Avacopan (granulomatosis with polyangiitis or microscopic polyangiitis)

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

EXTRACT

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Medical and scientific advice

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by 2 people.

IQWiG thanks the respondent and the patient organization 'Deutsche Rheuma-Liga Bundesverband e.V.' for participating in the written exchange and for their support. The respondent 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
AAV	ANCA-associated vasculitis
ACT	appropriate comparator therapy
ANCA	anti-neutrophil cytoplasmic antibodies
BVAS	Birmingham Vasculitis Activity Score
CI	confidence interval
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EULAR	European Alliance of Associations for Rheumatology
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)
IV	intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
MPA	microscopic polyangiitis
MPO	myeloperoxidase
PR3	proteinase-3
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 avacopan. 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 4 September 2025.

Research question

The aim of this report is to assess the added benefit 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 research question shown in Table 2 was defined in accordance with the ACT specified by the Federal Joint Committee (G-BA).

Table 2: Research question for the benefit assessment of avacopan in combination with a rituximab or cyclophosphamide regimen

Therapeutic indication	**ACT**[a, b, c]
Adults with severe, active GPA or MPA	▪ cyclophosphamide (induction phase) followed by rituximab (maintenance phase), each in combination with glucocorticoids (only for patients with GPA) or ▪ rituximab (induction and maintenance phase) in combination with glucocorticoids

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the treatment of GPA and MPA is divided into an induction phase and a maintenance phase. The glucocorticoid dose should be reduced gradually.
c. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who meet the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. To demonstrate the added benefit for the total population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis

On 26 August 2025, shortly before the dossier was submitted by the company, the G-BA modified the ACT to that shown in Table 2. Deviating from this, the company, referring to a consultation on 15 October 2020, named individualized treatment as the ACT, based on the treatment phase, the course of disease and previous therapy, and taking into account immunosuppressive drugs in combination with glucocorticoids. The deviation from the ACT will not be commented on further, as suitable data for the benefit assessment were lacking.

This benefit assessment was carried out versus the ACT specified by the G-BA as shown in Table 2.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit.

It should be noted that the treatment of GPA and MPA is generally divided into an induction phase and a maintenance phase. A study duration of 24 weeks allows an assessment of the remission induction phase at most; a longer study duration is necessary to assess remission maintenance.

Results

A review of the completeness of the study pool did not identify any relevant studies.

This deviated from the company's assessment, which, based on its information retrieval, identified the ADVOCATE study on the direct comparison of avacopan versus the ACT used by the company. The ADVOCATE study included by the company did not allow for a comparison versus the ACT. The ADVOCATE study and the company's approach are described below, and reasons are provided as to why the data presented by the company were unsuitable.

Evidence presented by the company – ADVOCATE study

The ADVOCATE study is a completed double-blind phase 3 study comparing avacopan with prednisone, each in combination with a rituximab or cyclophosphamide regimen, in patients aged 12 and older with GPA or MPA. Patients had to have newly diagnosed or relapsed GPA or MPA requiring treatment with rituximab or cyclophosphamide at enrolment.

In the intervention arm, avacopan was dosed orally at 30 mg twice daily for 52 weeks, in compliance with the specifications in the summary of product characteristics (SmPC). In the comparator arm, oral prednisone was completely tapered off within 20 weeks according to a fixed schedule. To maintain blinding, patients in the intervention arm and the comparator arm received a placebo in addition to prednisone (20 weeks) or avacopan (52 weeks). In addition, the patients in the ADVOCATE study received a treatment regimen with rituximab or cyclophosphamide. The treatment regimen was selected by the investigators prior to randomization. Patients who were assigned to a combination with rituximab received the 1st dose of rituximab on Day 1, and 3 further doses at weekly intervals. Patients who were assigned to a combination with cyclophosphamide received either 6 doses of cyclophosphamide intravenously (IV) until Week 13 or daily cyclophosphamide orally until the end of Week 14, each followed by azathioprine or (if azathioprine was not tolerated) mycophenolate from Week 15 to Week 52. Non-study-supplied glucocorticoid use was permitted in the intervention and comparator arm, e.g. in the event of worsening of the

disease or relapse, but were to be avoided as far as possible. Oral prednisone ≤ 20 mg/day (or equivalent) taken during the screening period had to be discontinued over a 4-week period from the start of treatment.

A total of 331 patients were included in the study and randomized in a 1:1 ratio to treatment with either avacopan (N = 166) or prednisone (N = 165), each in combination with a cyclophosphamide regimen (35% of the total population) or a rituximab regimen (65% of the total population). The treatment duration was 52 weeks. This was followed by an 8-week observation phase.

The primary outcomes of the ADVOCATE study were remission at Week 26 and sustained remission from Week 26 to Week 52. Secondary outcomes included outcomes in the categories of morbidity, health-related quality of life and side effects.

