Avacopan (TAVNEOS)

in ANCA-positive Granulomatosis with Polyangiitis and Microscopic Polyangiitis

National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description / Mechanism of Action

- Complement 5a receptor (C5aR) antagonist that inhibits interactions between C5aR and anaphylatoxin C5a and blocks C5a-mediated neutrophil activation and migration.[1]
- Second agent approved for the treatment of patients with antineutrophil cytoplasmic autoantibody (ANCA)-positive granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), but is the first drug approved for GPA / MPA as an adjunct to standard immunosuppressive therapy (IST) and glucocorticoids. Rituximab was approved as an IST for GPA / MPA.
- Avacopan differs from ravulizumab and eculizumab in being a small molecule rather than a biologic and in blocking the C5a receptor as opposed to being an antibody to the C5 complement protein. In addition, ravulizumab and eculizumab are not approved for ANCA or related indications.

Indication Under Review

- Adjunctive treatment of adult patients with severe active ANCA-associated vasculitis (AAV) (GPA and MPA) in combination with standard therapy including glucocorticoids. Does not eliminate glucocorticoid use.
- Note: Avacopan is not approved for the treatment of the third subtype of AAV, eosinophilic granulomatosis with polyangiitis (EGPA / Churg-Strauss syndrome).

Dosage and Administration

Pretreatment Tests

- Liver function tests including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin. Not recommended in patients with cirrhosis, especially severe hepatic impairment (Child-Pugh C).
- Hepatitis B (HBV) serology (hepatitis B surface antigen [HBsAg] and total antibody to hepatitis B core antigen [anti-HBc] titers). Clinicians should consult an expert in HBV management if test results are consistent with prior or current HBV infection to develop a management and monitoring plan and/or to determine whether HBV antiviral therapy is required before or during treatment with avacopan.

Dosage Regimen

- 30 mg (three 10-mg capsules) twice daily with food.
- Capsules should not be crushed, chewed, or opened.

Dosage Modifications

- *Strong CYP3A4 Inhibitors*: Reduce dosage to 30 mg once daily.
- No dosage adjustment is required for mild, moderate, or severe renal impairment. No data is available for patients with AAV on dialysis.
- No dosage adjustment is required for mild or moderate(Child-Pugh Class A or B) hepatic impairment. No data is available for patients with severe (Child-Pugh Class C) hepatic impairment.

Dosage Form Under Review

- 10-mg capsules supplied in bottles of 180 capsules

Clinical Evidence Summary

Efficacy Considerations

- A phase 3 randomized clinical trial (RCT) compared avacopan with a prednisone taper, each added to a background of investigator-selected standard immunosuppressive therapy (IST), to evaluate whether avacopan can replace chronic glucocorticoids and to determine its efficacy in inducing and sustaining remission in patients with ANCA-positive GPA or MPA.[2,3] Standard IST consisted of either rituximab induction without maintenance therapy or cyclophosphamide induction then azathioprine maintenance (or mycophenolate mofetil if azathioprine was inadvisable). The phase 3 trial is the focus of this review.
- Two small, 12-week, phase 2, placebo-controlled, dose-ranging RCTs with additional 12 weeks of follow-up assessed the safety and efficacy of avacopan.
    - The CLEAR trial (N = 67) evaluated avacopan treatment either with or without low-dose prednisone and a control group of high-dose prednisone alone.[4] Remission induction therapy consisted of rituximab or cyclophosphamide. Both avacopan groups (with or without prednisone) were noninferior to high-dose prednisone in achieving clinical response at Week 12 (86% and 81% vs 70%, respectively). Clinical response was defined as ≥ 50% reduction in Birmingham Vasculitis Activity Score and no worsening in any body system (BVAS-50).
    - The 12-week CLASSIC trial (N = 42) compared study treatments (avacopan 10 mg or 30 mg) vs placebo against a background of glucocorticoid-containing standard of care (high-dose prednisone plus either rituximab for 4 weeks or cyclophosphamide).[5] BVAS-50 response at Week 12 was similar among groups: 11/12 (92%) and 12/15 (80%) vs 11/13 (85%), respectively (no statistical analyses were performed). Other results of the CLASSIC trial suggested that avacopan produced dose-related improvements in early disease remission, renal responses, and renal function.
    - According to the FDA reviewer, the phase 2 RCTs provided no evidence to support the treatment benefit of avacopan because BVAS-50 response has an unknown clinical relevance.[6]

Phase 3 Randomized Clinical Trial

Study Design

- The Avacopan Development in Vasculitis to Obtain Corticosteroid elimination and Therapeutic Efficacy (ADVOCATE) trial was a 52-week, multinational, multicenter, phase 3, double-blind, double-dummy, active-controlled, noninferiority and superiority RCT comparing avacopan with prednisone taper, each in addition to background IST, in patients with newly diagnosed or relapsed active ANCA GPA or MPA.[2]
- Key Entry Criteria
    - Inclusion Criteria: Adult (or adolescent in certain countries) with diagnosis of GPA or MPA (newly diagnosed or relapsing); positive anti-proteinase-3 (PR3) or anti-myeloperoxidase (MPO) antibodies (past or current); evidence of active disease (defined as ≥ 1 major item or ≥ 3 minor

