RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Efficacy and safety of avacopan for treatment of patients with ANCA-associated vasculitis receiving cyclophosphamide

Duvuru Geetha,[1] Thomas Neumann,[2] Alexandre Karras,[3,4] Maria C. Cid,[5] Peter A. Merkel,[6] Sarah Bray,[7] Alana M. Bozeman ,[8] David R. W. Jayne ,[9] Members of the ADVOCATE Study Group

To cite: Geetha D, Neumann T, Karras A, *et al*. Efficacy and safety of avacopan for treatment of patients with ANCA-associated vasculitis receiving cyclophosphamide. *RMD Open* 2025;**11**:e005743. doi:10.1136/rmdopen-2025-005743

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/rmdopen-2025-005743).

Received 31 March 2025
Accepted 30 August 2025

For numbered affiliations see end of article.

Correspondence to
Dr Duvuru Geetha;
dgeetha1@jhmi.edu

ABSTRACT

Background This study evaluated the efficacy and safety of avacopan versus a prednisone taper in the subgroup of patients with antineutrophil cytoplasmic antibody-associated vasculitis (granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)) receiving cyclophosphamide (CYC) followed by azathioprine (or mycophenolate mofetil) in the ADVOCATE trial.

Methods Key efficacy outcomes were remission at week 26 and sustained remission at week 52. Additional outcomes included glucocorticoid toxicity, estimated glomerular filtration rate (eGFR), urinary albumin-to-creatinine ratio (UACR) and safety.

Results Of 330 patients receiving study medication, 116 (35.2%) received CYC (avacopan group, n=59; prednisone taper group, n=57). Remission at week 26 and sustained remission at week 52 were achieved by 37/59 (62.7%) and 33/59 (55.9%) patients in the avacopan group and 34/57 (59.6%) and 30/57 (52.6%) in the prednisone taper group, respectively. Over 52 weeks, relapses were observed in 13.0% in the avacopan group and 22.6% in the prednisone taper group. Improvement in eGFR, speed of albuminuria reduction and differences in glucocorticoid toxicity favoured the avacopan group. Serious adverse events occurred in 55.9% and 56.1% of patients in the avacopan and prednisone taper groups, respectively.

Conclusions This subgroup analysis of patients who received CYC shows similar rates of remission in the avacopan and prednisone taper groups. Compared with the prednisone taper regimen, the avacopan regimen was associated with a numerically lower relapse rate, greater improvement in eGFR, faster reduction in UACR, lower glucocorticoid-related toxicity and similar overall safety. These results support the use of avacopan in combination with CYC to treat GPA or MPA.

Trial registration number NCT02994927.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In the phase 3 randomised ADVOCATE trial in patients with antineutrophil cytoplasmic antibody-associated vasculitis (granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)) who received therapy to induce remission with rituximab (RTX) or cyclophosphamide (CYC), avacopan was non-inferior to a prednisone taper in achieving remission at week 26 and superior in sustaining remission at week 52. A previous subgroup analysis demonstrated the safety and efficacy of avacopan versus a prednisone taper in patients with GPA or MPA who received RTX to induce remission.

WHAT THIS STUDY ADDS

⇒ These post hoc analyses demonstrated the efficacy and safety of avacopan in the treatment of patients with GPA or MPA receiving background induction therapy with CYC.

⇒ Among patients who received CYC induction, those in the avacopan group had similar efficacy with respect to rates of remission at week 26 and sustained remission at week 52 compared with those in the prednisone taper group.

⇒ Compared with prednisone taper, receipt of avacopan was associated with improved kidney function, less glucocorticoid-related toxicity and fewer relapses. Overall safety outcomes were similar in both groups.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Results from this study support the use of avacopan in combination with CYC for the treatment of GPA or MPA.

INTRODUCTION

Effective management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) involves controlling the disease while reducing the side effects of treatment. For over five decades, cyclophosphamide (CYC), an alkylating agent, has been used in combination with glucocorticoids (GCs) to induce remission in patients with AAV.[1] CYC remains relevant as illustrated by its ongoing

inclusion in clinical guidelines as a treatment option for AAV.[2–6] Studies have found comparable effectiveness of rituximab (RTX) and CYC[7 8] in inducing remission in AAV, and both treatments have historically been combined with similar GC regimens. Nonetheless, some people with AAV continue to experience poor outcomes including death, relapse, end-stage kidney disease and GC toxicity.[9–13]

Avacopan is an orally administered small-molecule complement 5a (C5a) receptor 1 antagonist that selectively blocks the effects of C5a through this receptor, including blocking neutrophil chemoattraction and activation.[14] In the phase 3 randomised ADVOCATE trial in patients with AAV (granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)) who received RTX or CYC to induce remission, the addition of avacopan was non-inferior to a prednisone taper in achieving remission at week 26 and superior in sustaining remission at week 52.[14] A previous subgroup analysis evaluated the efficacy and safety of avacopan versus a prednisone taper in patients with GPA or MPA who received induction therapy with RTX.[15] Because CYC continues to be used in practice, especially when response to RTX is inadequate or access to RTX is limited, and as avacopan availability broadens, it is important to understand the efficacy and safety of concurrent use of CYC and avacopan. This subgroup analysis aims to investigate the efficacy and safety of avacopan in patients who received background induction therapy with CYC followed by azathioprine (AZA) or mycophenolate mofetil (MMF).

MATERIALS AND METHODS

Study design

This analysis of patients treated with CYC was a prespecified subgroup analysis of ADVOCATE—a multicentre, randomised, double-blind, double-dummy, active-controlled trial (NCT02994927).[14] Details of the ADVOCATE trial have been previously published.[14] Briefly, avacopan (30 mg twice a day) or a matching placebo was administered for 52 weeks, randomly assigned (1:1) using an interactive web-response system and a minimisation algorithm to maintain balance between the treatment groups. Prednisone or matching placebo was administered on a tapering schedule over 20 weeks (60 mg per day tapered to discontinuation by week 21). Selection of RTX or CYC induction immunosuppressive therapy was at the discretion of the investigator, and randomisation was performed centrally and stratified according to disease status (newly diagnosed or relapsing), ANCA type (anti-proteinase 3 (PR3) or anti-myeloperoxidase (MPO) positive), and immunosuppressive therapy chosen (RTX or CYC). CYC was administered intravenously at a dose of 15 mg/kg of body weight up to 1.2 g on day 1 and at weeks 2, 4, 7, 10 and 13 or orally at a dose of 2 mg/kg up to 200 mg per day for 14 weeks. Dosing was adjusted based on estimated glomerular filtration rate (eGFR), age, white blood cell (WBC) count at the study visit and WBC nadir between intravenous pulses. From week 15, CYC was followed by oral AZA at a target dose of 2 mg/kg per day or MMF at a target dose of 2 g/day if AZA was not tolerated. GC treatment during the screening period was tapered to ≤20 mg of prednisone-equivalent before the patient enrolled in the trial, and this open-label GC treatment was further tapered to discontinuation by the end of week 4 of the trial. Patients in either treatment group who had worsening disease that involved a major item in the Birmingham Vasculitis Activity Score (BVAS)[16] could be treated with rescue therapy consisting of intravenous GCs (typically 0.5–1 g/day of methylprednisolone for 3 days), oral GCs or both, tapered according to the patient's condition. BVAS V.3 was used, with major BVAS items derived from the BVAS for Wegener's granulomatosis version.[16 17] The study protocol and any changes made are available online as part of online supplemental material of the original ADVOCATE report.[14]

Patients

Patients with GPA or MPA were enrolled at 143 centres across 20 countries. Detailed inclusion and exclusion criteria for each study were previously reported.[14] Briefly, eligible patients had newly diagnosed or relapsing GPA or MPA, according to the Chapel Hill Consensus Conference definitions;[18] a current or history of a positive test result for anti-PR3 or anti-MPO; an eGFR of at least 15 mL/min/1.73 m^2 of body surface area; and at least one major or three minor items or at least the two renal items of haematuria and proteinuria on the BVAS V.3.[16]

Efficacy outcomes

The key efficacy outcomes were remission at week 26, defined as a BVAS of 0 and no receipt of GCs for GPA or MPA within 4 weeks before the week 26 visit, and sustained remission, defined as BVAS of 0 at weeks 26 and 52 without any use of GCs for GPA or MPA during the 4-week period preceding and including the weeks 26 and 52 visits and no relapse between weeks 26 and 52. Relapse was defined as a return of active vasculitis after previous achievement of a BVAS of 0 at any time that involved one or two minor BVAS items for at least two consecutive study visits, at least one major BVAS item, or at least three minor BVAS items. Exploratory analyses summarised the proportion of patients experiencing a relapse under two conditions: (1) the first time after achieving remission at week 26 and (2) the first time after achieving a BVAS of 0 at any time.