In Module 4 A, the company presented analyses on Week 26 for the total population of the ADVOCATE study and used these to derive the added benefit. For analyses at Week 52, the company referred exclusively to Module 5 of the dossier. The company justified its choice of analysis date by stating that Week 26 was a relevant time point for assessing the effectiveness of a drug therapy for remission induction of GPA or MPA.

Data unsuitable for the benefit assessment

The data available in Module 4 A were unsuitable for this benefit assessment.

In this therapeutic indication, remission induction is generally followed by remission maintenance therapy. For the given research question, the analysis date at Week 52 of the ADVOCATE study is therefore relevant in principle to assess the sustainability of the effects of the key outcome in this therapeutic indication (remission). Results at Week 26 only provide information on remission induction. However, these represent only part of the research question, since – if data is recorded beyond remission induction – it is relevant whether the remission is maintained after successful remission induction. This also applies in principle if remission maintenance therapy is not used in individual cases.

The data presented by the company for the total population as well as the data (not presented in Module 4 A) of the subpopulations with cyclophosphamide and rituximab regimens were not suitable for the benefit assessment. This applied both to the Week 52 analyses, which were to be generally used for the benefit assessment, and to the Week 26 results used by the company. Firstly, the patients in the ADVOCATE study with a cyclophosphamide regimen received a maintenance therapy other than the one defined by the G-BA as the ACT. Secondly, the patients with a rituximab regimen in the comparator arm did not receive maintenance therapy, although most of them were eligible for maintenance therapy with rituximab in principle. In addition, oral prednisone was completely tapered off within 20 weeks in patients

who received a rituximab regimen in the comparator arm. This means that the patients with a rituximab regimen in the comparator arm did not receive any preventive (i.e. remission maintenance) therapy after Week 21. Only in the event of disease worsening or relapse could patients with a rituximab regimen in the comparator arm receive glucocorticoids or other immunosuppressive drugs. In contrast, in the intervention arm, avacopan was administered continuously until Week 52 for remission maintenance. In the absence of disease worsening, a comparison was made between avacopan and placebo (for avacopan) from Week 21 to Week 52 in patients on the rituximab regimen.

It could not be ruled out that the lack of remission maintenance in patients in the comparator arm with the rituximab regimen, in particular the missing doses of rituximab, had an impact on the treatment effect at Week 52. In the outcome of sustained remission, this impact is suggested if the total population and the subpopulations with and without maintenance therapy are compared: Both in the total population and in the subpopulation with a rituximab regimen, there was a statistically significant effect in favour of avacopan (Institute's unadjusted calculation of RR [95% confidence interval (CI)] with p-values for the total population and the subpopulation with a rituximab regimen respectively as follows: 1.20 [1.002; 1.43] with p = 0.046, and 1.27 [1.03; 1.56] with p = 0.024. In contrast, there was no statistically significant difference between the treatment arms for the subpopulation with a cyclophosphamide regimen with maintenance therapy (Institute's unadjusted calculation of RR [95% CI] with p-value: 1.06 [0.76; 1.49] with p = 0.773.) Overall, the subpopulation with a rituximab regimen was unsuitable for the benefit assessment.

Results on added benefit

Since no suitable data were available for the benefit assessment, there is no hint of an added benefit of avacopan, in combination with a rituximab or a cyclophosphamide regimen, in comparison with the ACT; an added benefit is not proven.

Table 3 shows a summary of the probability and extent of the added benefit of avacopan, in combination with a rituximab or cyclophosphamide regimen.

Table 3: Avacopan in combination with a rituximab or cyclophosphamide regimen – probability and extent of added benefit[3]

Therapeutic indication	**ACT**[a, b, c]	**Probability and extent of added benefit**
Adults with severe, active GPA or MPA	▪ cyclophosphamide (induction phase) followed by rituximab (maintenance phase), each in combination with glucocorticoids (only for patients with GPA) or ▪ rituximab (induction and maintenance phase) in combination with glucocorticoids	▪ Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, the treatment of GPA and MPA is divided into an induction phase and a maintenance phase. The glucocorticoid dose should be reduced gradually. c. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who meet the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. To demonstrate the added benefit for the total population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis		

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment conducted in the context of the market launch in 2022, where the G-BA had determined a minor added benefit of avacopan. However, in the G-BA's assessment the added benefit was considered proven by the marketing authorization, regardless of the underlying data, due to the special situation for orphan drugs.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

I 2 Research question

The aim of this report is to assess the added benefit 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 research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of avacopan in combination with a rituximab or cyclophosphamide regimen

Therapeutic indication	ACT[a, b, c]
Adults with severe, active GPA or MPA	▪ cyclophosphamide (induction phase) followed by rituximab (maintenance phase), each in combination with glucocorticoids (only for patients with GPA) or ▪ rituximab (induction and maintenance phase) in combination with glucocorticoids

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the treatment of GPA and MPA is divided into an induction phase and a maintenance phase. The glucocorticoid dose should be reduced gradually.
c. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who meet the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. To demonstrate the added benefit for the total population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis

On 26 August 2025, shortly before the dossier was submitted by the company, the G-BA modified the ACT to that shown in Table 4. Deviating from this, the company, referring to a consultation on 15 October 2020, named individualized treatment as the ACT, based on the treatment phase, the course of disease and previous therapy, and taking into account immunosuppressive drugs in combination with glucocorticoids. The deviation from the ACT will not be commented on further, as suitable data for the benefit assessment were lacking. This benefit assessment was carried out versus the ACT specified by the G-BA as shown in Table 4.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit. The inclusion criteria concurred with those of the company.

