Benralizumab (eosinophilic granulomatosis with polyangiitis)

Addendum to Project A24-113 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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Abbreviation	Meaning
AE	adverse event
BVAS	Birmingham Vasculitis Activity Score
EGPA	eosinophilic granulomatosis with polyangiitis
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 corticosteroids
PGIS	Patient Global Impression of Severity
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 8 April 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-113 (Benralizumab – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the data and analyses presented by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure [2] and in the dossier [3] on the following outcomes:

- steroid-free remission (duration of 12 and 16 weeks)
- Patient Global Impression of Severity (PGIS)
- severe eosinophilic granulomatosis with polyangiitis (EGPA) symptoms

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

In benefit assessment A24-113 [1] of benralizumab as add-on treatment (hereinafter referred to as benralizumab + oral corticosteroids [OCS] ± immunosuppressant) in adult patients with relapsing or refractory EGPA, the double-blind randomized controlled trial (RCT) MANDARA, which compared benralizumab + OCS ± immunosuppressant with mepolizumab + OCS ± immunosuppressant, was used for research question 2 (adult patients without organ-threatening or life-threatening manifestations). A detailed description of the MANDARA study can be found in dossier assessment A24-113 [1].

In the following, the data and analyses subsequently submitted by the company in the commenting procedure [2] on the outcomes of steroid-free remission, severe EGPA symptoms, and symptoms (assessed using the PGIS) from the MANDARA study are assessed, taking into account the information in the dossier [3].

2.1 Assessment of the outcome of steroid-free remission

In the MANDARA study, the primary outcome of remission was defined as Birmingham Vasculitis Activity Score (BVAS) = 0 and OCS dose ≤ 4 mg/day and additionally as BVAS = 0 and OCS dose ≤ 7.5 mg/day. In Module 4 A of the dossier, in addition to analyses on these 2 definitions, the company also presented analyses on steroid-free remission (BVAS = 0 and OCS dose = 0 mg/day) for the outcome of remission. In the dossier, the company presented the proportions of patients in remission at Week 36 and Week 48, at Week 52, as well as at Week 24 with maintenance until Week 52. With its comments [2], the company presented 2 further analyses on the proportions of patients with steroid-free remission (BVAS = 0 and OCS dose = 0 mg/day) at Week 36 with maintenance until Week 48 (duration of 12 weeks) as well as at Week 36 with maintenance until Week 52 (duration of 16 weeks).

As described in the dossier assessment, the benefit assessment used the definition according to the recommendation of the current S3 guideline with the threshold value 7.5 mg of the daily OCS dose for the remission outcome (for justification see A24-113 [1]). The analyses on the outcome of steroid-free remission, in contrast, are not used for the benefit assessment, as these are post-hoc analyses. In compliance with the commission, however, the outcome of steroid-free remission is assessed below; a supplementary presentation of the results is provided in Appendix A.

The analyses on steroid-free remission submitted with the comments are also post-hoc analyses. In addition, it remains unclear whether a relevant proportion of the included patients did not even have the opportunity to achieve steroid-free remission at the time points presented by the company (possibly with the exception of the analysis at Week 52).

In the MANDARA study, 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. For this purpose, 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. At Week 4, at least 25% of patients in both study arms still had a BVAS ≥ 1. Depending on the time at which freedom from symptoms (BVAS = 0) was achieved and on the baseline OCS dose, a relevant proportion of patients was potentially unable to achieve steroid-free remission at Week 24 or Week 36 in accordance with the recommended dose reduction schedule.

The company itself described in its comments that an ideal reduction of the OCS dose to 0 mg/day within 24 weeks in accordance with the dose reduction schedule in the present patient population (on average, more than 5 years of EGPA disease, approx. 50% of patients with BVAS > 0 at baseline and approx. 23% with a daily OCS dose of ≥ 12 mg/day at baseline) cannot be regularly expected or, in some cases, may not be mathematically possible. According to the company, it is conceivable on a patient-specific level to arrange longer periods of treatment with a stable OCS dose before attempting complete tapering, especially in patients with a high OCS starting dose, a long EGPA history or severe disease.

The extent to which the aspects mentioned by the company regarding the achievability of steroid-free remission at Week 24 also limit the achievability of steroid-free remission at Week 36 remains unclear. In the oral hearing [4], the company was unable to provide any information on how many patients may not have been able to achieve steroid-free remission at Week 36 due to their OCS dose at baseline and their dose reduction schedule. However, the main publication of the MANDARA study [5] notes that due to the duration of the double-blind study phase and the different OCS doses at baseline, not all patients may have been able to discontinue OCS even by Week 52.

For a suitable analysis of steroid-free remission, the outcome should generally be achievable for almost all patients. Accordingly, a later observation period would be necessary, but this was limited to 52 weeks due to the double-blind treatment duration in the study. In addition, the analysis period should be chosen in such a way that it is ensured that potential effects are not solely due to patients in one treatment arm reaching the outcome only a few weeks earlier.

On the basis of the information presented with the dossier and in the context of the commenting procedure, due to the uncertainties described, it is concluded overall that the analyses on steroid-free remission are not suitable for the periods presented by the company

(from Week 36 in each case) . In contrast, the analysis of steroid-free remission at the end of the study (Week 52) only depicts a single time point. The results are presented only as supplementary information in Appendix A.

Regardless of the uncertainties described above, the various analyses presented in the dossier and in the company's comments showed some statistically significant and some not statistically significant differences between the treatment arms. The analyses of steroid-free remission at Week 36 with maintenance until Week 48 (duration of 12 weeks) and at Week 36 with maintenance until Week 52 (duration of 16 weeks) each showed a statistically significant effect in favour of benralizumab + OCS ± immunosuppressant. However, the analysis of steroid-free remission at the end of the study (Week 52) showed no statistically significant difference between the treatment arms, although the proportions of remission were notably higher in absolute terms. Similarly, the analysis of steroid-free remission at Week 24 with maintenance until Week 52 (duration of 28 weeks) showed no statistically significant difference between the treatment arms (see Table 3 in Appendix A). It remains unclear to what extent the aforementioned uncertainties influence the results for the different periods and dates of recording.