items or ≥ 2 renal items of proteinuria and hematuria due to vasculitis on the BVAS; eGFR ≥ 15 mL/min/1.73 m^2.
    - Exclusion Criteria: Alveolar hemorrhage requiring invasive pulmonary ventilation support; dialysis or plasma exchange within the past 12 weeks; kidney transplant; other multisystem autoimmune disease; > 3 g of intravenous glucocorticoids within 4 weeks; > 10 mg/d of oral prednisone or equivalent for more than 6 weeks continuously before screening.
    - Excluded medications included other biologics within the past 12 weeks and drugs that would duplicate or confound evaluation of the effects of study therapies.
- All patients received one of the following standard ISTs for induction and maintenance of remission:
    - IV cyclophosphamide (15 mg/kg up to 1.2 g maximum every 2–3 weeks for 13 weeks) then oral azathioprine (1 mg/kg/day starting at Week 15 and titrating up to 2 mg/kg/day) or mycophenolate (mofetil or sodium; target dose 2 g/day).
    - Oral cyclophosphamide (2 mg/kg/day, maximum 200 mg/day, for 14 weeks) then oral azathioprine or mycophenolate (mofetil or sodium).
    - IV rituximab (375 mg/m^2) once weekly for 4 weeks (without maintenance therapy).
- Patients were randomized to either one of the following:
    - Avacopan 30 mg twice daily for 52 weeks (plus placebo prednisone taper over 20 weeks) — in effect, avacopan + placebo then avacopan only in the remission induction period (Weeks 0–26) and avacopan in the remission maintenance (Weeks 27–52) period, or
    - Prednisone: Prednisone (60 mg/day if ≥ 55 kg or 45 mg/day if < 55 kg) tapered to 0 mg over 20 weeks with discontinuation by Week 21) plus placebo avacopan twice daily for 52 weeks — in effect, prednisone + placebo then placebo only in the remission induction period and placebo in the remission maintenance period.
- Randomization was stratified by newly diagnosed vs relapsing AAV; PR3-positive or MPO-positive AAV; and standard IST.
- Patients who were taking glucocorticoids during the screening period had to be tapered to ≤ 20 mg of prednisone equivalent by enrollment and further tapered to 0 mg by the end of Week 4 according to a protocolled schedule.
- Non-study supplied additional glucocorticoids were allowed per investigator discretion. The additional glucocorticoids were used for such purposes as pre-medication to reduce hypersensitivity reactions; tapering after screening-period glucocorticoids; treatment of persistent, worsened, or relapsed vasculitis; or adrenal insufficiency. Glucocorticoids above the protocolled tapering schedule were to be discontinued by Week 4.
- Allowed Concomitant Medications: Prophylaxis or treatment for *Pneumocystis* pneumonia / PCP (e.g., trimethoprim / sulfamethoxazole), osteoporosis, gastroprotection, and nausea.

Primary Efficacy Measures

- Co-primary Outcome Measures: Disease remission at Week 26 and sustained disease remission at Week 52, where BVAS remission was adjudicated by a panel of nine experts in AAV.
- Definitions
    - Clinical remission: A BVAS of 0 with no glucocorticoid use for treatment of GPA / MPA from Week 22 to Week 26.
    - Sustained remission: Remission at Week 26 and remission at Week 52 without relapse between Week 26 and Week 52.
    - Remission at Week 52: BVAS of 0 and no glucocorticoid use for treatment of GPA / MPA from Week 48 to Week 52.

- Relapse: Occurrence of one major item, at least three nonmajor items, or one or two nonmajor items for at least two consecutive visits on the BVAS after remission (BVAS = 0) had been achieved.

Patient Characteristics

- Mean age 60.9 years (range, 13 to 88 years, including 3 adolescents); male 56.4%; Caucasian 84.2%; 18% from North America; mean body mass index (BMI) 26.8 kg/m^2; newly diagnosed disease 69.4%; GPA 54.8%; MPA 45.2%; anti-PR3-positive 43.0%; anti-MPO-positive 57.0%; renal vasculitis (81%).[2,6]
- Active, mainly severe and life-threatening GPA / MPA. Manifestations: Renal component 81.2%; general component 68.2%; ear/nose/throat component 43.6%; chest component 43.0%.
- Standard IST: Rituximab 65%, IV cyclophosphamide 31%, oral cyclophosphamide 4%.

Primary Efficacy Results

- The results showed that avacopan was noninferior to prednisone taper in remission induction rates at Week 26 (72.3% vs 70.1%, respectively) and significantly better than prednisone taper (actually better than *placebo avacopan* following the prednisone taper) in achieving sustained remission at Week 52 (65.7% vs 54.9%, respectively; Table 1).

Table 1 Phase 3 RCT Primary Efficacy Results (Adjudicator BVAS Remission)

Outcome	Avacopan, n/N (%) (Avacopan + PBO / Avacopan†)	Prednisone, n/N (%) (Prednisone + PBO / PBO†)	Relative Risk (95% CI)	Absolute Difference (95% CI)	NNT (95% CI)	Q
Remission at Week 26	120/166 (72.3)	115/164 (70.1)	1.0 (0.9, 1.2)	3.4 (–6.0, 12.8)	NSD	L$^{\alpha}$
Sustained remission at Week 52	109 / 166 (65.7)	90 / 164 (54.9)	1.2 (1.0, 1.4)	12.5 (2.6, 22.3)	10 (5, 344)	L$^{\alpha}$

Sources: 1, 6

BVAS, Birmingham Vasculitis Activity Score; **CFB**, Change from baseline; **L**, Low; **Q**, GRADE quality of evidence

† Denotes the de facto therapy during the induction period (Weeks 0–26) / maintenance period (Weeks 27–52), respectively.

$^{\alpha}$ Downgraded for inconsistency (between adjudicator vs investigator assessments of remission – see text) and for imprecision (optimal information size not met and wide confidence intervals)

- The anticipated absolute effect for achieving adjudicated BVAS sustained remission at 52 weeks was 110 more (95% CI, 0 fewer to 220 more) per 1000 patients. The 95% CIs for the anticipated absolute effects include a worst case of no incremental sustained remission benefit with avacopan versus de facto placebo in the prednisone group.
- Analyses based on Investigator BVAS Assessments showed lower remission rates, and treatment differences (avacopan vs prednisone, respectively) were not significant for remission at Week 26 (62.7% vs 62.2%) and no longer significant for sustained remission at Week 52 (54.8% vs. 47.0%).[6]
    - The discrepancies between the Adjudicator and Investigator assessments were attributed to differences in scoring of *persistent* activity and whether or not the disease was considered *active*, with renal and general organ system assessments having the most discrepancies.[6]
    - The BVAS version 3 form used for the study was not to include the *persistent* disease manifestations (vasculitis items persistent for ≥ 3 months and not worsening).