It should be noted that the treatment of GPA and MPA is generally divided into an induction phase and a maintenance phase. A study duration of 24 weeks allows an assessment of the remission induction phase at most; a longer study duration is necessary to assess remission maintenance.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on avacopan (status: 16 June 2025)
- Bibliographical literature search on avacopan (last search on 16 June 2025)
- Search of trial registries / trial results databases for studies on avacopan (last search on 16 June 2025)
- Search on the G-BA website for avacopan (last search on 16 June 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on avacopan (last search on 11 September 2025); for search strategies, see I Appendix A of the full dossier assessment

A review of the completeness of the study pool did not identify any relevant studies.

This deviated from the company's assessment, which, based on its information retrieval, identified the ADVOCATE study [3-5] on the direct comparison of avacopan versus the ACT used by the company. The ADVOCATE study included by the company did not allow for a comparison versus the ACT. The ADVOCATE study and the company's approach are described below, and reasons are provided as to why the data presented by the company were unsuitable.

I 3.1 Evidence provided by the company

I 3.1.1 ADVOCATE study

The ADVOCATE study is a completed double-blind phase 3 study comparing avacopan with prednisone, each in combination with a rituximab or cyclophosphamide regimen, in patients aged 12 and older with GPA or MPA.

Patients had to have newly diagnosed or relapsed GPA or MPA requiring treatment with rituximab or cyclophosphamide at enrolment. The diagnosis was made using the revised Chapel Hill Consensus Conference Nomenclature [6]. To be included in the study, patients had to have ≥ 1 major item or ≥ 3 minor items or at least the 2 renal items of haematuria and proteinuria in the Birmingham Vasculitis Activity Score (BVAS). Patients with an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m² and patients with alveolar haemorrhage requiring invasive ventilation support were not allowed to participate in the ADVOCATE study. According to the study protocol, patients who had been taking > 3000 mg

methylprednisolone equivalent IV within 4 weeks prior to screening, or an oral daily dose of ≥ 10 mg prednisone equivalent for ≥ 6 weeks continuously prior to screening, were also excluded.

In the intervention arm, avacopan was dosed orally at 30 mg twice daily for 52 weeks, in compliance with the specifications in the summary of product characteristics (SmPC) [7]. In the comparator arm, oral prednisone was completely tapered off within 20 weeks according to a fixed schedule. To maintain blinding, patients in the intervention arm and the comparator arm received a placebo in addition to prednisone (20 weeks) or avacopan (52 weeks).

In addition, the patients in the ADVOCATE study received a treatment regimen with rituximab or cyclophosphamide. The treatment regimen was selected by the investigators prior to randomization. Patients who were assigned to a combination with rituximab received the 1st dose of rituximab on Day 1, and 3 further doses at weekly intervals. Patients who were assigned to a combination with cyclophosphamide received either 6 doses of cyclophosphamide IV until Week 13 or daily cyclophosphamide orally until the end of Week 14, each followed by azathioprine or (if azathioprine was not tolerated) mycophenolate from Week 15 to Week 52. In the intervention arm, the dosages of cyclophosphamide, azathioprine, mycophenolate and rituximab were in compliance with the specifications of the SmPC of avacopan [7]. In the comparator arm, the dosage of rituximab was in compliance with the SmPC with regard to remission induction [8]. Regarding the use of cyclophosphamide in the comparator arm, the oral administration was in compliance with the SmPC, and the IV administration was largely in compliance with the SmPC [9]. Azathioprine and mycophenolate are not authorized for the treatment of MPA or GPA, but the dosages used in the comparator arm are mentioned in the Kidney Disease: Improving Global Outcomes (KDIGO) guideline [10].

Non-study-supplied glucocorticoid use was permitted in the intervention and comparator arm, e.g. in the event of worsening of the disease or relapse, but were to be avoided as far as possible. Oral prednisone ≤ 20 mg/day (or equivalent) taken during the screening period had to be discontinued over a 4-week period from the start of treatment. In case of adrenal insufficiency, a prednisone equivalent dose of ≤ 10 mg per day was allowed, but also here the glucocorticoids were to be reduced or tapered as quickly as possible.

