outcomes for which usable data are available is rated as low.

I 4.2.3 Results

Table 12 summarizes the results of the comparison of benralizumab with mepolizumab, each in combination with OCS and if applicable immunosuppressants, in patients with relapsing or refractory EGPA. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The results on common AEs, SAEs and discontinuations due to AEs are presented in I Appendix B of the full dossier assessment.

Table 12: Results (mortality, morbidity, health-related quality of life and side effects, dichotomous) – RCT, direct comparison: benralizumab + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant (multipage table)

Study **Outcome category** **Outcome**	**Benralizumab + OCS ± immunosuppressant**		**Mepolizumab + OCS ± immunosuppressant**		**Benralizumab + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
MANDARA					
Mortality					
All-cause mortality[b] (within 52 weeks)	70	0 (0)	70	0 (0)	–
Morbidity					
Remission[c] (BVAS = 0 and OCS ≤ 7,5 mg/day)	70	41 (58.6)	70	40 (57.1)	1.12 [0.89; 1.40]; 0.336[d]
Absence of vasculitic disease activity (BVAS = 0[c]) (supplementary information)	*70*	*42 (60.0)*	*70*	*44 (62.9)*	*0.96 [0.73; 1.25]; 0.743[d]*
Severe EGPA symptoms	No suitable data[e]				
Asthma symptoms (ACQ-6, improvement averaged over Weeks 49-52)[f, g]	70	24 (34.3)	70	20 (28.6)	1.20 [0.73; 1.96]; 0.531
Sinonasal symptoms (SNOT-22, improvement at Week 52)[h]	70	18 (25.7)	70	13 (18.6)	1.39 [0.74; 2.60]; 0.338
Activity impairment (WPAI question 6, improvement at Week 52)[i]	70	22 (31.4)	70	20 (28.6)	1.10 [0.66; 1.83]; 0.792
Symptoms (PGIS, improvement at Week 52[j])	No suitable data[e]				
Health-related quality of life					
SF-36v2 (improvement at Week 52)[k, l]					
Physical Component Summary (PCS)[m]	70	7 (10.0)	70	8 (11.4)	0.88 [0.34; 2.28]; 0.862
Mental Component Summary (MCS)[m]	70	10 (14.3)	70	12 (17.1)	0.83 [0.39; 1.80]; 0.687

Table 12: Results (mortality, morbidity, health-related quality of life and side effects, dichotomous) – RCT, direct comparison: benralizumab + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant (multipage table)

Study Outcome category Outcome	Benralizumab + OCS ± immunosuppressant		Mepolizumab + OCS ± immunosuppressant		Benralizumab + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Side effects					
AEs (supplementary information)	70	63 (90.0)	70	67 (95.7)	–
SAEs	70	4 (5.7)	70	9 (12.9)	0.44 [0.14; 1.38]; 0.167
Discontinuation due to AEs	70	0 (0)	70	2 (2.9)	0.20 [0.01; 4.09]; 0.210

a. RR unadjusted, CI according to Wald; p-value: IQWiG calculation (unconditional exact test [CSZ method according to [26]]).
b. Deaths were recorded as AEs.
c. Within the first 24 weeks until Week 52.
d. RR, 95% CI and p-value are based on a log-binomial regression with treatment group, baseline BVAS (BVAS = 0 vs. BVAS > 0) and baseline OCS dose (< 12 mg/day vs. ≥ 12 mg/day) as factors.
e. No suitable data available; for the reasoning, see Section I 4.2.1 of the present dossier assessment.
f. Besides 5 questions on symptoms, the ACQ-6 total score includes one question on rescue medication.
g. A mean ACQ-6 score decrease by ≥ 0.9 points from baseline to Weeks 49–52 is considered a clinically relevant improvement (scale range: 0 to 6).
h. A SNOT-22 total score decrease by ≥ 16.5 points from baseline to Week 52 is considered a clinically relevant improvement (scale range: 0 to 110).
i. A WPAI score (question 6) decrease by ≥ 15 points from baseline to Week 52 is considered a clinically relevant improvement (scale range: 0 to 100).
j. A decrease by ≥ 1 point from baseline is considered a clinically relevant improvement (scale range: 0 “no symptoms” to 5 “very severe”).
k. Information on subscales was not available.
l. Discrepancy between data in Module 4 and 5 of the dossier; the data presented are from additional analyses in Module 5.
m. An increase in PCS score by ≥ 9.4 points or in MCS score by ≥ 9.6 points from baseline to Week 52 is considered a clinically relevant improvement (scale range of the Acute Version: 10.8 to 75.5 for PCS and 5.6 to 69.7 for MCS; determined using the 2009 norm sample [27]). The response thresholds used were determined on the basis of the range of the SF-36v2 Standard Version. In contrast, the company used the Acute Version of the SF-36v2 in the study. For the PCS, the response criteria of the Standard Version and the Acute Version of the SF-36v2 differ slightly from each other.