Additional outcomes in exploratory analyses included GC use (presented as mg prednisone-equivalent) and the Glucocorticoid Toxicity Index (GTI).[19] Lower scores indicate lesser severity of toxic effects for both the GTI Cumulative Worsening Score (GTI-CWS) and the GTI Aggregate Improvement Score (GTI-AIS), the two components of the GTI. In patients with kidney involvement at baseline, based on investigator-assessed BVAS, changes in eGFR and urinary albumin-to-creatinine ratio (UACR) (in patients with albuminuria (UACR ≥10 mg/g creatinine))

Table 1 Baseline demographics and clinical characteristics of study participants who received CYC in the ADVOCATE trial

Characteristic	Prednisone taper+CYC (N=57)	Avacopan+CYC (N=59)	Total (N=116)
Age, years, mean (SD)	61.7 (11.0)	63.8 (12.6)	62.7 (11.9)
Sex, n (%)			
Male	36 (63.2)	37 (62.7)	73 (62.9)
Female	21 (36.8)	22 (37.3)	43 (37.1)
Race, n (%)			
White	48 (84.2)	49 (83.1)	97 (83.6)
Asian	7 (12.3)	6 (10.2)	13 (11.2)
Black or African American	0 (0)	1 (1.7)	1 (0.9)
Other	2 (3.5)	3 (5.1)	5 (4.3)
Body mass index, kg/m^2, mean (SD)	27.1 (5.5)	27.0 (5.9)	27.1 (5.7)
Vasculitis disease status, n (%)			
Newly diagnosed	52 (91.2)	52 (88.1)	104 (89.7)
Relapsed	5 (8.8)	7 (11.9)	12 (10.3)
ANCA type, n (%)			
Anti-PR3	21 (36.8)	22 (37.3)	43 (37.1)
Anti-MPO	36 (63.2)	37 (62.7)	73 (62.9)
Type of vasculitis, n (%)			
Granulomatosis with polyangiitis	26 (45.6)	26 (44.1)	52 (44.8)
Microscopic polyangiitis	31 (54.4)	33 (55.9)	64 (55.2)
Duration of ANCA-associated vasculitis, months, median (range)	0.2 (0–69.5)	0.2 (0–65.3)	0.2 (0–69.5)
BVAS, mean (SD)	17.2 (4.7)	17.9 (5.9)	17.6 (5.3)
VDI score, mean (SD)	0.2 (0.7)	0.3 (1.1)	0.2 (0.9)
Kidney involvement at baseline, n (%)	52 (91.2)	53 (89.8)	105 (90.5)
eGFR, mL/min/1.73 m^2, mean (SD)* (number of patients)	43.7 (28.8) (52)	34.5 (20.3) (50)	ND
eGFR <30 mL/min/1.73 m^2, mean (SD)* (number of patients)	22.3 (4.6) (24)	21.2 (4.7) (26)	ND
UACR, mg/g, geometric mean†	307.6	608.4	ND
UACR ≥10 mg/g creatinine, n (%)	51 (89.5)	49 (83.1)	100 (86.2)
GC use during screening period, n (%)			
Any	49 (86.0)	42 (71.2)	91 (78.4)
Oral	37 (64.9)	30 (50.8)	67 (57.8)
Intravenous‡	36 (63.2)	23 (39.0)	59 (50.9)
Study supplied CYC, n (%)			
Oral	6 (10.5)	8 (13.6)	14 (12.1)
Intravenous	51 (89.5)	51 (86.4)	102 (87.9)

*Baseline eGFR in patients with kidney involvement at baseline on the basis of investigator-assessed BVAS.
†Baseline UACR in patients with albuminuria (≥10 mg/g creatinine).
‡Intravenous GCs typically consisted of 0.5–1 g/day of methylprednisolone for 3 days.
ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; GC, glucocorticoid; MPO, myeloperoxidase; ND, not determined; PR3, proteinase-3; UACR, urinary albumin-to-creatinine ratio; VDI, Vasculitis Damage Index.

were assessed. Change in eGFR among patients with a baseline eGFR less than 30 mL/min/1.73 m² was also analysed. eGFR (in mL/min/1.73 m²) was calculated using the serum creatinine-based formula (Modification of Diet in Renal Disease) for adults,[20] the Japanese equation for Japanese adults[21] and the modified Schwartz equation for adolescents.[22] Change from baseline in health-related quality of life (HRQoL) was assessed using

Table 2 Rates of remission, sustained remission and relapse by treatment group among study participants who received CYC in the ADVOCATE trial

Outcome	Prednisone taper+CYC (N=57)	Avacopan+CYC (N=59)
Remission* at week 26, n (%)	34 (59.6)	37 (62.7)
Difference in percentages (95% CI)	3.1 (–14.7 to 20.8)	
Sustained remission† at week 52, n (%)	30 (52.6)	33 (55.9)
Difference in percentages (95% CI)	3.3 (–14.8 to 21.4)	
Relapse‡ rate after remission at week 26, n/N1 (%)	3/34 (8.8)	3/37 (8.1)
Difference in percentages (95% CI)	–0.7 (–17.5 to –17.3)	
Relapse‡ rate after a BVAS of 0 at any time, n/N1 (%)	12/53 (22.6)	7/54 (13.0)
HR (95% CI)	0.53 (0.21 to 1.35)	

N1=number of patients with observed data.
*Remission was defined as a BVAS of 0 and no receipt of glucocorticoids for ANCA-associated vasculitis within 4 weeks before the week 26 visit.
†Sustained remission defined as a BVAS of 0 at week 26 and week 52 without any use of glucocorticoids for ANCA-associated vasculitis during the 4-week periods preceding and including the week 26 and week 52 visits and no relapse between week 26 and week 52.
‡Relapse was defined as a return of vasculitis activity on the basis of one or two minor BVAS items for at least two consecutive study visits, at least one major BVAS item, or at least three minor BVAS items.
ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; CYC, cyclophosphamide.

the 36-Item Short Form Health Survey Questionnaire (SF-36) V.2[23] and EuroQoL Group 5-Dimensions 5-Level Questionnaire (EQ-5D-5L).[24]

Safety outcomes

Safety outcomes included incidence of adverse events (AEs) and serious AEs (SAEs). Data were collected and coded using the Medical Dictionary for Regulatory Activities V.19.1[25] and graded according to the Common Terminology Criteria for Adverse Events V.5.0.[26]

Statistical analysis

The efficacy and safety analysis sets comprised the intention-to-treat population, which included all randomised patients who received at least one dose of the blinded study drug. The summary statistics for the outcome measures in this subgroup analysis were prespecified. No statistical inference or hypothesis testing was conducted.

Data were summarised descriptively by the treatment group. Means, medians, ranges, SDs and SEMs were calculated for continuous variables. Frequency counts and percentages were presented for categorical variables.

The proportion of patients achieving disease remission at week 26 and sustained disease remission at week 52 and two-sided 95% CIs for the difference in proportions (avacopan minus prednisone taper) were calculated using the Wald method. The Cox proportional hazard model was used to estimate the HR of time to relapse at any time between those receiving avacopan and those receiving prednisone taper. Missing data were imputed as not achieving remission (week 26) or sustained remission (week 52).

For changes from baseline, least squares (LS) means and 95% CIs or SEMs were reported and estimated from mixed-effects models for repeated measures with treatment group, visit and treatment-by-visit interaction as factors and baseline as a covariate. These analyses were exploratory in nature. Patients were considered as repeated measure units over visits. Logarithmic transformations were applied to the UACR data before fitting the model, and 95% CIs were transformed back to the original scale. Percent changes from baseline in UACR were calculated based on ratios of geometric means of visit over baseline. No imputation was performed for missing data. All statistical analyses were performed using Statistical Analysis System (SAS) software (V.9.4 of SAS for Windows, SAS Institute).

Site investigators collected data, and ChemoCentryx (a wholly owned subsidiary of Amgen) sponsored the trial and provided trial medication. Medpace conducted the trial and data analysis with guidance from ChemoCentryx. Amgen conducted additional data analysis.

