

Safety and Efficacy of Avacopan in Patients with Complement 3 Glomerulopathy

Randomized, Double-Blind Clinical Trial

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Key Points

- ACCOLADE was the first randomized trial in patients with complement 3 glomerulopathy investigating the use of avacopan, a complement component 5a receptor blocker.
- The trial did not meet its primary end point of change in disease activity index from baseline to 26 weeks.
- No new safety signals were reported; the results suggest a potential role of avacopan in milder forms of complement 3 glomerulopathy.

Abstract

Background Complement 3 (C3) glomerulopathy is a rare autoimmune disorder characterized by activation of the alternative complement pathway with isolated or dominant complement 3 deposition in glomeruli. Patients with C3 glomerulopathy may develop progressive deterioration in kidney function and kidney failure.

Methods We studied the safety and efficacy of avacopan 30 mg twice daily in patients with C3 glomerulopathy ($N=57$) with elevated (>244 ng/ml) and normal (≤ 244 ng/ml) levels of membrane attack complex or terminal complement complex (C5b-9) in a randomized, double-blind, placebo-controlled, phase 2 trial, with kidney biopsies performed prerandomization and at 26 and 52 weeks. The primary outcome was the percent change from baseline to week 26 in C3 Glomerulopathy Histological Index for disease activity.

Results The study was conducted in patients with C3 glomerulopathy, including C3 GN and dense deposit disease. The median study duration was 60.0 weeks (interquartile range, 59.9–61.0). There were no significant differences in the primary outcome between the avacopan and the placebo group—least squares mean treatment difference (95% confidence interval) = -0.0 (-1.9 to 1.8). The secondary measures of efficacy including C3 Glomerulopathy Histological Index for disease chronicity, urine protein:creatinine ratio, and eGFR were not different between treatment groups. The overall incidence and type of adverse events for both treatment groups were comparable. No deaths were reported during the study, and no new safety signals were detected.

Conclusions The primary end point for the study was not met; other clinical effects of avacopan to improve certain key kidney function parameters and slow disease progression were variable and require further evaluation.

Clinical Trial registry name and registration number: Controlled Trial Evaluating Avacopan in C3 Glomerulopathy (ACCOLADE), [NCT03301467](https://clinicaltrials.gov/ct2/show/study/NCT03301467).

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Introduction

Complement 3 (C3) glomerulopathy is a rare autoimmune disease characterized by alternative complement pathway activation leading to C3 deposition in the glomeruli.^{1,2} There are two forms of the disease: dense deposit disease

(DDD) and C3 GN. Clinical and laboratory findings are insufficient for diagnosis. C3 glomerulopathy is diagnosed by biopsy and requires isolated or dominant glomerular C3 deposition by immunofluorescence. Electron microscopy is needed to differentiate the two forms, DDD and C3 GN.^{3–5}

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Patients with C3 glomerulopathy generally experience progressive deterioration in kidney function, ultimately leading to kidney failure. The mechanism by which complement deposition leads to kidney damage likely involves chemotaxis of leukocytes resulting from cleavage of C5 to generate complement component 5a fragment (C5a), as well as the cytolytic effects of membrane attack complex or terminal complement complex (C5b-9).³

There is no approved treatment for patients with C3 glomerulopathy. Immunosuppressive drugs such as cyclophosphamide, mycophenolate mofetil, and glucocorticoids, and biologics, such as rituximab, have been used with variable success. The anti-C5 antibody eculizumab previously demonstrated evidence of clinical improvement among some but not all treated patients with C3 glomerulopathy.^{6,7} Eculizumab blocks the formation of C5a and C5b-9 from C5. Evidence from animal models suggests that inhibition of C5a may be more important than inhibition of C5b-9 in C3 glomerulopathy because deletion of complement 6, which is part of the C5b-9 complex, in complement factor H knockout mice failed to protect the mice from developing significant C3 glomerulopathy.⁸ This supports testing drugs that target the C5a receptor (C5aR), such as avacopan.

Avacopan is an orally administered, selective C5aR antagonist that has received regulatory approval in many countries, including the United States, for use in certain patients with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).^{9–11}

On the basis of evidence in GPA/MPA and supportive data for C5aR inhibition as a possible therapeutic target in C3 glomerulopathy, we conducted the largest randomized, double-blind, placebo-controlled study to date in C3 glomerulopathy to evaluate the efficacy, safety, and tolerability of avacopan.

Methods

Study Conduct

A total of 46 sites across the United States, Canada, and Europe (Supplemental Listing 1) conducted this study in full compliance with the principles of the Declaration of Helsinki, International Council of Harmonisation

guidelines, and the laws and regulations of the country in which the research was conducted. The study protocol was approved by and followed the requirements set by the designated Institutional Review Board.