Secondary Efficacy Results

- Secondary efficacy results numerically favored avacopan, but according to the FDA, did not support a clinically meaningful benefit of avacopan and were only exploratory because they were not adjusted for multiplicity.[6] The secondary results included the following:

- Disease relapse
- Early remission measured by BVAS = 0 at Week 4
- Vasculitis Damage Index
- Renal assessments (multiple renal end points were assessed): Overall, Week-52 improvements in eGFR were similar between treatment groups (7.3 vs 4.1 mL/min/1.73 m^2 for the avacopan and prednisone groups, respectively; difference 3.2; 95% CI 0.3, 6.1).[2,6] In patients with severe / stage 4 renal impairment (baseline eGFR < 30 mL/min/1.73 m^2), the mean Week-52 improvement in eGFR was significantly better in the avacopan than the prednisone group (13.7 vs 8.2 mL/min/1.73 m^2, respectively; difference 5.6; 95% CI 1.7, 9.5).[2,6]
- Health-related Quality of Life measures

- Glucocorticoid-induced toxicity was another secondary efficacy measure considered exploratory by the FDA**Error! Reference source not found.**.

Table 2 Assessments of Glucocorticoid-induced Toxicity

Safety Outcome	Time (Wks)	Avacopan	Prednisone	Absolute Difference (95% CI)
CFB in GTI-CWS, LSM	13	26.0	36.9	–10.9 (–18.2, –3.7)
	26	40.2	47.0	–16.8 (–27.0, –6.5)
CFB in GTI-AIS, LSM	13	10.0	23.3	–13.3 (–21.8, –4.8)
	26	11.2	23.4	–12.1 (–21.1, –3.2)
EULAR AE Possibly Related to GC, n/N (%)	52	NR (66.3)	NR (80.5)	–14.2 (–23.7, –3.8)

Sources: 2,6

AE, Adverse event; **AIS**, Aggregate Improvement Score, a measure of present toxicity (range, –317 to 410 with AIS < 0 indicating reduction in toxicity, AIS = 0 indicating no change, and AIS > 0 indicating increase in toxicity; minimal clinically important change is ≤ –10); **CFB**, Change from baseline; **CWS**, Cumulative Worsening Score (range, 0 to 410 with higher scores indicating development of a greater number of new toxicities from baseline); **EULAR**, European League Against Rheumatism; **GC**, Glucocorticoid; **GTI**, Glucocorticoid Toxicity Index; **LSM**, Least square mean; **NR**, Not reported

- The results appeared to suggest that avacopan was better than prednisone in reducing the number of new glucocorticoid toxicities (as reflected in lower GTI-Cumulative Worsening Scores [CWS]) and reducing the magnitude of increases in glucocorticoid toxicities (as measured with the GTI-Aggregate Improvement Scores [AIS]) from baseline to Weeks 13 and 26. The differences were mostly due to higher mean GTS-CWS and GTS-AIS scores in the prednisone group for body mass index and glucose tolerance from baseline to Week 13 and body mass index, lipids, neuropsychiatric toxicity, and infection from baseline to Week 26.
- However, the treatment differences in GTI may be explained by the protocolled prednisone doses in the control group rather than an effect of avacopan.[6] Analyses of cumulative total glucocorticoid use from Week 0 to 26 showed a mean prednisone-equivalent dose of 1,073 mg vs 3,192 mg or 6.1 mg/patient-day vs 17.9 mg/patient-day in the avacopan and prednisone groups, respectively. Lower exposure to glucocorticoids due to the study design may explain the lower GTI in the avacopan group.
- Of the cumulative total glucocorticoid dose from baseline to Week 26, 6.1 mg/patient-day vs 4.5 mg/patient-day, respectively, were due to nonstudy-supplied glucocorticoids used at the Investigator's discretion, showing greater use of additional glucocorticoids in the avacopan group than the prednisone group (difference of 1.6 mg/patient-day) during the first half of the trial.
- GTI was not assessed at later time points after the protocolled prednisone taper when nonstudy-supplied additional glucocorticoids could be given at the Investigator's discretion. The

prednisone group only received additional glucocorticoids in the second half of the study. The cumulative mean prednisone-equivalent dose from Week 27 to 52 was 276 mg vs 462 mg or 1.6 mg/patient-day vs 2.7 mg/patient-day in the avacopan and prednisone groups, respectively). It is unknown whether a difference in GTI was associated with this small difference in glucocorticoid doses per patient-day (1.1 mg).

- The FDA Division of Clinical Outcome Assessment also concluded that the GTI was not "fit-for-purpose to measure glucocorticoid-related toxicities or glucocorticoid-sparing effects for the context of use of this drug development program."[6] The level of validation of the GTI was deemed inadequate to support its context of use.[6] The reasons for the conclusion included problems with comprehensiveness, interpretability, clinical meaningfulness of within-patient changes, applicability to measuring avacopan toxicity, and multiplicity.[6]

Other Data: Glucocorticoid Use

- Glucocorticoid use was not a prespecified end point. Descriptive data of glucocorticoid use were provided[6] (Table 3).

Table 3 Glucocorticoid Use (Prednisone-equivalent Dose)

Time	Glucocorticoid Use	Avacopan (Avacopan + PBO / Avacopan†)	Prednisone (Prednisone + PBO / PBO†)	Relative Risk (95% CI)	Absolute Difference (95% CI)	Anticipated Absolute Effects Per 1000 (95% CI)	NNT (95% CI)	Q
Cumulative Total Glucocorticoid Use (All Sources)								
Wks 0–26	n/N (%)	143/166 (86.1)	164/164 (100.0)	0.86 (0.81, 0.92)	13.9 (8.90, 19.98)	140 (190 to 80) fewer	8 (6, 12)	M$^{\alpha}$
	Total (mg) / pt-d	6.1	17.9	—	–11.8	—	—	
Wks 27–52	n/N (%)	44/166 (26.5)	63/164 (38.4)	0.69 (0.50, 0.95)	11.9 (1.80, 21.68)	119 (192 to 19) fewer	9 (5, 53)	L$^{\alpha\beta}$
	Total (mg) / pt-d	1.6	2.7	—	–1.1	—	—	
Wks 0–52	n/N (%)	145/166 (87.3)	164/164 (100.0)	0.87 (0.82, 0.93)	12.7 (7.89, 18.62)	130 (180 to 70) fewer	8 (6, 14)	M$^{\alpha}$
	Total (mg) / pt-d	3.9	10.5	—	–6.6	—	—	
Non-study Supplied Glucocorticoid Use								
Wks 0–26	n/N (%)	143/166 (86.1)	149/164 (90.9)	0.95 (0.88, 1.03)	4.8 (–2.19, 11.83)	45 fewer (109 fewer to 27 more)	22 (NSD)	M$^{\alpha}$
	Total (mg) / pt-d	6.1	4.5	—	1.6	—	—	
Wks 27–52	n/N (%)	44/166 (26.5)	63/164 (38.4)	0.69 (0.50, 0.95)	11.9 (1.80, 21.68)	119 (192 to 19) fewer	9 (5, 53)	L$^{\alpha\beta}$
	Total (mg) / pt-d	1.6	2.7	—	–1.1	—	—	
Wks 0–52	n/N (%)	145/166 (87.3)	149/164 (90.9)	0.96 (0.89, 1.04)	3.6 (–3.25, 10.49)	36 fewer (100 fewer to 36 more)	29 (NSD)	M$^{\alpha}$
	Total (mg) / pt-d	3.9	3.6	—	0.03	—	—	