A total of 331 patients were included in the study and randomized in a 1:1 ratio to treatment with either avacopan (N = 166) or prednisone (N = 165), each in combination with a cyclophosphamide or rituximab regimen. Randomization was stratified by treatment regimen (rituximab versus IV cyclophosphamide versus oral cyclophosphamide), by positive test for anti-neutrophil cytoplasmic antibodies (ANCA) at diagnosis (proteinase-3 [PR3] versus myeloperoxidase [MPO]) and by disease status (newly diagnosed versus relapse). There were 3 adolescents among the patients included in the study. This did not correspond to the

marketing authorization of avacopan, which only covers adults. However, the proportion of adolescents in the study was very low and could therefore be disregarded.

The primary outcomes of the ADVOCATE study were remission at Week 26 and sustained remission from Week 26 to Week 52. Secondary outcomes included outcomes in the categories of morbidity, health-related quality of life and side effects.

The treatment duration was 52 weeks. This was followed by an 8-week observation phase.

Further details on the characterization of the study and the interventions used are presented in I Appendix B of the full dossier assessment.

I 3.1.2 Severity of the disease in the patients in the ADVOCATE study

Avacopan, in combination with a rituximab or cyclophosphamide regimen, is indicated for the treatment of adult patients with severe, active GPA or MPA [7]. According to current guidelines, there is no universal definition of severity, but a distinction is made between organ-threatening / life-threatening GPA/MPA and non-organ-threatening / non-life-threatening GPA/MPA [11-13]. The European Alliance of Associations for Rheumatology (EULAR) describes that even patients with less severe disease, particularly if they receive less intense treatment, are at risk of developing organ-threatening or life-threatening manifestations; it therefore rejects the categorization into non-severe and severe disease. The company described in Module 4 A, Section 4.2.1, that organ-/life-threatening manifestations are equivalent to severe active disease. However, it was not clear from the inclusion criteria and patient characteristics described in Section I 3.1.1 whether all patients included in the ADVOCATE study had organ-/life-threatening GPA or MPA at baseline.

The BVAS was used to assess vasculitis disease activity. It is assumed that an organ-threatening disease is present if there is ≥ 1 major item. The proportion of patients in the total population who had ≥ 1 major item in the BVAS at the time of screening was 62%. For the other patients, it cannot be ruled out that they did not have an organ-threatening disease because it was unclear whether meeting the other inclusion criteria relating to the BVAS (≥ 3 minor items or at least the 2 renal items of haematuria and proteinuria) also meant the presence of an organ-threatening disease. It should also be noted that the company classified 15 items as serious (‘major items’) in the BVAS submitted with the dossier, whereas in a validation study of version 3 of the BVAS [14], referred to by the company in the study protocol, there was no classification into serious (‘major items’) and less serious organ manifestations (‘minor items') that corresponded to the study protocol. Publicly available versions of the BVAS version 3 make a distinction between ‘minor’ and ‘major’ items, which does not fully correspond to the categorization of the version used in the ADVOCATE study [15]. For example, meningitis, sensory peripheral neuropathy, red blood cell casts and/or glomerulonephritis and episcleritis were classified as ‘major items’ in the BVAS version used in the ADVOCATE study. The ‘major

items' in the BVAS specified by the company suggested that the BVAS for Wegener's granulomatosis, a modified version of the BVAS for the therapeutic indication of GPA [16], was used for this purpose.

During the marketing authorization procedure, the fact that avacopan was administered exclusively in combination with a rituximab or cyclophosphamide regimen (patients had to require treatment with rituximab or cyclophosphamide to be included in the ADVOCATE study [see Section I 3.1.1]) was considered sufficient proof of severe, active GPA or MPA. According to the European Medicines Agency (EMA), cyclophosphamide and rituximab are considered the standard of care therapy for organ-/life-threatening ANCA-associated vasculitis (AAV) [17]. Both rituximab and cyclophosphamide are authorized exclusively for the treatment of severe, active GPA and MPA (rituximab only).

There was therefore an uncertainty as to whether all patients included in the ADVOCATE study had an organ-/life-threatening disease at the time of enrolment. However, given that there are no clear criteria for this, this uncertainty alone did not lead to an unsuitability of the study data.

I 3.1.3 Glucocorticoid use in the ADVOCATE study

According to various guidelines, in addition to remission induction and remission maintenance therapy with immunosuppressants, the use of glucocorticoids is recommended depending on the week of therapy and weight, in particular according to the dose-reduced scheme of the PEXIVAS study [10-13]. The oral starting dose is based body weight and is 50 mg (for a body weight of < 50 kg), 60 mg (for a body weight between 50 and 75 kg) or 75 mg (for a body weight > 75 kg) prednisolone equivalent/day for organ-threatening GPA/MPA. According to this scheme, the glucocorticoid dose is gradually tapered to 5 mg/day between Weeks 15 and 19, depending on the starting dose, and continued at this dose until at least Week 52 [18].