Trial Design and Patients

We performed a randomized, double-blind, placebo-controlled, phase 2 clinical study (ClinicalTrials.gov number NCT03301467) designed to evaluate the efficacy, safety, and tolerability of avacopan in patients aged 12–80 years with C3 glomerulopathy, including C3 GN and DDD. Patients were screened for enrollment on the basis of biopsy-proven C3 glomerulopathy (*i.e.*, ≥ 2 levels of magnitude greater staining of C3 than any combination of IgG, IgM, IgA, kappa and lambda light chains, and C1q) with evidence of proliferative GN (mesangial hypercellularity and/or endocapillary hypercellularity). The screening period was up to 42 days (6 weeks). The schematic of the study design is presented in Figure 1.

Eligible patients were adults at least aged 18 years, and where approved, adolescents (12–17 years of age), with biopsy-proven C3 glomerulopathy, including DDD and C3 GN, with or without a kidney transplant, providing written informed consent. Exclusion criteria included women who were pregnant or nursing, tubulointerstitial fibrosis that was more than 50%, use of eculizumab or another anti-C5 antibody within 26 weeks before dosing, and secondary C3 glomerulopathy disease (*e.g.*, detectable monoclonal gammopathy). The complete list of inclusion and exclusion criteria is provided in Supplemental Section 1. Information regarding prior and concomitant treatments, including use of immunosuppressant medications, is presented in Supplemental Section 2.

Initially, the study was open only to patients with elevated C5b-9 levels (*i.e.*, >244 ng/ml), and planned enrollment was 44 patients. Eligible patients with biopsy-proven C3 glomerulopathy (biopsy occurred within 12 weeks before signing informed consent or was to occur after consent during the screening period) were randomized 1:1 (22 patients in each arm) using a minimization algorithm to receive either avacopan or placebo twice daily (BID) in a double-blind manner starting on day 1 and

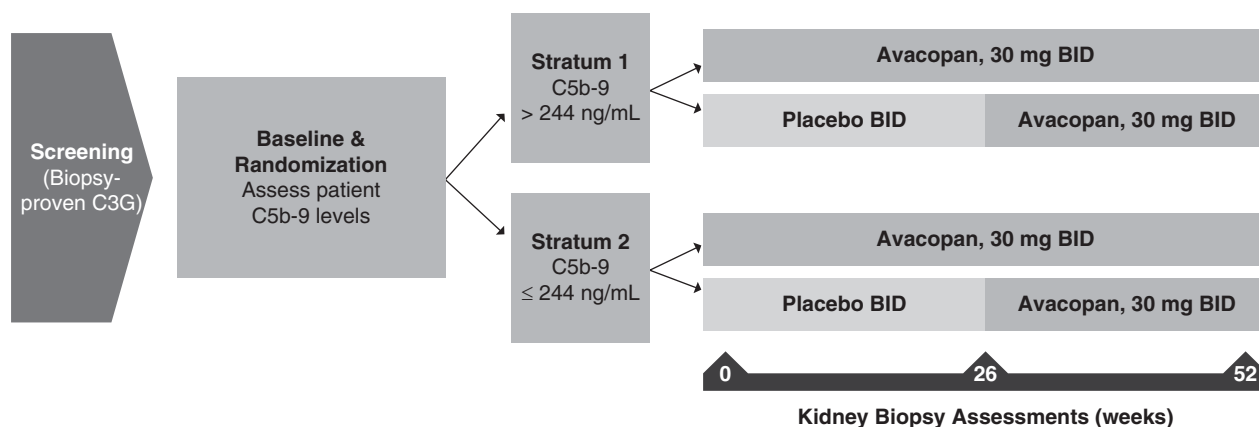


Figure 1. Schema of study design. BID, twice daily; C3G, complement 3 glomerulopathy; C5b-9, membrane attack complex or terminal complement complex.

continuing for 26 weeks (182 days). The randomization was stratified by C3 glomerulopathy type (C3 GN, DDD) and kidney transplant history. Owing to the high unmet medical need to treat patients with C3 glomerulopathy and the potential to study a subpopulation relevant to clinical practice, the study was amended to also enroll patients with normal C5b-9 concentrations (*i.e.*, ≤ 244 ng/ml), and planned enrollment was doubled to allow up to 88 patients (44 patients per C5b-9 strata). However, enrollment in the stratum with normal C5b-9 concentrations could be terminated early if patient enrollment in the elevated stratum reached target enrollment. During this period, eligible patients were stratified by C5b-9 concentration in addition to the above stratification plan.

The first eligible patient was enrolled in December 2017, and the last patient was enrolled by the end of August 2020. The 24th patient was enrolled in the normal (≤ 244 ng/ml C5b-9) stratum after the protocol was amended to include the normal C5b-9 stratum. The last patient's last visit was in October 2021. The 26-week double-blind placebo-controlled treatment period was followed by a 26-week open-label period during which all patients who had not withdrawn from investigational product received avacopan 30 mg BID. After the open-label period, all patients were followed for an additional 8 weeks (56 days) without study drug treatment. Target enrollment was reached in the elevated C5b-9 strata, and the study was completed after the last participant completed follow-up.

Follow-up kidney biopsies were performed at the following time points: (1) within 2 weeks of the week 26 visit, before dosing with open-label treatment and (2) if a patient was withdrawn early from the study, or (3) after the 52-week open-label period. The 52-week biopsy was optional for adolescent patients.