Source: 6

L, Low; **M**, Moderate; **Pt-d**, Patient-day; **Q**, GRADE quality of evidence

† Denotes the de facto therapy during the induction period (Weeks 0–26) / maintenance period (Weeks 27–52), respectively.

α Downgraded for indirectness to a clinically important outcome

β Downgraded for imprecision (optimal information size not met)

Cumulative Total Glucocorticoid Use

- The cumulative total (study plus nonstudy supplied) glucocorticoid use per patient over 52 weeks was 1349 mg vs 3655 mg and 3.9 mg/patient-day vs 10.5 mg/patient-day in the avacopan and prednisone groups, respectively.[6] The cumulative glucocorticoid use over 52 weeks in the avacopan group was 37% of that in the prednisone group.

- For the first 26 weeks (induction period), the mean doses were 1073 mg vs 3193 mg or 6.1 mg/patient-day vs 17.9 mg/patient-day in the avacopan and prednisone groups, respectively (cumulative glucocorticoid use over 26 weeks in the avacopan group was 34% of that in the prednisone group).[6]
- Although the protocol did not specify glucocorticoids for the avacopan group, 86.1% of those patients received glucocorticoids in the first half of the study.[6] From Week 27 to 52, patients in both groups received nonstudy-supplied additional glucocorticoids, with the cumulative glucocorticoid use in the avacopan group averaging 60% (276 mg) of that in the prednisone group (462 mg), and 1.6 mg/patient-day vs 2.7 mg/patient-day, respectively.[6]
- In the first half of the study, it was difficult to attribute differences in glucocorticoid use to avacopan efficacy because glucocorticoid use in the prednisone arm was expected to have greater glucocorticoid use during this time period (prednisone with tapering was protocolled for up to Week 20). The clinical relevance of the absolute differences were also uncertain. After the prednisone taper, the mean daily doses were comparable between treatment groups.

Non-study Supplied Glucocorticoid Use

- Additional glucocorticoids were used by 87.3% vs 90.9% of patients in the avacopan and prednisone groups, respectively, over 52 weeks. The percentage of patients that used additional glucocorticoids was higher in the avacopan group in the first half of the study (up to Week 26) and higher in the prednisone group in the second half (after completion of protocolled prednisone tapering at Week 20).[6] The mean cumulative daily additional glucocorticoid use was similar (3.9 mg/patient-day vs 3.6 mg/patient-day in the avacopan and prednisone groups, respectively) over 52 weeks.
- The mean dose of additional glucocorticoids was higher on avacopan than prednisone in the first half of the study (6.1 vs 4.5 mg/patient-day, respectively), whereas it was numerically lower in the second half of the study (1.6 vs 2.7 mg/patient-day, respectively). The differences between treatment groups were small.

Reasons for Additional Glucocorticoid Use

- In the first and second halves of the study, a numerically higher percentage of patients in the prednisone group were given additional glucocorticoids for relapse: 11 patients (6.6%) vs. 29 patients (17.7%) of avacopan vs prednisone groups from Week 0 to 26, and 8 (4.8%) vs 25 (15.2%), respectively, from Week 27 to 52.[6] Relapse in the prednisone group could have been at least partly due to the rapid taper required by the study protocol.
- Additional glucocorticoid use for controlling increased disease activity (i.e., for worsening vasculitis, persistent vasculitis, and maintenance of remission) was similar between treatment groups.

Glucocorticoid Use and Responder Categorization

- The definition of remission required no glucocorticoid use, as described above under Primary Efficacy Measures. However, it is important to note that glucocorticoid use did not necessarily preclude categorization of patients as remission responders. Patients who relapsed after initially achieving remission during induction (up to Week 26) and patients who received glucocorticoids for vasculitis within 4 weeks of assessment at Week 26 or 52 were counted as nonresponders. Outside these parameters, patients could still be counted as responders even if they received glucocorticoids. In some cases counted as responders, multiple courses of high-dose IV glucocorticoids or PO glucocorticoids were used for vasculitis (e.g., vasculitis-related nasal congestion, pulmonary hemorrhage, worsening lung nodules).

Subgroup Analyses

Sustained Remission

- Significant differences in Week-52 sustained remission response were seen in the following subgroups categorized by patient characteristics at baseline (avacopan vs prednisone, respectively); however, the subgroup analyses are inconclusive:
    - Rituximab induction 71.0% vs 56.1% (n = 107 vs 107)
    - MPO positivity 70.2% vs 53.2% (n = 94 vs 94)
    - Relapsed AAV 76.5% vs. 48.0% (n = 51 vs 50)
    - MPA subtype 70.7% vs 51.4% (n = 75 vs 74)
- No significant treatment differences were seen in patients who had cyclophosphamide then azathioprine, PR3-positive ANCA, newly diagnosed AAV, and the GPA subtype of AAV.
- The FDA Office Director considered the Week-52 sustained remission treatment benefit to be a compelling result despite the subgroup analyses suggesting that the result seems to have been driven primarily by rituximab without maintenance IST.[6]

Relapse

- Relapse rates at Week 52 were numerically lower with avacopan than prednisone in both standard IST subgroups, with relapse curves separating after 40 days when prednisone was still administered and rituximab effects still persisted (avacopan vs prednisone, respectively)[7]:
    - Rituximab 8% vs 20%
    - Cyclophosphamide 10% vs 21%

Onset of Effects and Duration of an Adequate Therapeutic Trial

- Estimates of the time to onset of treatment benefit and duration of an adequate therapeutic trial are shown in Table 4. Time course data to estimate onset of effects and duration of therapeutic trials were limited.