ACQ: Asthma Control Questionnaire; AE: adverse event; BVAS: Birmingham Vasculitis Activity Score; CI: confidence interval; CSZ: convexity, symmetry, z-score; EGPA: eosinophilic granulomatosis with polyangiitis; MCS: Mental Component Summary; n: number of patients with (at least one) event; N: number of analysed patients; OCS: oral corticosteroids; PCS: Physical Component Summary; PGIS: Patient Global Impression of Severity; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form 36-version 2 Health Survey; SNOT-22: 22-item Sino-Nasal Outcome Test; SOC: System Organ Class; WPAI: Work Productivity and Activity Impairment

Based on the available information, no more than indications, e.g. of an added benefit, can be determined for all outcomes.

Mortality

Overall survival

No deaths occurred during the double-blind phase of the study. There is no hint of added benefit of benralizumab in comparison with mepolizumab, each as add-on treatment; an added benefit is therefore not proven.

Morbidity

Remission

For the outcome of remission with the 7.5 mg/day OCS threshold, no statistically significant difference between treatment groups was found. There is no hint of added benefit of benralizumab in comparison with mepolizumab, each as add-on treatment; an added benefit is therefore not proven.

Severe EGPA symptoms

No suitable data are available for the outcome of severe EGPA symptoms (see Section I 4.2.1 for reasons). There is no hint of added benefit of benralizumab in comparison with mepolizumab, each as add-on treatment; an added benefit is therefore not proven.

Asthma symptoms (recorded using ACQ-6)

For the outcome of asthma symptoms (recorded using the ACQ-6), no statistically significant difference between treatment groups was found. There is no hint of added benefit of benralizumab in comparison with mepolizumab, each as add-on treatment; an added benefit is therefore not proven.

Sinonasal symptoms (recorded using SNOT-22)

For the outcome of sinonasal symptoms (recorded using SNOT-22), no statistically significant difference between treatment groups was found. There is no hint of added benefit of benralizumab in comparison with mepolizumab, each as add-on treatment; an added benefit is therefore not proven.

Activity impairment (recorded using WPAI question 6)

For the outcome of activity impairment (recorded using the WPAI question 6), no statistically significant difference between treatment groups was found. There is no hint of added benefit of benralizumab in comparison with mepolizumab, each as add-on treatment; an added benefit is therefore not proven.

Symptoms (recorded using PGIS)

No suitable data are available for the outcome of symptoms (recorded using the PGIS) (see Section I 4.2.1 for reasons). There is no hint of added benefit of benralizumab in comparison with mepolizumab, each as add-on treatment; an added benefit is therefore not proven.

Health-related quality of life (recorded using SF-36v2)

For the outcome of health-related quality of life (recorded using the SF-36v2), no statistically significant difference between treatment groups was found. There is no hint of added benefit of benralizumab in comparison with mepolizumab, each as add-on treatment; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from benralizumab in comparison with mepolizumab, each as add-on treatment; greater or lesser harm is therefore not proven.

I 4.2.4 Subgroups and other effect modifiers

The following potential effect modifiers are taken into account in the present benefit assessment:

- age (≤ 65 versus > 65)
- sex (female versus male)

The mentioned subgroup characteristics and cut-off values had been prespecified for the primary outcome as well as for the AE outcomes.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

In accordance with the described methods, no relevant effect modification by the characteristics of age or sex was identified for the outcomes for which suitable data are available.

I 4.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 4.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 4.2 (see Table 13).

Table 13: Extent of added benefit at outcome level: benralizumab vs. mepolizumab (multipage table)

Outcome category **Outcome**	**Benralizumab + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser/added benefit not proven
Morbidity		
Remission	58.6% vs. 57.1% RR: 1.12 [0.89; 1.40]; p = 0.336	Lesser/added benefit not proven
Severe EGPA symptoms	No suitable data	Lesser/added benefit not proven
Asthma symptoms (ACQ-6, improvement averaged over Weeks 49–52)	34.3 vs. 28.6% RR: 1.20 [0.73; 1.96] p = 0.531	Lesser/added benefit not proven
Sinonasal symptoms (SNOT-22, improvement at Week 52)	25.7% vs. 18.6% RR: 1.39 [0.74; 2.60]; p = 0.338	Lesser/added benefit not proven
Activity impairment (WPAI question 6, improvement at Week 52)	31.4% vs. 28.6% RR: 1.10 [0.66; 1.83]; p = 0.792	Lesser/added benefit not proven
Symptoms (PGIS, improvement at Week 52)	No suitable data	Lesser/added benefit not proven

Table 13: Extent of added benefit at outcome level: benralizumab vs. mepolizumab (multipage table)

Outcome category **Outcome**	**Benralizumab + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Health-related quality of life		
SF-36v2 (improvement at Week 52)		
Physical Component Summary (PCS)	10.0% vs. 11.4% RR: 0.88 [0.34; 2.28]; p = 0.862	Lesser/added benefit not proven
Mental Component Summary (MCS)	14.3% vs. 17.1% RR: 0.83 [0.39; 1.80]; p = 0.687	Lesser/added benefit not proven
Side effects		
SAEs	5.7% vs. 12.9% RR: 0.44 [0.14; 1.38]; p = 0.167	Greater/lesser harm not proven
Discontinuation due to AEs	0% vs. 2.9% RR: 0.20 [0.01; 4.09]; p = 0.210	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).