A reduced prednisone starting dose (0.5 mg/kg/day) can be considered for patients without organ-/life-threatening disease [11-13]. However, as the required duration and dose of glucocorticoid therapy has not yet been sufficiently evaluated, the glucocorticoid dosage during remission maintenance should be individually weighed against the risk of relapse and the risk of glucocorticoid-induced comorbidities [11]. In the RAVE study for example, a prednisone dose of 1 mg/kg/day was started after 1 to 3 doses of methylprednisolone (1000 mg each), which was gradually tapered off completely after 5 months [19]. This was similar to the prednisone tapering scheme in the comparator arm of the ADVOCATE study. In the assessment of the regulatory authority, the dose reduction scheme in the ADVOCATE study was similar to other studies in the therapeutic indication. Overall, glucocorticoid treatment in the comparator arm was considered to be adequate [17].

As described above, oral prednisone ≤ 20 mg/day (or equivalent) taken during the screening period had to be discontinued over a 4-week period from the start of treatment. In case of adrenal insufficiency, a prednisone equivalent dose of ≤ 10 mg per day was allowed, but the glucocorticoids had to be reduced or tapered as quickly as possible also in this case.

In the intervention arm of the ADVOCATE study, patients generally did not receive glucocorticoids, as avacopan was to be used to minimize the use of glucocorticoids. In the comparator arm, the prednisone starting dose was 60 mg/day for adult patients with a baseline body weight ≥ 55 kg, and 45 mg/day for patients < 55 kg. For patients with a lower body weight (< 55 kg), the prednisone starting dose was slightly lower than according to the PEXIVAS scheme. Patients with a body weight > 75 kg received 15 mg/day less prednisone at study start compared with the PEXIVAS scheme. Around 50% of the patients included weighed at least 75 kg at baseline. However, it was generally assumed that the prednisone starting dose in the ADVOCATE study was not substantially too low, especially in view of the fact that it could not be ruled out that some of the patients did not have organ-threatening disease (see Section I 3.1.2).

Oral prednisone was completely tapered off within 20 weeks in the comparator arm of the ADVOCATE study. This means that the patients who received a rituximab regimen in the comparator arm did not receive any preventive (i.e. remission maintenance) therapy after Week 20. Patients in the comparator arm who received a cyclophosphamide regimen were not without remission maintenance therapy until the end of treatment at Week 52, as they received azathioprine or alternatively mycophenolate.

(Re-)administration of glucocorticoids (so-called ‘non-study-supplied glucocorticoid use’) or, if necessary, other immunosuppressants was only permitted reactively, i.e. in the event of a worsening of the disease or a relapse. In the total population, 145 patients (87.3%) in the intervention arm and 149 patients (90.9%) in the comparator arm did not receive non-study-supplied glucocorticoids during the entire treatment period up to Week 52. Data on how many patients with a rituximab regimen received glucocorticoids or other immunosuppressants for the treatment of GPA or MPA after Week 20 until Week 52 were not available in Module 4 A.

I 3.1.4 Approach of the company

In Module 4 A, the company presented analyses on Week 26 for the total population of the ADVOCATE study and used these to derive the added benefit. There were 2 analysis dates in the study: at Week 52 (database lock on 20 November 2019) and at Week 60 (database lock on 27 January 2020). For the benefit assessment, the company used analyses at Week 26, with the database lock on 20 November 2019. For analyses at Week 52, the company referred exclusively to Module 5 of the dossier. The company justified its choice of analysis date by stating that Week 26 was a relevant time point for assessing the effectiveness of a drug

therapy for remission induction of GPA or MPA. It considered that with the presentation of the results for Week 26, all G-BA requirements as set out in the rules of procedure were met, and that the ADVOCATE study was therefore presented in a manner that complied with regulatory, guideline and SmPC requirements.

I 3.2 Assessment of the company's approach and consequence for the benefit assessment

The available data were unsuitable for this benefit assessment. The following section describes which analysis date from the ADVOCATE study should, in principle, be used for this benefit assessment, and explains why there are no suitable data for comparing avacopan versus the comparator therapy specified by the G-BA.

I 3.2.1 Analysis date to be considered

GPA and MPA are conditions that can become life threatening. According to the S3 guideline on the diagnosis and treatment of ANCA-associated vasculitis, the treatment goals are remission, prevention of chronic organ damage, improving or maintaining quality of life and reducing mortality [11]. In this therapeutic indication, remission induction is generally followed by remission maintenance therapy [10-13].

According to the S3 guideline, remission maintenance therapy should generally last at least 36 months for treatment with rituximab, and at least 48 months for conventional therapies such as azathioprine. A continuation beyond this period or a shortening (e.g. in MPO-ANCA-positive patients with rapid onset of remission and sustained ANCA negativity) must be decided on an individual basis. However, recommendations for the omission of remission maintenance therapy for a certain ANCA status are based on data with a low level of evidence [11]. Consequently, the results of the ADVOCATE study at the end of treatment at Week 52 should generally be used in this therapeutic indication, as these allow conclusions to be drawn about a period of remission maintenance, albeit limited, in addition to for remission induction. It should be noted that a treatment duration that is much longer than 52 weeks is necessary to assess the sustainability of the effects of remission maintenance. However, according to the S3 guideline, the use of avacopan should be limited to a maximum of 12 months for the time being, as there is a lack of study data beyond this period [11]. It can be assumed that maintenance therapy is generally administered following avacopan treatment of 52 weeks. However, this was not investigated in the ADVOCATE study.