Table 4 Onset of Benefit and Adequate Therapeutic Trial

Outcome Measure Used as Basis	Onset of Significant Treatment Benefit (Wks)	Duration of an Adequate Therapeutic Trial (Wks)
Time to remission (BVAS = 0)†	4	28
CFB in eGFR‡	10	52

† Week 4 was the first time point at which the Kaplan-Meier plot curves for probability of BVAS = 0 vs weeks to remission seemed to separate, with a difference in probability of remission of about 0.1. Week 28 was the time point at which the lowest probability of remission was reached.

‡ In patients with baseline renal disease (N = 268). Week 10 was the first visit at which the change in eGFR vs time curves seemed to separate. No statistical analyses were performed. At Week 10, the difference between treatments in change in eGFR was about 1.75 mL/min/1.73 m2. For perspective, the treatment difference at Week 52 was 5.7 mL/min/1.73 m^2 and described as small.[6] Week 52 was the time of peak change in eGFR.

Durability of Response

- Durability of response was supported by the sustained remission outcome measure.

Persistence of Effect

- Follow-up evaluations showed that the percentage of patients with relapse or worsening in BVAS in the 8 weeks after treatment discontinuation (from Week 52 to 60) were numerically lower in the avacopan group.[6]
- In addition, the difference in eGFR was lost after treatment discontinuation.[6]

Study Limitations and Contentious FDA Reviews

Remission Induction and the Use of Noninferiority as the Primary Comparison

- The phase 3 trial was not designed or conducted to directly assess avacopan's role as induction vs maintenance therapy.[6]
- The treatment effect of avacopan was further confounded by including patients who received significant amounts of additional glucocorticoids in the count of responders and by the remission induction effects of the standard IST, which could explain the lack of statistically significant superiority at Week 26.
- There was also a question as to whether the noninferiority results at Week 26 were robust, since ultimately the study design artifactually led to a comparison between avacopan plus lower dose, protocol-allowed additional glucocorticoids and higher dose glucocorticoids (tapered prednisone plus protocol-allowed additional glucocorticoids).
- The additional benefit of glucocorticoids when added to standard IST is unclear. There have also been data suggesting that a lower-dose glucocorticoid regimen may be similar to higher dose regimens in reducing disease activity.[8] Although there might be sufficient data to support a clinically meaningful benefit of avacopan at Week 26, there were inadequate data to determine an appropriate noninferiority margin and many uncertainties (including those listed in the two preceding bullet points above), making it difficult to draw firm conclusions based on the primary noninferiority comparison.[6]
- The prednisone tapering schedule was short. The target was 0 mg by Week 20 and inconsistent with recommendations to taper to a dose of 7.5–10 mg by 3–5 months,[12] and may have led to flares of vasculitis that would have prompted use of additional glucocorticoids. The remission induction period of the study (Week 0–26) did not necessarily reflect a realistic clinical scenario.
- The FDA reviewer concluded that the Week-26 efficacy results did not support the efficacy of avacopan.[6]

Remission Maintenance

- The efficacy of avacopan in the treatment of AAV was limited to a single outcome measure at a single time point (sustained remission at Week 52) and was not confirmed by further evidence.
- The superiority of avacopan at Week 52 was lost when remission was defined using the Investigator Birmingham Vasculitis Activity Score (BVAS) Assessment. The differences between results using the pre-specified remission measure vs the Investigator Assessment was due to attribution of persistent vasculitis.
- Since patients did not receive protocolled prednisone after Week 21, the superiority of avacopan relative to prednisone at Week 52 is uncertain.
- The rituximab regimen without maintenance doses was inconsistent with the 2021 American College of Rheumatology / Vasculitis Foundation (ACR/VF) guideline which conditionally recommendations rituximab maintenance therapy over methotrexate or azathioprine in patients with severe GPA / MPA in remission.[13] The remission maintenance period of the study (Weeks 27–52) did not necessarily reflect a realistic clinical scenario because rituximab maintenance therapy was not provided.

Glucocorticoid Sparing Ability

- The avacopan and prednisone groups could receive additional glucocorticoids. One could not determine that differences in cumulative glucocorticoid use, observed mainly in the first half of the study, were due to beneficial effects of avacopan (as opposed to the study design).[6]
- Although one of the objectives was to assess the glucocorticoid-sparing effects of avacopan, 86% of patients on avacopan received glucocorticoids from Week 0 to 26 at nominally lower mean doses than in the prednisone group during the first 20 weeks of the study.
- Therefore, a glucocorticoid-sparing effect was not established for avacopan since any differences in glucocorticoid use could have been due to study design rather than an effect of avacopan. (A better

study design would have been to compare avacopan with placebo and measure rescue glucocorticoid requirements in both groups.[6])

Glucocorticoid Toxicity

- Another methodological limitation was the use of a novel measure, the Glucocorticoid Toxicity Index (GTI), which was designed and validated to systematically measure patient-level changes in glucocorticoid toxicity and glucocorticoid-sparing ability of therapies.[6,9,10] The FDA deemed that the GTI was inappropriate for its intended purpose.

Subgroup Analyses

- The ADVOCATE trial stratified randomization by certain subgroups but was not powered to compare treatments by subgroups.
- Avacopan was ineffective in Week-52 sustained remission in the subgroup that received cyclophosphamide induction then azathioprine maintenance therapy and effective in the subgroup that received an induction regimen of rituximab. The FDA reviewers noted that these results suggested a possibility that avacopan is effective in sustaining remission in patients not receiving maintenance therapy (i.e., those who could be considered undertreated) but ineffective in patients receiving standard maintenance IST.[6]
- It is unclear whether avacopan adds benefit over standard IST.[5] On the other hand, avacopan efficacy was supported in the rituximab induction subgroup since those patients did not receive maintenance therapy but did receive placebo (i.e., placebo avacopan), resulting in a "de facto" placebo-controlled comparison.[6] Interpretation of these results was difficult because the effect size of avacopan in this subgroup was limited by imprecision.