RESULTS

Patients

A total of 331 patients were randomised but 1 patient did not receive study medication. Of the 330 patients who received study medication, 116 (35.2%) received CYC and comprised the subgroup analysis set (avacopan group, n=59; prednisone taper group, n=57). A total of 14 patients received oral CYC and 102 received intravenous CYC. Of the 14 patients receiving oral CYC, six stopped before completing week 14 (avacopan group, n=5 (stopping day range: 47–92); prednisone taper group, n=1 (CYC use not recorded)). Of the remaining 102 patients receiving intravenous CYC, 26 (avacopan group, n=12; prednisone taper group, n=14) received fewer than six doses from day 1 to week 13.

Most demographic and baseline clinical characteristics of the CYC subgroup were similar between the two

Table 3 Glucocorticoid use and GTI among patients by treatment group

Outcome	Prednisone taper+CYC (N=57)	Avacopan+CYC (N=59)
Glucocorticoid use		
Screening (weeks −2 to 0)		
n (%)	49 (86.0)	42 (71.2)
Dose (mg prednisone-equivalent)*		
Mean	1270	988
Median (range)	1038 (0–4185)	500 (0–4010)
Weeks 0 to 26		
n (%)	57 (100.0)	40 (67.8)
Dose (mg prednisone-equivalent)*		
Mean	3550	1296
Median (range)	2810 (760–9945)	280 (0–11 705)
Weeks 26 to 52		
n/N1 (%)	22 (41.5)	16 (30.2)
Dose (mg prednisone-equivalent)*		
Mean	642	310
Median (range)	0 (0–4375)	0 (0–2980)
Weeks 0 to 52		
n (%)	57 (100.0)	42 (71.2)
Dose (mg prednisone-equivalent)*		
Mean	4147	1575
Median (range)	2920 (760–11 665)	285 (0–12 725)
GTI		
GTI-CWS†		
Week 13	40.7 (29.2, 52.2)	28.0 (16.7, 39.3)
Difference (95% CI)	−12.7 (−28.8 to 3.4)	
Week 26	65.7 (53.9, 77.4)	45.3 (33.7, 56.8)
Difference (95% CI)	−20.4 (−36.9 to −3.9)	
GTI-AIS†		
Week 13	27.0 (15.4, 38.7)	9.6 (−1.9, 21.1)
Difference (95% CI)	−17.4 (−33.8 to −1.1)	
Week 26	33.1 (21.2, 45.0)	11.6 (−0.1, 23.4)
Difference (95% CI)	−21.5 (−38.2 to −4.8)	

N1=number of patients with observed data.
*All doses were converted to prednisone-equivalent (mg) and are calculated as total dose during a specified period. The prednisone-equivalent dose includes both intravenous and oral use of glucocorticoids. The n (%) data are the number of patients who used any glucocorticoids during the period, and mean and median (range) data are for all patients in the period.
†Data represent LS mean (95% CI). The GTI-CWS ranges from 0 to 410, with higher scores indicating greater severity of toxic effects. The GTI-AIS ranges from −317 to 410, with higher scores indicating greater severity of toxic effects.
AIS, Aggregate Improvement Score; CWS, Cumulative Worsening Score; CYC, cyclophosphamide; GTI, Glucocorticoid Toxicity Index; LS, least squares.

treatment groups (table 1) and did not differ appreciably from those of the entire ADVOCATE study population, except that the proportion of newly diagnosed patients was higher in this subgroup (89.7%) than in the whole study population (69.4%).[14] Mean (SD) age was 62.7 (11.9) years; 62.9% of patients were male, and 83.6% were white. More patients were positive for anti-MPO (avacopan group, 62.7%; prednisone taper group, 63.2%) than for anti-PR3. Most patients had kidney involvement (90.5%) and a UACR ≥10 mg/g (93.1%). Mean (SD) baseline eGFR for patients with kidney involvement was 34.5 (20.3) mL/min/1.73 m^2 in the avacopan group and 43.7 (28.8) mL/min/1.73 m^2 in the prednisone taper group. Baseline geometric mean UACR was higher in the avacopan group than in the prednisone taper group (608.4 vs 307.6 mg/g). GC use during the screening

Table 4 Use of non-protocol non-glucocorticoid immunosuppressive medications

	Prednisone taper+CYC (N=57)	Avacopan+CYC (N=59)
Combined use of all non-protocol immunosuppressive medications*, n (%)		
Week 0 to week 52	14 (24.6)	10 (16.9)
Week 0 to week 26	11 (19.3)	7 (11.9)
Week 26 to week 52	7 (12.3)	3 (5.1)
Rituximab, n (%)		
Week 0 to week 26	10 (17.5)	4 (6.8)
Week 26 to week 52	6 (10.5)	2 (3.4)
Week 0 to week 52	13 (22.8)	6 (10.2)
CYC†, n (%)		
Week 15 to week 26	2 (3.5)	2 (3.4)
Week 26 to week 52	1 (1.8)	1 (1.7)
Week 15 to week 52	2 (3.5)	3 (5.1)
Azathioprine†, n (%)		
Week 0 to week 15	0 (0.0)	1 (1.7)

*Non-protocol immunosuppressive medications could have included abatacept, alemtuzumab, azathioprine administered prior to week 15†; belimumab, CYC administered after week 15†; cyclosporine, leflunomide, methotrexate, methotrexate sodium, MMF and/or mycophenolate sodium prior to week 15†; rituximab, tacrolimus or other medications.
†Receiving CYC after week 15, azathioprine prior to week 15 or MMF and/or mycophenolate sodium prior to week 15 was considered non-protocol administration.
CYC, cyclophosphamide; MMF, mycophenolate mofetil.

period was lower in the avacopan than in the prednisone taper group (71.2% vs 86.0%).

Efficacy

Remission

Remission at week 26 was observed in 37/59 patients (62.7%) in the avacopan group and 34/57 patients (59.6%) in the prednisone taper group (difference, 3.1%; 95% CI −14.7 to 20.8) (table 2). Sustained remission at week 52 was observed in 33/59 patients (55.9%) in the avacopan group and 30/57 patients (52.6%) in the prednisone taper group (difference, 3.3%; 95% CI −14.8 to 21.4).

Relapse

The relapse rate after achieving a BVAS of 0 at any time was 13.0% (7/54 patients) in the avacopan group compared with 22.6% (12/53 patients) in the prednisone taper group (HR, 0.53; 95% CI 0.21 to 1.35; reduction in relapse risk, 47%). The relapse rate for patients who achieved remission at week 26 was 8.1% (3/37 patients) in the avacopan group and 8.8% (3/34 patients) in the prednisone taper group (table 2).

Glucocorticoid use

The total GC use over 52 weeks was lower in the avacopan group than in the prednisone taper group (table 3), with a mean total prednisone-equivalent dose of all oral and intravenous GCs of 1575 mg in the avacopan group and 4147 mg in the prednisone taper group (median dose of 285 mg (range, 0–12 725 mg) and 2920 mg (range, 760–11 665 mg), respectively).

Glucocorticoid toxicity

GC-induced toxicity, as assessed by the GTI, was greater in the prednisone taper group than in the avacopan group (table 3). The LS mean (95% CI) GTI-CWS at week 26 was 45.3 (33.7 to 56.8) in the avacopan group and 65.7 (53.9 to 77.4) in the prednisone taper group, with an LS mean (95% CI) difference of −20.4 (−36.9 to −3.9). The LS mean (95% CI) GTI-AIS at week 26 was 11.6 (−0.1 to 23.4) in the avacopan group and 33.1 (21.2 to 45.0) in the prednisone taper group, with an LS mean (95% CI) difference of −21.5 (−38.2 to −4.8).

Use of immunosuppressive medications in addition to CYC

The use of non-protocol non-GC immunosuppressive medications in addition to CYC is shown in table 4. In the avacopan and prednisone taper groups, respectively, non-protocol immunosuppressive medications were used in 11.9% (7/59) and 19.3% (11/57) of patients between week 0 and week 26; 5.1% (3/59) and 12.3% (7/57) of patients between week 26 and week 52; and 16.9% (10/59) and 24.6% (14/57) of patients between week 0 and week 52. All use of immunosuppressive medications during the trial is detailed in online supplemental table S1.