In principle, the subsequently submitted analyses on steroid-free remission are not preferable to the predefined analysis on the outcome of remission (BVAS = 0, OCS ≤ 7.5 mg/day; at Week 24 with maintenance until Week 52) already used in the dossier assessment. Overall, the analyses on steroid-free remission presented by the company with the comments thus do not change the assessments from dossier assessment A24-113.

2.2 Assessment of the outcome of severe EGPA symptoms

As described in the benefit assessment, it remained unclear for severe EGPA symptoms (operationalized as EGPA-related hospitalization) whether the results presented in the dossier were EGPA-related hospitalizations or hospitalizations due to adverse events (AEs).

In its comments, the company explained that EGPA-related hospitalizations and hospitalizations due to AEs could be differentiated on the basis of AEs (AEs, serious adverse events [SAEs], severe AEs) without disease-related events. Even after these explanations, it remains unclear which hospitalizations (EGPA-related hospitalizations or hospitalizations due to AEs) were presented in the dossier, so that there are still no suitable data available for the outcome of severe EGPA symptoms. Regardless of this, the results presented by the company in Module 4 A show no statistically significant difference between the study arms, as described in the benefit assessment.

2.3 Assessment of the outcome of symptoms assessed using the PGIS

As described in the benefit assessment, the study documents contained no information on the wording of the patient-reported single-item PGIS scale. For this reason, the results of the PGIS were not used for the benefit assessment. The company presented this wording with the comments. The responder analyses at Week 52 (improvement of at least 15%) presented in the dossier can now be used for the benefit assessment.

Risk of bias

The risk of bias of the results of the outcome of symptoms, assessed using the PGIS, is rated as high due to a high proportion (> 10%) of values imputed by non-responder imputation. At Week 52, values were only available from 61 of 70 patients per treatment arm (87%), so only these patients were included in the analyses with their actual values. Nevertheless, the company based its analyses on 70 patients per treatment arm, so that it can be assumed that 9 patients were imputed as non-responders in the analyses. This procedure is not adequate, as it cannot be assumed that all patients with missing values did not achieve an improvement of at least 15%.

Results

Table 1 shows the result of the comparison of benralizumab + OCS ± immunosuppressant with mepolizumab + OCS ± immunosuppressant for the outcome of symptoms (assessed using the PGIS) at the end of the study (Week 52).

Table 1: Results (morbidity) – RCT, direct comparison: benralizumab + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant

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					
Morbidity					
Symptoms (PGIS; improvement at Week 52)[b]	70	26 (37.1)	70	33 (47.1)	0.79 [0.53; 1.17]; 0.250

a. RR unadjusted, CI according to Wald; p-value: IQWiG calculation (unconditional exact test [CSZ method according to [6]]).
b. A decrease by ≥ 1 point from baseline is considered a clinically relevant improvement (scale range: 0 “no symptoms” to 5 “very severe”).

CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; OCS: oral corticosteroids; PGIS: Patient Global Impression of Severity; RCT: randomized controlled trial; RR: relative risk

Because of the high risk of bias, at most a hint, e.g. of an added benefit, can be derived on the basis of the available information for the outcome of symptoms, assessed using the PGIS.

No statistically significant difference between the treatment arms was shown for the outcome of symptoms, assessed using the 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.

Subgroups and other effect modifiers

The following potential effect modifiers are taken into account for the present benefit assessment (see dossier assessment A24-113 [1]):

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

The methods described in Section I 4.2.4 of dossier assessment A24-113 [1] are used for this purpose.

In accordance with the methods described there, no relevant effect modification by the characteristics of age or sex was identified for the outcomes of symptoms, assessed using the PGIS.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion on the added benefit of benralizumab drawn in dossier assessment A24-113.

Table 2 below shows the result of the benefit assessment of benralizumab, taking into account dossier assessment A24-113 and the present addendum.

Table 2: 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 2: 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 [7-9] 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 [10] 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 G-BA decides on the added benefit.

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Appendix A Supplementary presentation of results on the outcome of steroid-free remission

Table 3: Results (steroid-free remission) – RCT, direct comparison: benralizumab + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant

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					
Morbidity					
Steroid-free remission (BVAS = 0 and OCS = 0 mg/day, Week 36 to Week 48)[b] *(supplementary information)*	*70*	*16 (22.9)*	*70*	*8 (11.4)*	*2.19 [1.01; 4.75]; 0.047*
Steroid-free remission (BVAS = 0 and OCS = 0 mg/day, Week 36 to Week 52) (supplementary information)	*70*	*15*[c] *(21)*	*70*	*7*[c] *(10)*	*2.34 [1.02; 5.34]; 0.044*
Steroid-free remission (BVAS = 0 and OCS = 0 mg/day, Week 24 to Week 52) (supplementary information)	*70*	*6 (9)*	*70*	*2 (3)*	*3.07 [0.68; 14.55]; 0.158*
Steroid-free remission (BVAS = 0 and OCS = 0 mg/day, at Week 52) (supplementary information)	*70*	*26 (37.1)*	*70*	*21 (30.0)*	*1.31 [0.82; 2.08]; 0.259*

a. 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.
b. Identical proportions of patients with steroid-free remission at Week 36 and Week 48.
c. Institute's calculation.

BVAS: Birmingham Vasculitis Activity Score; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; OCS: oral corticosteroids; RCT: randomized controlled trial; RR: relative risk