Role of Avacopan in Therapy

- The FDA clinical and statistical review teams were concerned that there was uncertainty in the evidence of efficacy and about the place in therapy of avacopan in AAV because the subgroup analyses suggested that avacopan may be ineffective in patients receiving standard-of-care maintenance therapy, the evidence of superiority was not robust using different methods of assessing remission, and secondary outcome measures and phase 2 study results did not provide evidence supporting efficacy of avacopan.[6]
- The FDA's clinical and statistical review teams concluded that the evidence did not inform how to use avacopan in clinical practice (induction, maintenance, add-on to glucocorticoids, and/or background treatment).[6]
- However, the FDA Division Director, considering that avacopan could potentially fill unmet needs in the treatment of a rare, life-threatening disorder with limited treatment options, determined that the evidence of efficacy of avacopan met the threshold for substantial evidence of efficacy and that the benefit-risk profile was favorable. Therefore, the Director recommended marketing approval with a revised and limited indication.[6]

Gaps in Clinical Outcomes

- Survival / Mortality
- Hospitalization or readmission
- Functional ability / Disability
- Patient satisfaction

Meta-analyses

- No network meta-analyses that included avacopan were found.
- A Cochrane systematic review / meta-analysis of treatments for renal vasculitis included comparisons of avacopan vs prednisolone as induction therapy from the phase 2 CLEAR RCT.[11] The phase 3 RCT of avacopan was ongoing and not included. Although the CLEAR RCT showed benefit with avacopan as a

glucocorticoid replacement in the eGFR outcome (mean difference, 3.3 [95% CI 0.57, 6.03]), there were no significant differences in the risk of any adverse event, serious infection, or serious adverse events. The authors of the Cochrane review concluded that using avacopan as a glucocorticoid replacement seemed unlikely because of clinicians' familiarity with the use of glucocorticoids and the low price of glucocorticoids. Furthermore, equivalence with glucocorticoids seems to be insufficient justification for complement inhibitors to "feature significantly in treatment protocols in vasculitis."[11] Additional research was needed to determine avacopan's place in therapy.

Safety Considerations

- The overall safety database for avacopan was relatively small (n = 239) and only 155 patients received avacopan for up to 52 weeks.[6] No postmarketing surveillance data was available at the time of the FDA review. Alvacopan is approved in Japan and the EU for GPA and MPA.
- **Boxed Warnings**: None
- **Contraindications**: Serious hypersensitivity to avacopan or product excipients
- **Other Warnings / Precautions**: See Table 5.

Table 5 Summary of Warnings and Precautions

Warning / Precaution	Clinical Trial Events	Pretreatment Evaluation and Tests	Monitoring During Therapy	Other Management
Hepatotoxicity	Transaminase elevations Hepatobiliary events Serious liver function test abnormalities (reversible with drug discontinuation) 4 cases of probable or highly likely drug-induced liver injury due to avacopan	Liver tests: ALT, AST, ALP, TBIL Not recommended in patients with active, untreated and/or uncontrolled chronic liver disease (e.g., chronic active HBV, untreated HCV, uncontrolled autoimmune hepatitis) and cirrhosis. Consider risks vs benefits.	Liver tests every 4 weeks for the first 6 months, then as clinically indicated. Monitor patients closely for hepatic adverse reactions.	Consider withholding treatment if ALT or AST > 3 x ULN. Discontinue treatment if AST or ALT > 5 x ULN or if AST or ALT > 3 x ULN with TBIL > 2 x ULN or until avacopan-induced liver injury is ruled out.
Hypersensitivity Reactions	Angioedema Hospitalization	Assess for history of avacopan-induced angioedema. Avacopan must not be re-administered to patients with a history of avacopan-induced hypersensitivity.	—	Discontinue avacopan and institute treatment for a hypersensitivity reaction if it occurs. Educate patients about hypersensitivity reactions.
HBV Reactivation	Life-threatening HBV reactivation (1 patient [0.6%])	Screen for HBV (HBsAg, [total] anti-HBc) If patient is HbsAg-positive or HbsAg-negative but anti-HBc-positive, consult with expert in HBV management.	For patients with evidence of current or prior HBV infection, monitor for clinical and laboratory signs of hepatitis during therapy [at frequency recommended by HBV expert] and for 6 months after avacopan therapy.	Monitor for evidence of HBV reactivation during therapy and for 6 months after avacopan therapy.

Warning / Precaution	Clinical Trial Events	Pretreatment Evaluation and Tests	Monitoring During Therapy	Other Management
Serious Infections	Fatalities Pneumonia and urinary tract infections were most common	Avoid avacopan therapy in patients with active, serious infection including localized infections. Consider risks vs benefits in patients with chronic or recurrent infection, exposure to TB, history of serious or opportunistic infection, residence or travel in areas of endemic TB or mycoses, or an underlying condition that predisposes to infection.	Closely monitor for evidence of infection during and after avacopan therapy.	Interrupt avacopan therapy if serious or opportunistic infection develops. If a patient develops new infection during avacopan therapy and does not respond to antimicrobial therapy, interrupt avacopan therapy. Avacopan may be resumed once the infection is controlled.