Kidney function

Kidney function improved in patients with kidney involvement at baseline with both treatments. From a baseline mean eGFR (SD) of 34.5 (20.3) mL/min/1.73 m^2 in the avacopan group and 43.7 (28.8) mL/min/1.73 m^2 in the prednisone taper group, LS mean change (SEM) in eGFR at week 52 was 9.5 (1.9) mL/min/1.73 m^2 in the avacopan group and 6.4 (1.8) mL/min/1.73 m^2 in the prednisone taper group (figure 1). For the 50 patients with an eGFR <30 mL/min/1.73 m^2 at baseline, where mean eGFR (SD) at baseline was similar between treatment groups (21.2 (4.7) mL/min/1.73 m^2 for the avacopan group (n=26); 22.3 (4.6) mL/min/1.73 m^2 for the prednisone taper group (n=24)), LS mean change (SEM) in eGFR at week 52 was 19.2 (2.1) mL/min/1.73 m^2 in the avacopan group and 9.9 (2.1) mL/min/1.73 m^2 in the prednisone taper group.

In patients with albuminuria ≥10 mg/g creatinine at baseline, improvement in UACR occurred more rapidly in the avacopan group than in the prednisone taper group (figure 2). At week 2 and week 4, LS mean change in UACR was −21% and −36%, respectively, in the avacopan group and 10% and −9%, respectively, in the prednisone taper group. LS mean (95% CI) difference

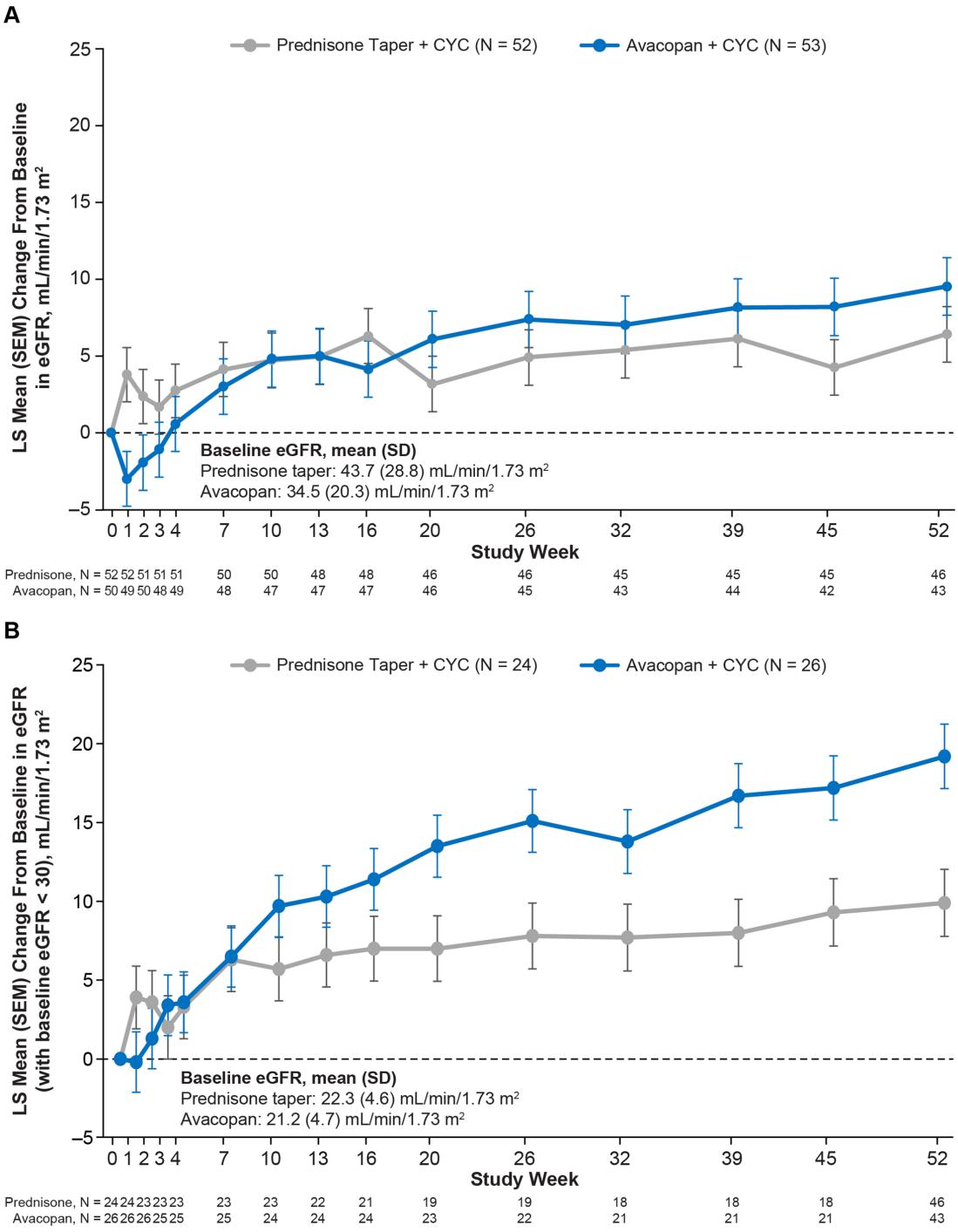

Figure 1 Change from baseline in eGFR in patients with (A) kidney involvement at baseline and (B) kidney involvement and an eGFR <30 mL/min/1.73 m^2 at baseline. LS mean and SEM are from mixed-effects models for repeated measures with treatment group, visit and treatment-by-visit interaction as factors and baseline as a covariate. CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; LS, least squares.

between treatments at week 2 and week 4 was −28% (−52 to 8) and −30% (−53 to 5), respectively. By week 52, the improvements in UACR were similar in both treatment groups, with a >75% decrease from baseline.

Health-related quality of life

HRQoL, evaluated using the SF-36 and EQ-5D-5L questionnaires, improved with both treatments (online supplemental figure S1A, B and table S2). LS mean change from baseline was greater in the avacopan group than in the prednisone taper group at week 26 and week 52 across all SF-36 domains (online supplemental table S2). LS mean (95% CI) for EQ-5D-5L Index Score and EQ-5D-5L Visual Analogue Scale score improved more in patients in the avacopan group than in those in the prednisone taper group (online supplemental figure S1C, D and table S2).

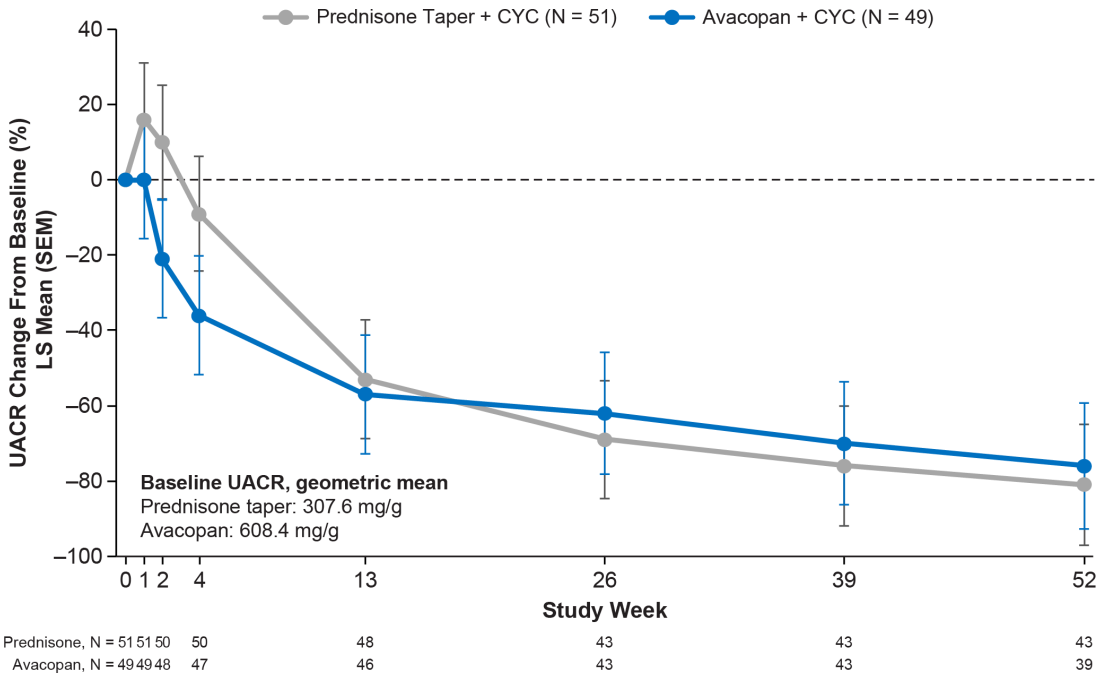

Figure 2 Percentage change from baseline in UACR in patients with albuminuria (≥10 mg/g creatinine) at baseline. Geometric means are from mixed-effects models for repeated measures with the treatment group, visit and treatment-by-visit interaction as factors and baseline as a covariate. Logarithmic transformations were applied to the data before fitting the model. Percent changes from baseline are based on ratios of geometric means of visit over baseline. CYC, cyclophosphamide; LS, least squares; UACR, urinary albumin-to-creatinine ratio.

