

Avacopan (granulomatosis with polyangiitis or microscopic polyangiitis)

Addendum to Project A25-114
(dossier assessment)¹

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List of abbreviations

Abbreviation	Meaning
AAV	ANCA-associated vasculitis
ACT	appropriate comparator therapy
ANCA	anti-neutrophil cytoplasmic antibodies
BVAS	Birmingham Vasculitis Activity Score
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GPA	granulomatosis with polyangiitis
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MPA	microscopic polyangiitis
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics

1 Background

On 27 January 2026, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-114 (Avacopan – Benefit assessment according to §35a Social Code Book V) [1].

The commission involves assessing the analyses submitted by the pharmaceutical company (hereinafter referred to as 'the company') in the commenting procedure regarding the outcome 'remission at Week 26' for the subpopulation of study participants treated with rituximab in the randomized controlled trial (RCT) ADVOCATE, taking into account the information contained in the dossier.

The responsibility for this 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

For the benefit assessment of avacopan, in combination with a rituximab or cyclophosphamide regimen, in comparison with the appropriate comparator therapy (ACT), in adult patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA), the company had used the RCT ADVOCATE [2-4] and presented analyses of the overall population in Module 4 A. A detailed description of the study can be found in benefit assessment A25-114 [1]. It was also described there that the total population used by the company was not relevant for the benefit assessment, as a relevant proportion of 35% of patients in the comparator arm received a cyclophosphamide regimen with subsequent maintenance therapy with azathioprine/mycophenolate from Week 15, which did not correspond to the maintenance therapy with rituximab defined by the G-BA as the ACT. In the commenting procedure, the company addressed this issue and submitted analyses for Week 26 that took into account only patients with a rituximab regimen.

However, it remains unclear whether Week 26 in the ADVOCATE study was an appropriate analysis date for assessing remission induction, or whether maintenance therapy with rituximab would already have been indicated for some patients by that point. Such treatment was not provided for in the ADVOCATE study, but should be initiated no sooner than 16 weeks after the last rituximab infusion and consists of 2 doses of rituximab 2 weeks apart, followed by further doses of rituximab every 6 months thereafter, according to the summary of product characteristics (SmPC) [5]. It is therefore possible that it could have been an option for some patients to start rituximab maintenance therapy by Week 26. The impact a possible omission of the first 2 doses of rituximab as part of maintenance therapy might have had on the study results at Week 26 remains unclear. It should also be noted that some patients in the total population had not achieved remission by Week 26.

In accordance with the G-BA's commission, the assessment of the analyses of the outcome 'remission at Week 26' is set out below.

2.1 Outcome 'remission at Week 26'

Operationalization

The outcome 'remission at Week 26' was operationalized as follows in the ADVOCATE study:

- Achieving a Birmingham Vasculitis Activity Score (BVAS [Version 3]) = 0 (determined by an assessment committee) and
- not taking steroids for the treatment of anti-neutrophil cytoplasmic antibodies [ANCA]-associated vasculitis (AAV) within 4 weeks prior to Week 26, and
- no BVAS > 0 within 4 weeks prior to Week 26, provided that an unscheduled recording was carried out.

The BVAS (Version 3) is an instrument for measuring disease activity in patients with systemic vasculitis [6], whereby a BVAS = 0 indicates no disease activity.

In principle, it is appropriate in this therapeutic indication to take into account the administration of steroids in the remission outcome. If a steroid threshold value is anchored in the remission outcome, it should generally be possible for almost all patients to fall below this threshold value from the selected time point onwards, based on the specified dose reduction regimens. Steroid reduction (below a relevant threshold value) should exist for a relevant period of time and not just at a single point in time. In the comparator arm of ADVOCATE, it was not possible to achieve freedom from steroids before Week 21, due to the chosen tapering regimen. A 4-week steroid-free period was therefore a reasonable timeframe when assessing remission at Week 26. It was not possible to assess with certainty whether 4-week freedom from steroids was long enough in the given therapeutic indication to assume that this will prevent steroid-related side effects in the long term. Compared with other therapeutic indications, the required steroid-free period of 4 weeks is relatively short (12 weeks freedom from steroids in the case of Crohn's disease [7,8] and 28 weeks of steroid tapering for eosinophilic granulomatosis with polyangiitis [EGPA] [9]).

Risk of bias

The risk of bias of the results for the outcome 'remission at Week 26' was rated as low.

Results

Table 1 shows the results for the outcome 'remission at Week 26' for patients in the ADVOCATE study who were assigned to the rituximab regimen prior to randomization.

Table 1: Results (remission at Week 26) – RCT, direct comparison: avacopan + rituximab regimen vs. prednisone + rituximab regimen

Study Outcome category Outcome	avacopan + rituximab regimen		prednisone + rituximab regimen		avacopan + rituximab regimen vs. prednisone + rituximab regimen
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value ^a
ADVOCATE					
Morbidity					
Remission (at Week 26) ^b	107	83 (77.6)	107	81 (75.7)	1.02 [0.88; 1.19]; 0.819
a. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [10]). b. According to the information provided by the company in Module 4 A of the dossier, remission is defined as a BVAS = 0 (BVAS Version 3; determined by an assessment committee) without the use of steroids for treating AAV within 4 weeks prior to Week 26, and no BVAS > 0 within 4 weeks prior to Week 26, provided that an unscheduled recording was carried out. According to the European assessment report [11], within the rituximab regimen, 95 patients (88.8%) in the intervention arm and 92 patients (86.0%) in the comparator arm achieved a BVAS = 0 by Week 26, regardless of any steroid use. However, no data are available on the proportion of patients who were steroid-free (regardless of whether they achieved a BVAS = 0) within 4 weeks prior to Week 26 (neither for patients on the rituximab regimen nor for the total population). Similarly, no data are available on the proportion of patients who did not have a BVAS > 0 within 4 weeks prior to Week 26, provided an unscheduled recording was carried out. However, it is unclear whether an unscheduled BVAS recording actually took place within the 4 weeks prior to Week 26. AAV: ANCA-associated vasculitis; ANCA: anti-neutrophil cytoplasmic antibodies; BVAS: Birmingham Vasculitis Activity Score; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk					

No statistically significant difference between treatment groups was shown for the outcome 'remission at Week 26'.

Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present analysis:

- Age (< 65 years versus ≥ 65 years)
- Sex (male versus female)

No relevant subgroup characteristic was identified in relation to disease severity. It is questionable whether distinguishing between levels of disease severity is at all meaningful in the given therapeutic indication. Although the company presented the subgroup characteristic BVAS at baseline for disease severity, it did not explain to what extent scores of < 15 or ≥ 15 are suitable for distinguishing between levels of disease severity.

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 ($p\text{-value} < 0.05$) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Using the methods described above, the available subgroup results did not reveal any effect modifications.

2.2 Summary

There is neither an advantage nor a disadvantage for avacopan in combination with a rituximab regimen compared with prednisone in combination with a rituximab regimen for the outcome 'remission at Week 26'.

The G-BA decides on the added benefit.

3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

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