Sources: 1,2,6
TBIL, Total bilirubin; ULN, Upper limit of normal

- **Deaths and Serious Adverse Events (SAEs)**
  - Deaths within 52 weeks: 2 (1.2%) on avacopan vs 4 (2.4%) on prednisone.[1]
  - Most frequent SAEs more common on avacopan than prednisone therapy: Pneumonia, GPA, acute kidney injury, urinary tract infection.[1]
  - Over the 52-week treatment period in the phase 3 RCT, serious infections occurred in 13.3% and 15.2% of patients (difference, –2.0% [95% CI –9.5, 5.6]; 15.7 vs 14.1 per 100 patient-years[6]) at median times of 126 days vs 97 days in the avacopan and prednisone groups, respectively.[2] Serious infections were not reported by induction or maintenance treatment period.
  - Serious opportunistic infections were reported in 3.6% and 6.7% of patients, respectively.
  - Serious herpes zoster infection occurred in no patients and 2 patients, respectively.[2]
- **Withdrawals Due to Adverse Events**: Most frequently due to **hepatic function abnormality** (1.8%).[1] Overall, 7 patients (4.2%) vs 2 patients (1.2%) on avacopan vs prednisone, respectively, discontinued therapy because of hepatic-related adverse events, including hepatobiliary events and liver enzyme abnormalities.[1]
- **Common Adverse Events (≥ 5% of patients and higher in the avacopan than prednisone group)**: Nausea, headache, hypertension, diarrhea, vomiting, rash, fatigue, upper abdominal pain, dizziness, blood creatinine increased, paresthesia.
- **Adverse Events of Interest**
  - **Hepatotoxicity**: 22 patients (13.3%) in the avacopan group and 19 patients (11.6%) in the prednisone group experienced hepatic-related adverse events, including hepatobiliary adverse events and liver enzyme abnormalities.[1] Treatment was interrupted or discontinued because of hepatic events in 9 patients (5.4%) and 6 patients (3.7%) in the avacopan and prednisone groups, respectively.[1] Hepatic events were serious in 9 patients (5.4%) and 6 patients (3.7%), respectively.[1]
  - **Angioedema**: 2 patients (1.2%) in the avacopan group.[1] One patient required hospitalization.
  - **Elevated Creatine Phosphokinase (CPK)**: 6 patients (3.6%) vs 1 patient (0.6%) in the avacopan vs prednisone groups, respectively.[1] One of the avacopan-treated patients discontinued therapy because of increased CPK.

Drug Interactions

- Avoid coadministration with strong and moderate CYP3A4 INDUCers.

- Consider dose reduction of concomitant CYP3A4 substrates with narrow therapeutic margins. Avacopan inhibits CYP3A4.

Other Considerations

- Methotrexate or leflunomide co-therapy was not allowed in the ADVOCATE trial.
- Methotrexate was not used as rescue therapy in the avacopan treatment arm in phase 2 RCTs.

Other Therapeutic Options

- The pharmacotherapy of AAV involves induction therapy for typically 3 to 6 months to achieve remission and maintenance therapy to prevent relapse. The optimal duration of maintenance therapy is unknown, although at least 24 months has been recommended.[12]
- Selection of therapy is based on disease severity and stage of treatment. Disease severity may be severe (e.g., organ- or life-threatening disease) or nonsevere. Recommendations from the 2021 ACR / VF guideline for management of AAV is summarized in Table 6. All therapies are conditionally recommended; none were strongly recommended.

Table 6 Selection of therapy for GPA and MPA

	ACTIVE SEVERE GPA / MPA		ACTIVE NONSEVERE GPA	
Stage of Therapy	**Disease Status**	**Therapy**	**Disease Status**	**Therapy**
Remission Induction	**Untreated severe active GPA / MPA**	RTX over CYC Add-on IV pulse GCs for up to 3–5 days or high-dose oral GCs GC Taper: Reduced dose GC over standard dose GC	**Untreated nonsevere active GPA**	GC + MTX over GC + RTX GC + CYC GC + AZP GC + MMF GC alone
	Active GPA / MPA despite first induction therapy	Switch induction therapy (CYC or RTX) over combine induction therapies	**Active GPA despite first induction therapy**	Consider switching to a different induction therapy
Remission Maintenance	**Severe GPA / MPA in remission**	In order of preference: RTX MTX or AZP MMF or LEF	**Nonsevere GPA in remission induced on MTX, AZP, or MMF**	Continue same therapy
			Nonsevere GPA in remission induced on RTX or CYC	Consider RTX, MTX, AZP, or LEF
Remission Re-induction for Relapse	**Severe flare on RTX**	CYC over RTX	**Nonsevere GPA flare on maintenance therapy**	Consider switching to a different induction therapy
	Severe flare on non-RTX therapy	RTX		

Source: 13
AZP, Azathioprine; **CYC**, Cyclophosphamide; **GC**, Glucocorticoid; **LEF**, Leflunomide; **MMF**, Mycophenolate mofetil; **MTX**, Methotrexate

- Glucocorticoids are potential alternative treatments to avacopan for GPA / MPA (Table 7).

Table 7 Adjunctive Systemic Immunosuppressive Treatment Alternatives for GPA and MPA

Drug Route	Formulary	FDA-approved AAV Indication	Place in Therapy	Safety Considerations	Other Considerations
Avacopan PO	TBD	Adjunctive treatment for patients with active severe AAV (GPA, MPA) with standard IST including GCs. Does not eliminate GC use.	Unclear. Potentially as add-on therapy to limit use of GCs, in combination with reduced-dose GC.	Hepatotoxicity. Not recommended in patients with cirrhosis. Hypersensitivity / Angioedema HBV reactivation Avoid in patients with active, serious infection. Avoid with moderate and strong CYP3A4 inducers. Reduce dose with strong CYP3A4 inhibitors.	Novel mechanism. Contentious evidence of efficacy. FDA indication limits its use to adjunctive therapy for active severe GPA or MPA. Not studied in patients refractory to standard ISTs. Lacks approval for GC-sparing effects.
Glucocorticoids (GCs) PO, IV Methylprednisolone Prednisone Others	Yes	Off-label	Add-on therapy for remission induction. High-dose pulse GC is generally used for organ- or life-threatening GPA / MPA.	Reduced-dose regimen was noninferior to standard-dose regimen in all-cause mortality or ESRD (PEXIVAS RCT[8]).	Benefit of GCs added to RTX or CYC is unclear. Desired target is to taper dose to 7.5–10 mg/d prednisone equivalent by 3 months but may take 5 months to achieve.