As the company itself described, results at Week 26 only provide information on remission induction. However, these represent only part of the research question, since – if data is recorded beyond remission induction – it is relevant whether the remission is maintained after successful remission induction. This also applies in principle if remission maintenance therapy is not used in individual cases. Furthermore, it is questionable whether the analysis date of

Week 26 in the ADVOCATE study was appropriate for the assessment of remission induction. It can be inferred from the European assessment report (Institute's calculation) that 75 of the patients in the total population (22.7%) were fully observed until Week 26 and had not achieved remission by then [17]. Remission at Week 26 was defined as freedom from symptoms (BVAS = 0) at Week 26 and freedom from steroids in the previous 4 weeks. Achievement of remission at Week 26 was a primary outcome of the study, but an analysis at Week 26 for all outcomes was not prespecified.

In addition, outcomes were recorded 8 weeks after the planned end of study medication (at Week 60). The recording at Week 60 was prespecified for some outcomes, but the outcome remission was not analysed again. For outcomes in the side effects category, it would in principle be conceivable to use the results at Week 60 or to consider these results in addition to Week 52. However, the overall rates of adverse events at Week 52 and Week 60 were identical. In addition, patients who received a rituximab regimen in the comparator arm did not receive remission maintenance therapy from Week 21 onwards, as treatment with prednisone was also discontinued from this point onwards in accordance with the tapering schedule. The consideration of Week 60 thus reinforced the problem of the lack of maintenance therapy in patients who received a rituximab regimen in the comparator arm. Therefore it would have been preferable to consider the results at Week 52 alone if the subpopulation with a rituximab regimen had been suitable for the benefit assessment (see Section I 3.2.2). Irrespective of this, the company did not present any analyses for Week 52 in Module 4 A.

I 3.2.2 Comparator therapies in the ADVOCATE study do not correspond to the comparator therapy specified by the G-BA

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 that did not correspond to the maintenance therapy with rituximab defined by the G-BA as the ACT. The patients with a rituximab regimen (65% of the patients included) only received induction therapy without subsequent remission maintenance with rituximab. In this therapeutic indication, maintenance therapy is routinely given, and the proportion of patients who received remission induction with rituximab in the comparator arm and for whom maintenance therapy with rituximab was not (strictly) indicated was considered to be very low. The unsuitability of the subpopulations who received a cyclophosphamide regimen or a rituximab regimen in the ADVOCATE study is explained in detail below.

Maintenance therapy in patients with cyclophosphamide regimens des not correspond to the comparator therapy specified by the G-BA

For the therapeutic indication to be assessed, the results at Week 52 of the ADVOCATE study should generally be used, as these allow conclusions to be drawn about a period of remission

maintenance, albeit a limited one (see Section I 3.2.1). In accordance with the comparator therapy defined by the G-BA and in line with the recommendations of the guidelines, an induction phase with cyclophosphamide should generally be followed by a maintenance phase with rituximab [11-13]. In the ADVOCATE study, 59 patients in the intervention group and 57 patients in the control group received a cyclophosphamide regimen in which remission induction with oral or IV cyclophosphamide was followed by maintenance therapy with azathioprine (of mycophenolate if azathioprine was not tolerated) from Week 15. In addition, the patients received a prednisone dosage regimen for 20 weeks alongside the aforementioned immunosuppressive drugs.

The 2 cyclophosphamide regimens in the ADVOCATE study deviated from the comparator therapy specified by the G-BA, as they used maintenance therapy with azathioprine (or mycophenolate) rather than rituximab. This applied both to the Week 52 analyses, which were to be generally used for the benefit assessment, and to the Week 26 results used by the company. The results of the subpopulation with cyclophosphamide regimen were therefore not suitable for this benefit assessment.

Regardless of this, the allocation to a cyclophosphamide regimen was made irrespective of the presence of GPA. Only for these patients does a cyclophosphamide regimen represent an option of the ACT (see Table 4). The subpopulation receiving a cyclophosphamide regimen included 26 patients with GPA and 31 patients with MPA in the comparator arm [17]. This means that in the ADVOCATE study, 31 patients with MPA, for whom a cyclophosphamide regimen was not an option of the ACT, received treatment with cyclophosphamide.