ACQ: Asthma Control Questionnaire; AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; EGPA: eosinophilic granulomatosis with polyangiitis; MCS: Mental Component Summary; OCS: oral corticosteroids; PCS: Physical Component Summary; PGIS: Patient Global Impression of Severity; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form 36 Health Survey Version 2; SNOT-22: 22-item Sino-Nasal Outcome Test; WPAI: Work Productivity and Activity Impairment

I 4.3.2 Overall conclusion on added benefit

Table 14 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 14: Positive and negative effects from the assessment of benralizumab in comparison with mepolizumab

Positive effects	**Negative effects**
–	–
No suitable data are available for the outcomes of severe EGPA symptoms and symptoms (PGIS).	

EGPA: eosinophilic granulomatosis with polyangiitis; PGIS: Patient Global Impression of Severity

Overall, neither positive nor negative effects of benralizumab were found in comparison with the ACT. In summary, there is no hint of an added benefit of benralizumab in comparison with the ACT mepolizumab, each as add-on treatment, for patients with relapsing or refractory EGPA without organ-threatening or life-threatening manifestations; an added benefit is therefore not proven.

The assessment described above differs from that of the company, which derived an indication of a considerable added benefit for research question 2 based on the results for steroid-free remission at Weeks 36 and 48, as well as on the average OCS dose of 0 mg/day averaged over Weeks 49 to 52 in the MANDARA study.

I 5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of benralizumab in comparison with the ACT is summarized in Table 15.

Table 15: Benralizumab – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Add-on treatment for adult patients with relapsing or refractory EGPA with organ-threatening or life-threatening manifestations	Treatment of physician's choice, selecting from cyclophosphamide and rituximab to induce remission, followed by mepolizumab to maintain remission, each in combination with corticosteroids[b]	Added benefit not proven
2	Add-on treatment for adult patients with relapsing or refractory EGPA without organ-threatening or life-threatening manifestations	Mepolizumab[c]	Added benefit not proven

Table 15: Benralizumab – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, the treatment of severe EGPA is divided into 2 treatment phases: remission induction and remission maintenance.
- Remission induction: Current guidelines [3-5] recommend the use of either cyclophosphamide or rituximab together with high-dose corticosteroid treatment to induce remission in the event of a relapse with organ-threatening or life-threatening manifestations. There is very limited evidence base for this specific situation in this generally rare disease. Corticosteroids and mepolizumab (as add-on treatment for relapsing-remitting or refractory EGPA) are approved for patients with EGPA. Even though the approved therapeutic indication for mepolizumab generally covers all degrees of severity, the SPC [6] points out that mepolizumab has not been studied in patients with organ-threatening or life-threatening manifestations of EGPA. Since guidelines also do not recommend mepolizumab for inducing remission in this severe form of the disease, mepolizumab is not considered standard therapy for this patient population. Corticosteroids are used in combination with other drugs, but are not an option as the sole therapy for patients with organ-threatening or life-threatening manifestations of EGPA. According to the G-BA, the off-label use of cyclophosphamide and rituximab as add-on treatment to corticosteroids is medically necessary and, according to generally accepted medical knowledge, is considered standard treatment in adults with relapsing or refractory EGPA with organ-threatening or life-threatening manifestations, and is generally preferable to the drug mepolizumab, which is currently approved in the therapeutic indication, §6 (2), sentence 3, number 2, AM-NutzenV.
- Remission maintenance: According to the G-BA and pursuant to §35a (7) sentence 4 SGB V, treatment with conventional nonsteroidal immunosuppressants (EULAR: methotrexate, azathioprine; EU expert panel: general nonsteroidal immunosuppressants; United States: azathioprine/methotrexate/mycophenolate mofetil), mepolizumab and rituximab should be considered to maintain remission in patients with organ-threatening or life-threatening manifestations (after new-onset or relapse), in accordance with the above-mentioned guidelines and the scientific and medical societies. The EULAR guideline refers to a prospective study on methotrexate in comparison with cyclophosphamide, as well as to observational studies on azathioprine, mepolizumab and rituximab. Overall, according to the G-BA, it cannot be clearly inferred from the available evidence that the use of the mentioned off-label treatment options is medically imperative, as mepolizumab, an approved drug recommended by guidelines and German medical societies, is an ACT option for remission maintenance in organ-threatening or life-threatening manifestations of EGPA.

c. According to the G-BA, it is assumed that patients in both study arms are offered guideline-compliant basic therapy with corticosteroids. It is also assumed that for patients who are eligible for treatment with benralizumab, treatment with corticosteroids alone is not suitable.

ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; EGPA: eosinophilic granulomatosis with polyangiitis; EULAR: European League Against Rheumatism; G-BA: Federal Joint Committee; SGB V: Social Code Book V

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. 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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