Sources: 12, 13
AAV, ANCA-associated vasculitis; **CYC**, Cyclophosphamide; **ESRD**, End-stage renal disease; **GC**, Glucocorticoid; **IST**, Immunosuppressive therapy; **RTX**, Rituximab

Projected Place in Therapy

- **Epidemiology and Prevalence of Antineutrophil Cytoplasmic Antibody (ANCA)-associated Vasculitis (AAV)**. AAV is a group of rare, chronic, relapsing, multisystem, autoimmune-mediated, necrotizing vasculitides that cause inflammation and necrosis predominantly of small arteries, without substantial deposition of immune complexes.[14] Non–organ-threatening disease includes rhinosinusitis, arthritis, and/or pulmonary nodules. In organ- or life-threatening disease, the lungs, kidneys, nervous system, and other organs are affected with > 75% of patients developing renal disease, usually rapidly progressive glomerulonephritis.[15] If untreated, AAV results in death, frequently due to respiratory failure and renal failure, with a mean survival of < 1 year. AAV is associated with ANCAs against proteinase 3 (PR3) or myeloperoxidase (MPO), although ANCA-negative AAV is possible. The incidence of AAV has been estimated to be about 20 per million people per year in Europe and North America. The prevalence of AAV is 200 to 400 cases per million people. AAV is more common in males, people aged 60 to 70 years, and in White and Asian people.[6,15] The three main types of AAV are granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA; Churg-Strauss). Although there can be much overlap in manifestations between GPA and MPA, GPA often presents with granulomatous inflammation of the upper and lower respiratory tract and necrotizing,

pauci-immune glomerulonephritis, whereas MPA commonly manifests with necrotizing glomerulonephritis and/or pulmonary capillaritis.

- **Place in Therapy Based on Medical Society Guidelines**. Although the American College of Rheumatology / Vasculitis Foundation published a guideline for the management of AAV in 2021,[13] no current medical society guidelines for AAV include avacopan.
- **Potential Place in Therapy Based on the Evidence**. The ADVOCATE active-controlled trial provided uncertain evidence about the place in therapy of avacopan in the treatment of GPA / MPA AAV. Based on low-quality evidence, the contentious FDA reviews, and the approved limited indication, avacopan plus additional glucocorticoids as compared with prednisone taper plus additional glucocorticoids (either regimen given in addition to single-dose rituximab without maintenance doses or cyclophosphamide induction followed by azathioprine or mycophenolate maintenance), may potentially (with some uncertainty) provide noninferior remission induction rates in patients with newly diagnosed or relapsing, severe active ANCA-positive GPA or MPA. In the presence of either possible residual effects of rituximab induction or azathioprine maintenance therapy, avacopan plus additional glucocorticoids was superior to de facto placebo plus additional glucocorticoids in remission maintenance rates (small to negligible effects). Avacopan reduced but did not eliminate glucocorticoid use or glucocorticoid toxicity. According to an FDA multidisciplinary review, the evidence did not clearly support the use of avacopan without glucocorticoids or as a replacement for glucocorticoids during induction therapy.[6] The effects of avacopan on eGFR are promising but efficacy for improving renal vasculitis or renal function require further studies. Improvements in disease relapse, vasculitis damage, and health-related quality of life were also promising but inconclusive. The efficacy of avacopan plus additional glucocorticoids in sustaining remission in the presence of rituximab maintenance therapy, which is highly effective in reducing major relapse,[16] is unknown. Avacopan has been associated with serious infections and has not been shown to reduce the risk of glucocorticoid-related serious infections. The durability of beneficial effects and longer-term (> 1 year) safety of avacopan, particularly hepatotoxicity, serious infections, and hypersensitivity / angioedema, need to be evaluated in further trials and postmarketing surveillance. Cost-benefit analyses are needed.
- **Potential Place in Therapy in VHA**. Because AAV is a rare disease, utilization of avacopan is expected to be low. Whether or not avacopan can reduce glucocorticoid-associated severe, patient-important adverse events remains uncertain. The resulting opportunity cost could be substantial as cost-effectiveness has not been established. Avacopan may be used in VHA under the following parameters:
    - Avacopan is prescribed by rheumatologists, nephrologists, or other locally designated clinicians with expertise in the management of AAV.
    - Avacopan is used with immunosuppressive induction therapy (rituximab or cyclophosphamide) in patients with severe (organ- or life-threatening), active, newly diagnosed or relapsing ANCA-positive GPA or MPA who need rapid reduction of glucocorticoid therapy due to severe, otherwise unmanageable glucocorticoid-induced complications or toxicity (e.g., glucocorticoid-related psychosis, myopathy, or herpetic keratitis).
    - Avacopan is not added to existing therapy with the intent of reducing risk of relapse in patients in remission. Avacopan is not intended for improving remission induction or maintenance in the presence of current guideline recommended induction or maintenance therapy. The efficacy of avacopan in this regard is uncertain.
    - If avacopan is continued during remission of severe disease, it should be used in the presence of standard maintenance therapy (rituximab, azathioprine, or mycophenolate) for a duration based on clinician discretion (e.g., up to 1 to 2 years). Discontinuing avacopan when maintenance therapy is initiated (e.g., after 6 months) may be considered; however, the safety and efficacy of this practice were not evaluated in clinical trials. Avacopan is unlikely to provide additional benefit over current guideline recommended maintenance therapy, and the safety and efficacy

of continuing avacopan beyond 1 year are uncertain. Since persistent organ (e.g., kidney) dysfunction and nonspecific symptoms and biomarker abnormalities are common in GPA / MPA, determining when to discontinue avacopan for lack of efficacy is problematic. It is difficult to predict whether the patient's condition would have been worse without avacopan.

- Avacopan is discontinued when current guideline recommended maintenance therapy is withdrawn (e.g., up to 2 years) since the efficacy of avacopan monotherapy is unknown.
- Avacopan should not be used in patients
    (1) with active, untreated and/or uncontrolled chronic liver disease and cirrhosis;
    (2) with active, serious, systemic or localized infection, including undrained abscess (however, avacopan may be started / restarted once the infection is controlled);
    (3) with untreated latent or active tuberculosis infection;
    (4) who are hepatitis B surface antigen (HBsAg)-positive and not on antiviral prophylaxis (avacopan may be initiated after starting antiviral prophylaxis);
    (5) who are HBsAg-negative but antibody-to-hepatitis-B-core-antigen (anti-HBc)-positive (avacopan may be initiated after starting antiviral prophylaxis or a locally designated hepatologist or infectious diseases expert approved proceeding without antiviral prophylaxis);
    (6) on hemodialysis; or
    (7) on concomitant strong and moderate CYP3A4 INDUCers.
- Avacopan is not recommended for use with methotrexate. Although co-use of methotrexate is neither a contraindication nor therapy to be avoided according to avacopan prescribing information, it was not evaluated for safety or efficacy in clinical trials and may be inadvisable because of potential additive risk of hepatotoxicity.

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