No remission maintenance with rituximab in the comparator arm in patients with a rituximab regimen

If rituximab is used for remission induction, rituximab should routinely be used for remission maintenance, in accordance with the comparator therapy specified by the G-BA and in line with the recommendations of the guidelines [11-13]. [11-13]. In the ADVOCATE study, 107 patients in each of the 2 treatment arms received a rituximab regimen. According to the SmPC, following induction of remission with rituximab, maintenance treatment should be initiated no sooner than 16 weeks after the last rituximab infusion. This maintenance treatment consists of 2 doses of rituximab 2 weeks apart, followed by further doses of rituximab every 6 months thereafter. Patients should receive rituximab for at least 24 months after achievement of remission, according to the SmPC [8]. The S3 guideline recommends a maintenance phase of at least 36 months for rituximab [11]. In the ADVOCATE study, however, patients in the comparator arm with a rituximab regimen only received remission induction therapy with rituximab (4 doses over a period of 3 weeks). As a result, patients in the comparator arm who received a rituximab treatment regimen lacked a total of 2 to 3 doses of

rituximab for remission maintenance during the 52-week treatment period of the ADVOCATE study.

Even though remission maintenance is the standard of care for GPA/MPA, and the SmPC for rituximab in this therapeutic indication generally also recommends maintenance therapy after remission has been achieved [8], in individual cases there may be specific reasons against maintenance therapy (e.g. advanced age, fragility, greatly increased susceptibility to infection, need for dialysis) or which render remission maintenance unnecessary. According to the S3 guideline, it may make sense, for example, to shorten remission maintenance therapy in patients who are initially MPO-ANCA positive and persistently negative after remission induction, or to forego remission maintenance therapy under close monitoring. On the other hand, a (persistent positive) PR3-ANCA status and/or a PR3-ANCA increase are associated with an increased risk of relapse [11].

No relevant data were available for patients on a rituximab regimen that would speak against maintenance therapy or may render remission maintenance unnecessary (see below). However, according to the inclusion criteria of the study, patients were not allowed to have required dialysis within 12 weeks prior to screening and the eGFR had to be at least 15 mL/min/1.73 m² at screening. Furthermore, the patients had to be fit enough to participate in the study. This implied consideration of the medical history, physical investigation (including electrocardiogram) and laboratory values. Patients with alveolar haemorrhage requiring invasive ventilation support were also not allowed to take part in the ADVOCATE study. The inclusion criteria mentioned above generally indicate that the patients were eligible for remission maintenance therapy. In order to assess whether remission maintenance was generally an option for the patients included in the study, data on the characteristics of patients receiving a rituximab regimen (see Table 5) were also used, where available, and, in addition, approximate data on the total population.

Table 5: Characteristics of the subpopulation with rituximab regimen

Study **Characteristic** **Category**	**avacopan + rituximab regimen** **N[a] = 107**	**prednisone + rituximab regimen** **N[a] = 107**
ADVOCATE study		
Age at baseline [years]		
Mean (SD)	60 (15)	60 (16)
Sex [F/M], %	43/57	51/49
Disease duration at baseline [months]		
Mean (SD)	32.8 (62.3)	29.6 (47.0)
Median	0.5	0.8
AAV status, n (%)		
Initial diagnosis	63 (59)	62 (58)
Relapsed	44 (41)	45 (42)
AAV type, n (%)		
GPA	65 (61)	64 (60)
MPA	42 (39)	43 (40)
ANCA status at baseline, n (%)		
PR3	ND	ND
MPO	ND	ND
MPO-ANCA-negative in the course of study	ND	ND
BVAS inclusion criteria, n (%)		
≥ 1 major item	ND	ND
≥ 3 minor items	ND	ND
2 renal items of proteinuria and haematuria	ND	ND
BVAS at screening[b]		
Mean (SD)	15.5 (5.7)	15.6 (6.1)
eGFR at baseline [mL/min/1.73 m^2]		
Mean (SD)	57.1 (32.2)	56.0 (33.4)
Renal disorder at baseline	81 (76)	82 (77)
Dialysis required during the course of study	ND[c]	ND[c]

a. Number of randomized patients who received at least one dose of the respective treatment. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Scale range: 0 to 63.
c. In the total population, 4 vs. 4 patients developed a requirement for dialysis during the course of the study.

AAV: ANCA-associated vasculitis; AE: adverse event; ANCA: anti-neutrophil cytoplasmic antibodies; BVAS: Birmingham Vasculitis Activity Score; eGFR: estimated glomerular filtration rate; F: female; GPA: granulomatosis with polyangiitis; M: male; MPA: microscopic polyangiitis; MPO: myeloperoxidase; n: number of patients in the category, N: number of randomized patients; ND: no data; PR3: proteinase-3; RCT: randomized controlled trial; SD: standard deviation

The patients who received a rituximab regimen in the comparator arm were on average 60 years old and had a mean BVAS score of 15.6 (scale range: 0 to 63) at the time of screening. The mean baseline eGFR in the comparator arm was 56.0 mL/min/1.73 m². This means that the majority of patients with a rituximab regimen in the comparator arm did not have severely impaired renal function at baseline, which might have precluded remission maintenance therapy. In the total population, 4 patients in the comparator arm required temporary or permanent dialysis during the study. The proportion of MPO-ANCA-positive patients in the comparator arm of the total population was 57% at baseline. During the study, a total of 30.1% (Week 26) and 35.3% (Week 52) of the MPO-ANCA-positive patients in the comparator arm of the total population became MPO-ANCA-negative.