Safety

Safety results for the overall study population have been previously published.[14] For the 116 patients who received CYC as background induction therapy, SAEs occurred in 33/59 patients (55.9%; 54 events) in the avacopan group and 32/57 patients (56.1%; 75 events) in the prednisone taper group (table 5). Serious infections occurred in 11/59 patients (18.6%; 13 events) in the avacopan group and 10/57 patients (17.5%; 12 events) in the prednisone taper group. The SAE of an abnormality on liver-function testing occurred in six patients (10.2%) in the avacopan group and two patients (3.5%) in the prednisone taper group. These SAEs occurred between days 43 and 131 in the avacopan group and days 8 to 10 in the prednisone taper group. Two patients (3.4%) died in the avacopan group (one patient developed pneumonia and had been off avacopan for 110 days; one patient developed worsening GPA and had been off avacopan for 79 days), and one patient (1.8%) died in the prednisone taper group (infectious pleural effusion).

Table 5 Summary data on treatment emergent adverse events among study participants

Outcome	Prednisone taper+CYC (N=57)	Avacopan+CYC (N=59)
Any adverse event, n (%)	56 (98.2)	59 (100.0)
Number of events	900	705
Any infection, n (%)	47 (82.5)	45 (76.3)
Number of events	103	97
Any serious adverse event, n (%)	32 (56.1)	33 (55.9)
Number of events	75	54
Any serious infection, n (%)	10 (17.5)	11 (18.6)
Number of events	12	13
Discontinuation of trial medication due to adverse event, n (%)	12 (21.1)	14 (23.7)
Serious adverse event of abnormality on liver-function testing, n (%)	2 (3.5)	6 (10.2)
Death, n (%)	1 (1.8)	2 (3.4)

CYC, cyclophosphamide.

DISCUSSION

Results of this subgroup analysis suggest that avacopan in combination with CYC followed by AZA or MMF has comparable efficacy to a prednisone taper in achieving remission at week 26 and sustaining remission at week 52 in patients with GPA or MPA. Furthermore, rates of relapse after achieving a BVAS of 0 at any time were lower in the avacopan group than in the prednisone taper group, despite most patients receiving a mainly AZA-based maintenance immunosuppressive therapy during this period. In addition to the efficacy outcomes of remission and relapse rates, other outcomes reported in this study support the benefits of combining avacopan with

CYC for inducing remission, including improvement in eGFR, reduction in GC exposure and associated GC-related toxicity, and improvement in HRQoL.

While the LS mean increase in eGFR from baseline to week 52 for patients with kidney involvement at baseline favours the avacopan group, the overall mean eGFR at baseline for patients receiving CYC in the avacopan group was numerically lower than that for those in the prednisone taper group, making interpretation of these results challenging. However, after restricting this analysis to participants with a baseline eGFR <30 mL/min/1.73 m^2, baseline eGFR became more comparable between groups, and improvements in eGFR still favoured avacopan. These kidney benefits are supported even further by the early improvements in UACR for the avacopan group. Collectively, these observations support the key role of avacopan in combination with CYC in achieving rapid and sustained improvement in kidney function compared with a prednisone taper.

Though the avacopan and prednisone taper groups had similar efficacy outcomes, numerically fewer patients in the avacopan group compared with the prednisone group used non-protocol non-GC immunosuppressive medications over 52 weeks, with both groups having similar evaluated patterns of background CYC use. Furthermore, patients receiving avacopan in combination with CYC followed by AZA or MMF achieved these outcomes while also experiencing a reduced burden of GC exposure, as reflected in the difference in total GC dose and the GTI scores. The exact mechanism by which avacopan exerts its effect in GPA/MPA remains unknown. However, as a C5a receptor 1 antagonist blocking neutrophil chemoattraction and activation, avacopan may impact an aspect of the pathophysiology of GPA/MPA not directly addressed by other treatments.

The overall rates of SAEs, including serious infections, were similar between the avacopan and prednisone taper groups. However, the SAE of an abnormality on liver-function testing occurred in 10.2% of patients who received avacopan and 3.5% of those who received a prednisone taper. Hepatic-related AEs are a known risk of avacopan and detailed monitoring for and management of these have been incorporated into the drug label in many countries.[27]

This subgroup analysis of patients treated with CYC in ADVOCATE is particularly relevant for settings in which CYC remains commonly used to treat GPA/MPA, particularly in areas with less access to RTX or in patients unable to tolerate or unresponsive to RTX. However, this study has some limitations. First, patients with an eGFR <15 mL/min/1.73 m^2 and those with alveolar haemorrhage requiring mechanical ventilation were not included in this study, and findings of the efficacy and safety of avacopan combined with CYC to induce remission need to be confirmed in these excluded groups. Second, the data presented are from a subgroup of a small number of patients in each treatment group; thus, only descriptive evaluations are provided. When assessing the rates of sustained remission in each treatment group, the number of patients available for analysis was even smaller because only patients achieving remission are included. For these reasons, caution is needed when comparing the observed efficacy outcomes here to those reported in the overall trial or between treatment groups. Third, selection of CYC as background therapy was at the discretion of the investigator, which may further confound differences in outcomes when comparing results among those treated with CYC versus RTX because of the differences in baseline patient characteristics. For instance, those treated with CYC compared with those treated with RTX more often had newly diagnosed GPA/MPA and were MPO-ANCA positive, both of which may have selected for patients less likely to relapse,[28] potentially influencing relapse rate and sustained remission results. This study adds to a previous report on the efficacy of avacopan when combined with RTX. Still, there remains an absence of data on the efficacy of avacopan with the combination of CYC with RTX or with CYC followed by RTX instead of AZA, both of which are treatment strategies recommended by current guidelines.[2 3 15]

In conclusion, this analysis of the subgroup of patients who received CYC followed by AZA or MMF in ADVOCATE suggests similar rates of remission in the avacopan and prednisone taper groups. Compared with a standard prednisone taper, use of avacopan with a markedly reduced GC regimen was associated with a numerically lower relapse rate, greater improvement in eGFR, faster reduction in UACR, less GC-related toxicity and greater improvements in HRQoL with a safety profile similar to what was seen in the overall study. These results support the use of avacopan in combination with CYC to treat GPA or MPA.

Author affiliations
[1]Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[2]Kantonsspital St Gallen, St. Gallen, Switzerland
[3]Universite Paris Descartes, Paris, France
[4]Hopital Europeen Georges Pompidou, Paris, France
[5]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
[6]University of Pennsylvania, Philadelphia, Pennsylvania, USA
[7]Amgen Ltd, Cambridge, UK
[8]Amgen Inc, Thousand Oaks, California, USA
[9]University of Cambridge, Cambridge, UK

Acknowledgements The authors thank all the many study coordinators, investigators and patients involved for their valuable contributions. Martha Mutomba, PhD (on behalf of Amgen), provided medical writing support for this manuscript. Bob Dawson provided figure support for this manuscript. Rachel Gurlin, PhD (Amgen), provided insights on the data and analysis and critically reviewed the manuscript.

Collaborators Members of the ADVOCATE Study Group as listed in Supplemental Material: C Au Peh (Royal Adelaide Hospital, Adelaide SA, Australia), A Chakera (Sir Charles Gairdner Hospital, Nedlands, WA, Australia), B Cooper (Royal North Shore Hospital, St Leonards, Australia), J Kurtkoti (Griffith University, Southport, Australia), D Langguth (Wesley Medical Research, Auchenflower, Australia), V Levidiotis (Western Health, St. Albans, Victoria, Australia), G Luxton (Prince of Wales Hospital, Randwick, NSW, Australia), P Mount (Austin Health, Heidelberg, Victoria, Australia), D Mudge (Princess Alexandra Hospital, Woolloongabba, QLD, Australia), E Noble (Sunshine Coast University Hospital, Birtinya, Australia), R Phoon (Westmead

Hospital, Westmead, NSW, Australia), D Ranganathan (Royal Brisbane and Women's Hospital, Herston, QLD, Australia), A. Ritchie (Concord Repatriation General Hospital, Concord, Australia), J Ryan (Monash Medical Centre, Clayton, Victoria, Australia), M Suranyi (Liverpool Hospital, Liverpool, NSW, Australia), A Rosenkranz (Medizinische Universitaet Graz, Graz, Austria), K Lhotta (Landeskrankenhaus Feldkirch, Feldkirch, Austria), A Kronbichler (Medical University of Innsbruck, Innsbruck, Austria), N Demoulin (Cliniques Universitaires Saint-Luc, Brussels, Belgium), C. Bovy (Centre Hospitalier Universitaire de Liege, Liege, Belgium), R Hellemans (Antwerp University Hospital (UZA), Edegem, Belgium), J Hougardy (Université Libre de Bruxelles (ULB) - Hôpital Erasme, Brussels, Belgium), B Sprangers (University Hospital (UZ) Leuven, Leuven, Belgium), K Wissing (University Hospital Brussels, Brussels, Belgium), C Pagnoux (University of Toronto, Toronto, Canada), S Barbour (St. Paul Hospital, Vancouver, Canada), S Brachemi (Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montréal, Canada), S Cournoyer (CISSS de la Monteregie-Centre – Hôpital Charles LeMoyne, Greenfield Park, Canada), L. Girard (University of Calgary, Calgary, Canada), L Laurin (Hospital Maisonneuve-Rosemont, Montréal, Canada), P Liang (Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Canada), D Philibert (CHUQ-L'Hotel-Dieu de Quebec, Quebec City, Canada), M Walsh (St. Josephs Healthcare, Hamilton, Canada), V Tesar (Department of Nephrology, General University Hospital, Prague, Czech Republic), R Becvar (Rheumatology Institute, Prague, Czech Republic), P Horak (University Hospital Olomouc, Olomouc, Czech Republic), I Rychlik (University Hospital Vinohrady, Prague, Czech Republic), W Szpirt (Copenhagen University Hospital, Copenhagen, Denmark), H Dieperink (Odense University Hospital, Odense, Denmark), J Gregersen (Aalborg University Hospital, Aalborg, Denmark), P. Ivarsen (Aarhus University Hospital - Skejby, Aarhus, Denmark), E Krarup (Herlev Hospital, Herlev, Denmark), C Lyngsoe (Sjaellands Universitets Hospital Roskilde, Roskilde, Denmark), C Rigothier (CHU Bordeaux - Hospital Pellegrin, Bordeaux, France), J Augusto (CHU Angers, Angers, France), A Belot (CHU Lyon- Hôpital Femme- Mere-Enfant, Bron, France), D Chauveau (CHU de Toulouse - Hospital Rangueil, Toulouse, France), D Cornec (CHU de Brest - Hôpital de la Cavale Blanche, Brest, France), N Jourde-Chiche (APHM - Hôpital de la Conception, Marseille, France), M Ficheux (CHU de Caen, Caen, France), A Karras (Hôpital Européen Georges Pompidou, Paris), A Klein (Hopitaux Civils de Colmar, Colmar, France), F Maurier (Hopitaux Prives de Metz, Metz, France), R Mesbah (Centre Hospitalier Boulogne sur Mer, Boulogne sur Mer, France), O Moranne (CHU Nimes – Hôpital Caremeau, Nimes, France), A Neel (CHU Nantes Medicine Interne, Nantes, France), T Quemeneur (Centre Hospitalier de Valenciennes, Valenciennes, France), D Saadoun (Hospital Pitie Salpetriere, Paris, France), B Terrier (Hôpital Cochin, Paris, France), P Zaoui (CHU de Grenoble, Grenoble Isere Cedex, France), M Schaier (University Clinic Heidelberg, Heidelberg, Germany), U Benck (University Clinic Mannheim, Mannheim, Germany), R Bergner (Clinic of Ludwigshafen am Rhein, Ludwigshafen, Germany), M Busch (University Clinic Jena, Jena, Germany), J. Floege (University Clinic Aachen, Aachen, Germany), F Grundmann (University Clinic Cologne, Cologne, Germany), H Haller (Medizinische Hochschule Hannover, Hannover, Germany), M Haubitz (Klinikum Fulda, Fulda, Germany), B Hellmich (Medius Clinic Kirchheim, Kirchheim-unter-Teck, Germany), J Henes (University Hospital Tuebingen, Tuebingen, Germany), B Hohenstein (Nephrological Center Villingen-Schwenningen, Villingen-Schwenningen, Germany), C Hugo (University Clinic Carl Gustav Carus, Dresden, Germany), C Iking-Konert and F Arndt (Klinikum Bad Bramstedt GmbH, Bad Bramstedt, Germany), T. Kubacki and I. Kotter (Asklepios Kinik, Hamburg, Germany), P Lamprecht (University Clinic Schleswig-Holstein, Luebeck, Germany), T Lindner and J Halbritter (University Clinic Leipzig, Leipzig, Germany), H Mehling (Charité - Universitaetsmedizin Berlin, Berlin, Germany), U Schönermarck (Universität München – Großhadern, Munich, Germany), N Venhoff (University Clinic Freiburg, Freiburg, Germany), V Vielhauer (University Clinic Munich, Munich, Germany), O Witzke (University Clinic Essen, Essen, Germany), I Szombati (Qualiclinic Kft, Budapest, Hungary), G Szucs (DEOEC Rheumatology Faculty, Debrecen, Hungary), G. Garibotto (IRCCS Azienda Ospedaliera Universitaria San Martino, Genova, Italy), F Alberici (ASST Santi Paolo e Carlo-Presidio Ospedale San Carlo, Milan, Italy), E Brunetta (Istituto Clinico Humanitas, Rozzano, Italy), L Dagna (IRCCS Ospedale San Raffaele, Milan, Italy), S De Vita (Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy), G Emmi (Azienda Ospedaliero Universitaria Careggi, Florence, Italy), A Gabrielli (AOU Ospedali Riuniti di Ancona, Torrette Ancona, Italy), L Manenti (Azienda Ospedaliero Universitaria di Parma, Parma, Italy), F Pieruzzi (ASST di Monza-Ospedale San Gerardo, Monza, Italy), D Roccatello (ASL Città di Torino - Ospedale San Giovanni Bosco, Torino, Italy), C Salvarani (Azienda Unità Sanitaria Locale di Reggio Emilia, Reggio Emilia, Italy). M Harigai (Tokyo Women's Medical University, Tokyo, Japan), H Dobashi (Kagawa University Hospital, Kagawa, Japan), T Atsumi (Hokkaido University Hospital, Hokkaido, Japan), S Fujimoto (University of Miyazaki Hospital, Miyazaki, Japan), N Hagino (Teikyo University Chiba Medical Center, Chiba, Japan), A Ihata (National Hospital Organization Yokohama Medical Center, Yokohama, Japan), S Kaname (Kyorin University Hospital, Tokyo, Japan), Y Kaneko (Keio University Hospital, Tokyo, Japan), A Katagiri (Juntendo University Shizuoka Hospital, Shizuoka, Japan), M Katayama (Nagoya Medical Center, Aichi, Japan), Y Kirino (Yokohama City University Hospital, Kanagawa, Japan), K Kitagawa (National Hospital Organization Kanazawa Medical Center, Ishikawa, Japan), A Komatsuda (Akita University Hospital, Akita City, Japan), H Kono (Teikyo University Hospital, Tokyo, Japan), T Kurasawa (Saitama Medical Center, Saitama, Japan), R Matsumura (National Hospital Organization Chiba East Hospital, Chiba, Japan), T. Mimura (Saitama Medical University Hospital, Saitama, Japan), A Morinobu (Kobe University Hospital, Hyogo, Japan), Y Murakawa (Shimane University Hospital, Shimane, Japan), T Naniwa (Nagoya City University Hospital, Aichi, Japan), T Nanki (Toho University Omori Medical Center, Tokyo, Japan), N Ogawa (Hamamatsu University Hospital, Shizuoka, Japan), H Oshima (National Hospital Organization Tokyo Medical Center, Tokyo, Japan), K Sada (Okayama University Hospital, Okayama, Japan), E Sugiyama (Hiroshima University Hospital, Hiroshima, Japan), T Takeuchi (Osaka Medical College Hospital, Osaka, Japan), H Taki (Toyama University Hospital, Toyama, Japan), N Tamura (Juntendo University Hospital, Tokyo, Japan), T Tsukamoto (Tazuke Kofukai Medical Research Institute Kitano Hospital, Osaka, Japan), K Yamagata (University of Tsukuba Hospital, Ibaraki, Japan), M Yamamura (Okayama Saiseikai General Hospital, Okayama, Japan), P van Daele (Erasmus MC, Rotterdam, The Netherlands), A Rutgers (Groningen Universitair Medisch Centrum, Groningen, The Netherlands), Y Teng (Leids Universitair Medisch Centrum, Leiden, The Netherlands), R Walker (Dunedin Hospital, Dunedin, New Zealand), I Chua (Christchurch Clinical Studies Trust, Christchurch, New Zealand), M Collins (Auckland City Hospital, Auckland, New Zealand), K Rabindranath (Waikato Hospital, Hamilton, New Zealand), J de Zoysa (North Shore Hospital, Takpuna, Auckland, New Zealand), M. Svensson (Akershus Universitetssykehus, Nordbyhagen, Norway), B. Grevbo (Oslo Universitessykkehus, Oslo, Norway), S Kalstad (University Hospital of North Norway, Tromso, Norway), M Little (Beaumont Hospital, Dublin, Republic of Ireland), M Clarkson (Cork University Hospital, Cork, Republic of Ireland), E Molloy (St. Vincent's University Hospital, Dublin, Republic of Ireland), I Agraz Pamplona (Hospital Vall D Hebron, Barcelona, Spain), J Anton (Hospital Sant Joan de Deu, Barcelona, Spain), V Barrio Lucia (Hospital Universitario Infanta Sofia, San Sebastian de los Reyes, Madrid, Spain), S Ciggaran (Hospital Da Costa, Burela, Spain), M C Cid (Hospital Clinic Barcelona – Autoimmune Diseases Department, Barcelona), M Diaz Encarnacion (Fundacio Puigvert, Barcelona, Spain), X Fulladosa Oliveras (Hospital Universitari de Bellvitge, Barcelona, Spain), M Jose Soler (Hospital del Mar, Barcelona, Spain), H Marco Rusinol (Hospital Germans Trias i Pujol, Badalona, Spain), M Praga (Hospital 12 de Octubre, Madrid, Spain), L Quintana Porras (Hospital Clinic Barcelona, Barcelona, Spain), A Segarra (Hospital Universitari Arnau de Vilanova, Lleida, Spain), A Bruchfeld (Karolinska University Hospital, Stockholm, Sweden), M Segelmark (Linköping University, Linköping, Sweden), I Soveri (Uppsala University Hospital, Uppsala, Sweden), E Thomaidi (Örebro University Hospital, Örebro, Sweden), K Westman (Skane University Hospital, Malmo, Sweden), T Neumann (Kantonsspital St. Gallen, St. Gallen), M Burnier (CHUV Lausanne, Lausanne, Switzerland), T Daikeler (University Hospital Basel, Basel, Switzerland), J Dudler (Hôpital Fribourgeois, Fribourg, Switzerland), T Hauser (Immunologie-Zentrum Zürich, Zürich, Switzerland), H Seeger (Universitätsspital Zürich, Zürich, Switzerland), B Vogt (Inselspital, Universitätsspital Bern, Bern, Switzerland), D R W Jayne (Addenbrooke's Hospital - Cambridge University Hospitals, Cambridge), J. Burton and R Al Jayyousi (Leicester General Hospital, Leicester, United Kingdom), T Amin (Leeds Childrens Hospital, Leeds, United Kingdom), J Andrews (Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom), L Baines (Freeman Hospital, Newcastle upon Tyne, United Kingdom), P Brogan (Great Ormond Street Hospital for Children, London, United Kingdom), B. Dasgupta (Southend University Hospital, Westcliff on Sea, United Kingdom), T Doulton (Kent and Canterbury Hospital, Canterbury, Kent, United Kingdom), O Flossmann (Royal Berkshire Hospital, Reading, Berkshire, United Kingdom), S Griffin (University Hospital of Wales, Cardiff, United Kingdom), J Harper (Royal Liverpool University Hospital, Liverpool, United Kingdom), L Harper (University of Birmingham, Birmingham, United Kingdom), D Kidder (University Aberdeen, Aberdeen, United Kingdom), R Klocke (Russells Hall Hospital, Dudley, United Kingdom), P Lanyon (Queens Medical Centre, Nottingham, United Kingdom), R Luqmani (Nuffield Orthopaedic Centre, Oxford, United Kingdom), J McLaren (Whytemans Brae Hospital, Fife, United Kingdom), D Makanjuola (St Helier Hospital, Carshalton, United Kingdom), L McCann (Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom), A Nandagudi and S Selvan (Basildon University Hospital, Basildon, United Kingdom), E O'Riordan (Salford Royal NHS Foundation Trust Manchester, Salford, United Kingdom), M Patel (University of Manchester, Manchester Royal Infirmary, Manchester, United Kingdom), R Patel (Queen Elizabeth University Hospital, Glasgow, United Kingdom), C Pusey (Imperial College Healthcare NHS Trust, London, United Kingdom), R Rajakariar (The Royal London Hospital, London, United Kingdom), J Robson (Bristol Royal Infirmary, Bristol, United Kingdom), M Robson (Guy's and St Thomas's NHS Foundation Trust, London, United Kingdom), A Salama (UCL Centre for Nephrology Royal Free, London, United Kingdom), L Smyth (Royal Devon and Exeter Hospital, Exeter, United Kingdom), J Sznajd (Raigmore Hospital, Inverness, United Kingdom), J Taylor (Dorset County Hospital, Dorchester, United Kingdom), P A Merkel and A Sreih (University of Pennsylvania, Philadelphia, USA), E Belilos (Winthrop University Hospital, Mineola, USA), A Bomback (Columbia University Medical Center, New York, USA), J Carlin (Virginia Mason Medical Center, Seattle, USA), Y Chang Chen Lin (University of South Florida, Tampa, USA), V Derebail (University of North Carolina Hospitals, Chapel Hill, USA), S Dragoi (MedStar Georgetown University Hospital,