Based on the inclusion and exclusion criteria of the ADVOCATE study and the characteristics of the patients with a rituximab regimen and of the total population of the ADVOCATE study, it was assumed that the patients were generally eligible for maintenance therapy. It could not be ruled out that there were patients for whom only remission induction with rituximab might have been the appropriate therapy. However, the proportion of patients with a rituximab regimen for whom maintenance therapy with rituximab was not (strictly) indicated was assessed to be very low.

Apart from the lack of maintenance therapy with rituximab, glucocorticoids were completely discontinued over 20 weeks in the comparator arm of the ADVOCATE study (see Section I 3.1.3). This means that the patients who received a rituximab regimen in the comparator arm did not receive any preventive (i.e. remission maintenance) therapy after Week 20. Only in the event of disease worsening or relapse could patients with a rituximab regimen in the comparator arm receive glucocorticoids or other immunosuppressive drugs. In contrast, in the intervention arm, avacopan was administered continuously until Week 52 for remission maintenance. In the absence of disease worsening, a comparison was made between avacopan and placebo (for avacopan) from Week 21 to Week 52 in patients on the rituximab regimen.

It could not be ruled out that the lack of remission maintenance in patients in the comparator arm with the rituximab regimen, in particular the missing 2 to 3 doses of rituximab, had an impact on the treatment effect at Week 52. In the outcome of sustained remission (defined as remission at Weeks 26 and 52 without relapse between Weeks 26 and 52), this impact is suggested if the total population and the subpopulations with and without maintenance therapy are compared: Both in the total population and in the subpopulation with a rituximab regimen with no maintenance therapy in the comparator arm, there was a statistically significant effect in favour of avacopan in the outcome of sustained remission (Institute's unadjusted calculation of RR [95% confidence interval (95% CI)] with p-values for the total population and the subpopulation with a rituximab regimen respectively as follows:

1.20 [1.002; 1.43] with p = 0.046, and 1.27 [1.03; 1.56] with p = 0.024; p-values from unconditional exact tests [CSZ method according to [20]]). In contrast, there was no statistically significant difference between the treatment arms in the outcome of sustained remission for the subpopulation with a cyclophosphamide regimen with maintenance therapy (Institute's unadjusted calculation of RR [95% CI] with p-value: 1.06 [0.76; 1.49] with p = 0.773; p-value from unconditional exact test [CSZ method according to [20]]). With regard to the results from the Institute's unadjusted calculations presented here, it should be noted that adjusted analyses are generally preferable where feasible; however, the data required for this were not available in this case. Irrespective of this, no results were available for the subpopulation of patients with rituximab regimen in Module 4 A.

I 3.3 Summary

In the therapeutic indication of avacopan, remission induction and maintenance therapy are usually carried out. For the given research question, the analysis date at Week 52 is therefore relevant in principle to assess the sustainability of the effects of the key outcome in this therapeutic indication (remission). The data presented by the company for the total population as well as the data (not presented in Module 4) of the subpopulations with cyclophosphamide and rituximab regimens were not suitable for the benefit assessment. Firstly, the patients in the ADVOCATE study with a cyclophosphamide regimen received a maintenance therapy other than the one defined by the G-BA as the ACT. Secondly, the patients with a rituximab regimen in the comparator arm did not receive maintenance therapy, although most of them were eligible for maintenance therapy with rituximab in principle. Thus, no suitable data were available for the benefit assessment.

I 4 Results on added benefit

No suitable data were available to assess the added benefit of avacopan, in combination with a rituximab or cyclophosphamide regimen, in adult patients with severe, active GPA or MPA. There is no hint of an added benefit of avacopan, in combination with a rituximab or cyclophosphamide regimen, in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 6 summarizes the result of the assessment of the added benefit of avacopan, in combination with a rituximab or cyclophosphamide regimen, in comparison with the ACT.

Table 6: Avacopan in combination with a rituximab or cyclophosphamide regimen – probability and extent of added benefit

Therapeutic indication	**ACT**[a, b, c]	**Probability and extent of added benefit**
Adults with severe, active GPA or MPA	▪ cyclophosphamide (induction phase) followed by rituximab (maintenance phase), each in combination with glucocorticoids (only for patients with GPA) or ▪ rituximab (induction and maintenance phase) in combination with glucocorticoids	▪ Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the treatment of GPA and MPA is divided into an induction phase and a maintenance phase. The glucocorticoid dose should be reduced gradually.
c. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who meet the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. To demonstrate the added benefit for the total population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis

The assessment described above deviates from that of the company, which derived a hint of a minor added benefit.

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment conducted in the context of the market launch in 2022, where the G-BA had determined a hint of a minor added benefit of avacopan in combination with a rituximab or cyclophosphamide regimen. However, in the G-BA's assessment the added benefit was considered proven by the marketing authorization, regardless of the underlying data, due to the special situation for orphan drugs.

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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The full report (German version) is published under https://www.iqwig.de/en/projects/a25-114.html.