Washington, USA), A Dua (University of Chicago Medical Center Rheumatology, Chicago, USA), L Forbess (Cedars-Sinai Medical Center, Los Angeles, USA), D Geetha (Johns Hopkins Bayview Medical Center, Baltimore), P Gipson (University of Michigan, Ann Arbor, USA), R Gohh (Rhode Island Hospital, Providence, USA), GT Greenwood (Brookview Hills Research Associates, Winston-Salem, USA), S Hugenberg (Indiana University Nephrology, Indianapolis, USA), R Jimenez (Western Washington Arthritis Clinic, Bothell, USA), M Kaskas (Northwest Louisiana Nephrology, Shreveport, USA), T Kermani (University of California, Los Angeles, Santa Monica, USA), A Kivitz (Altoona Center for Clinical Research, Duncansville, USA), C Koening (University of Utah, Salt Lake City, USA), C Langford (Cleveland Clinic, Cleveland, USA), G Marder (Northwell Health, Great Neck, USA), A Mohamed (University of Kentucky Medical Center, Lexington, USA), P Monach (Boston University, Boston, USA), N Neyra (Arizona Kidney Disease and Hypertension Center Flagstaff, Flagstaff, USA), G Niemer (Articularis Healthcare Group, Charleston, USA), J Niles (Massachusetts General Hospital, Boston, USA), R Obi (East Carolina University, Greenville, USA), C. Owens (Renal Disease Research Institute, Dallas, USA), D Parks (Washington University School of Medicine, St. Louis, USA), A Podoll (Colorado Kidney Care, Denver, USA), B Rovin (Ohio State University, Columbus, USA), R Sam (San Francisco General Hospital Dialysis Center, San Francisco, USA), W Shergy (Rheumatology Associates of North Alabama, Huntsville, USA), A. Silva (Boise Kidney & Hypertension, PLLC – Meridian, Caldwell, USA), U Specks (Mayo Clinic - Division of Pulmonary & Critical Care Medicine, Rochester, USA), R Spiera (Hospital for Special Surgery, New York, USA), J Springer (University of Kansas Medical Center, Kansas City, USA), C Striebich (University of Colorado Denver - School of Medicine, Aurora, USA), A Swarup (Arizona Arthritis & Rheumatology Research, Phoenix, USA), S Thakar (University of Minnesota, Minneapolis, USA), A Tiliakos (Emory University School of Medicine, Atlanta, USA), Y Tsai (Arthritis, Autoimmune and Allergy LLC, Daytona Beach, USA), D Waguespack (University of Texas Health Sciences Center, Houston, USA), M Chester Wasko (Allegheny General Hospital, Pittsburgh, USA).

Contributors DG, PAM and DJ conceived and designed the study. DG, TN, AK, MC, PAM and DJ acquired the data. DG, TN, AK, MC, PAM, SB, AMB and DJ contributed to the analysis and interpretation of data and critically reviewed the manuscript for scientific content. All authors approved the final draft of the manuscript and take responsibility for the manuscript content. DG is the guarantor of the manuscript.

Funding Funding for this study was provided by ChemoCentryx (a wholly owned subsidiary of Amgen). Some data analysis and medical writing support were provided by Amgen.

Competing interests DG received consulting fees from Amgen, ChemoCentryx (a wholly owned subsidiary of Amgen), Aurinia, Otsuka, Calliditas, Vera Therapeutics, and GlaxoSmithKline (GSK). TN received consulting fees from GSK AG, AstraZeneca GmbH, Amgen Switzerland AG, and Vifor Pharma Switzerland. AK received consulting fees or honoraria from GSK, Vifor, Novartis, AstraZeneca, and Otsuka. MC received grant/research support from Kiniksa Pharmaceuticals; was a paid instructor for GSK; received payment on Speaker's bureau for GSK and CSL Vifor; received royalties from UpToDate; and was a consultant for CSL Vifor, GSK, AstraZeneca, Alexion, Boehringer Ingelheim, AbbVie, Novartis, and Royalty Pharma. She was supported by Ministerio de Ciencia, Innovación y Universidades/AEI/(PID2023-152265OB-I00)/FEDER-EU). PAM received grant/research support from AbbVie/Abbott, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eicos, Electra, Genentech, GSK, InflaRx, Neutrolis, and Takeda; received consulting fees from AbbVie, Amgen/ChemoCentryx, Argenx, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Cabaletta, CSL Behring, GSK, HiBio, InflaRx, Janssen, Jubilant, Kyverna, Novartis, NS Pharma, Q32, Regeneron, Sanofi, Sparrow, Takeda, and Visterra; holds stock or stock options in Kyverna, Q32, and Sparrow; and received royalties from UpToDate. SB is an employee of Amgen Ltd and owns stock in Amgen Inc. AMB is an employee of Amgen Inc. and owns stock in Amgen Inc. DJ received grant/research support from CSL Vifor; received consulting fees from Alentis, Amgen, AstraZeneca, Chinook, CSL Vifor, GSK, Hansa, and Roche; received honoraria from CSL Vifor; and was a Member of the Board of Aurinia.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the research protocol was approved by ethics committees and institutional review boards at participating sites (see ADVOCATE Site List/Study Group in the supplement). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available on reasonable request. Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://www.amgen.com/science/clinical-trials/clinicaldata-transparency-practices/clinical-trial-data-sharing-request.

ORCID iDs
Alana M. Bozeman http://orcid.org/0009-0002-5516-315X
David R. W. Jayne http://orcid.org/0000-0002-1712-0637

REFERENCES

1 Fauci AS, Katz P, Haynes BF, *et al*. Cyclophosphamide therapy of severe systemic necrotizing vasculitis. *N Engl J Med* 1979;301:235–8.
2 Floege J, Jayne DRW, Sanders J-SF, *et al*. KDIGO 2024 Clinical Practice Guideline for the management of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis. *Kidney Int* 2024;105:S71–116.
3 Hellmich B, Sanchez-Alamo B, Schirmer JH, *et al*. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. *Ann Rheum Dis* 2024;83:30–47.
4 Chung SA, Langford CA, Maz M, *et al*. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheumatol* 2021;73:1366–83.
5 Mendel A, Ennis D, Go E, *et al*. CanVasc consensus recommendations for the management of antineutrophil cytoplasm antibody-associated vasculitis: 2020 update. *J Rheumatol* 2021;48:555–66.
6 Turgeon D, Bakowsky V, Baldwin C, *et al*. CanVasc consensus recommendations for the use of avacopan in antineutrophil cytoplasm antibody-associated vasculitis: 2022 addendum. *Rheumatology (Oxford)* 2023;62:2646–51.
7 Geetha D, Specks U, Stone JH, *et al*. Rituximab versus cyclophosphamide for ANCA-associated vasculitis with renal involvement. *J Am Soc Nephrol* 2015;26:976–85.
8 Jones RB, Tervaert JWC, Hauser T, *et al*. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010;363:211–20.
9 Ahn SS, Lee SW. Management of antineutrophil cytoplasmic antibody-associated vasculitis: a review of recent guidelines. *J Rheum Dis* 2023;30:72–87.
10 Westman K, Flossmann O, Gregorini G. The long-term outcomes of systemic vasculitis. *Nephrol Dial Transplant* 2015;30 Suppl 1:i60–6.
11 Gopaluni S, Flossmann O, Little MA, *et al*. Effect of disease activity at three and six months after diagnosis on long-term outcomes in antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheumatol* 2019;71:784–91.
12 Flossmann O, Berden A, de Groot K, *et al*. Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011;70:488–94.
13 Rhee RL, Hogan SL, Poulton CJ, *et al*. Trends in long-term outcomes among patients with antineutrophil cytoplasmic antibody-associated vasculitis with renal disease. *Arthritis Rheumatol* 2016;68:1711–20.
14 Jayne DRW, Merkel PA, Schall TJ, *et al*. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med* 2021;384:599–609.
15 Geetha D, Dua A, Yue H, *et al*. Efficacy and safety of avacopan in patients with ANCA-associated vasculitis receiving rituximab in a randomised trial. *Ann Rheum Dis* 2024;83:223–32.
16 Mukhtyar C, Lee R, Brown D, *et al*. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis* 2009;68:1827–32.
17 Stone JH, Hoffman GS, Merkel PA. A disease-specific activity index for Wegener's granulomatosis: Modification of the Birmingham Vasculitis Activity Score. *Arthritis Rheum* 2001;44:912–20.
18 Jennette JC, Falk RJ, Bacon PA, *et al*. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013;65:1–11.
19 Stone JH, McDowell PJ, Jayne DRW, *et al*. The glucocorticoid toxicity index: measuring change in glucocorticoid toxicity over time. *Semin Arthritis Rheum* 2022;55:152010.

20 Levey AS, Coresh J, Greene T, *et al*. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006;145:247–54.
21 Kasai T, Miyauchi K, Kajimoto K, *et al*. Prognostic significance of glomerular filtration rate estimated by the Japanese equation among patients who underwent complete coronary revascularization. *Hypertens Res* 2011;34:378–83.
22 Schwartz GJ, Muñoz A, Schneider MF, *et al*. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009;20:629–37.
23 Ware JE Jr. SF-36 Health Survey Update. *Spine (Phila Pa 1986)* 2000;25:3130–9.
24 Herdman M, Gudex C, Lloyd A, *et al*. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727–36.
25 International Conference on Harmonisation (ICH). Introductory guide meddra version 19.1. 2016. Available: https://admin.meddra.org/sites/default/files/guidance/file/intguide_19_1_english.pdf [accessed 20 Jan 2025]
26 U.S Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE) version 5.0. 2017. Available: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf#search=%22CTCAE%22.pdf [Accessed 20 Jan 2025].
27 TAVNEOS (avacopan). Prescribing information. Thousand Oaks, CA, USA Amgen. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214487s000lbl.pdf [accessed 14 Mar 2025]
28 Hilhorst M, van Paassen P, Tervaert JWC, *et al*. Proteinase 3-ANCA Vasculitis versus Myeloperoxidase-ANCA Vasculitis. *J Am Soc Nephrol* 2015;26:2314–27.