Investigational Drug Treatment

Adult patients randomized to the avacopan group received a 30 mg oral dose (3×10 mg capsules) BID. For adolescent patients (12–17 years), the BID dose of avacopan or placebo was based on body weight and area under the plasma concentration-time curve for 0–6 hours after dosing (AUC 0–6hr) or avacopan trough concentrations. Adolescent patients were enrolled only in countries and at study centers for which respective approval by Regulatory Authorities and Institutional Review Board/Ethics Committees was granted. Patients randomized to the placebo group received an equal number of matching-placebo capsules.

Study End Points

Kidney biopsies were evaluated by a single central histopathologist (L.C. Herlitz) blinded to treatment assignment. At the beginning of the study, the central histopathologist was also blinded to the study timepoint. To minimize intrapatient variability, the central histopathologist was unblinded to study timepoint and performed sequential readings of each patient's biopsies, as reflected in the primary and other analyses.

The primary end point was based on kidney histological evaluation using the C3 Glomerulopathy Histological Index and defined as the percent change from baseline to week 26 in the disease activity.¹ The disease activity used a score

from 0 to 21 and was calculated by summing the scores from seven defined lesions. Because the test for normality failed at a level of 0.10 for percent change from baseline ($P < 0.0001$) but not for change from baseline ($P = 0.1051$), change from baseline was used as the primary end point.

Secondary efficacy end points were the percent change from baseline in urine protein:creatinine ratio (UPCR) and eGFR over the placebo-controlled 26-week treatment period.^{12,13} Other secondary end points were the percent change from baseline in disease chronicity¹ (using a score of 0–10 calculated by summing the scores of four defined chronic kidney injuries) over the placebo-controlled 26-week treatment period; the proportion of patients who had a histologic response, defined as a decrease (improvement) in the disease activity of at least 35% from baseline to week 26; and changes in urine monocyte chemoattractant protein-1 (MCP1):creatinine ratio.

Secondary safety end points were the incidence of serious adverse events (SAEs), adverse events (AEs), and withdrawals from investigational product due to AEs—change from baseline and shifts from baseline in all safety laboratory parameters and change from baseline in vital signs.

Statistical Analysis

A sample size of 22 patients per treatment group in each C5b-9 level strata will provide 90% power of testing the avacopan group and the placebo group with two-sided $\alpha = 0.05$ assuming the between-treatment difference of -35% in the disease activity at week 26, SD 34% .

The intent-to-treat (ITT) population included all randomized patients who received at least one dose of the investigational product and had a non-zero histologic activity score at baseline. The safety population for each study period included all randomized patients who received at least one dose of the investigational product during that period. All safety data were analyzed according to the actual treatment received.

The primary analysis was conducted when the last participant enrolled in the C5b-9 elevated stratum had completed their week 26 visit. The primary efficacy analysis included participants in the elevated C5b-9 stratum who had reached week 26 or discontinued. To control for the type 1 error rate in the efficacy analysis, a gate-keeping procedure was applied, whereby the secondary end points were only tested if the primary efficacy end point (percent change or change in disease activity, as applicable) reached statistical significance (See [Supplemental Section 3](#)).

The methods used in the primary end point analysis were analysis of covariance with treatment group as factor and baseline disease activity as a covariate were used to estimate least squares (LS) mean and 95% confidence interval (CI). Missing data were handled using multiple imputation method assuming the Missing at Random. Additional statistical analysis methods for secondary end points are provided in [Supplemental Section 3](#).

A secondary analysis was conducted when all participants had completed the study and included both strata combined (elevated and normal C5b-9 levels).

All clinical safety and tolerability data were listed by treatment group, by patient, and were summarized by treatment group. All reported AEs were coded using the

Medical Dictionary for Regulatory Activities, version 20.1. Shift tables were generated and evaluated for shifts in laboratory parameters by study visit.

Results

Patient Enrollment and Disposition

Overall, 104 patients were screened for the study; most screen failures were due to not meeting entry criteria, withdrawal by patient, or related to coronavirus disease 2019. A total of 57 patients (28 avacopan, 29 placebo) were enrolled and randomized into the study. Twenty-six (93%) patients who received avacopan and 28 (97%) patients who received placebo completed the double-blind treatment period. Two patients in the elevated C5b-9 stratum were ongoing in the double-blind treatment period at the time of the primary analysis and are not included in the primary analyses of efficacy. Three patients (two avacopan, one placebo) discontinued the investigational product and the study during the double-blind period; the reasons for withdrawal were sponsor decision and other (one avacopan patient each) and AE (one placebo patient). The remaining 54 (95%) patients (26 avacopan, 28 placebo) entered the open-label avacopan treatment period. Forty-nine (86%) patients completed the avacopan and follow-up

treatment period; 47 (83%) patients completed avacopan treatment. A summary of patient disposition is presented in Figure 2.

The ITT analysis set included 56 (98%) of the 57 patients who were randomized; one patient randomized to the avacopan group had a histologic activity score of 0 at baseline. Two of the 56 patients were adolescents, and both received placebo in the double-blind phase of the study. The demographics and baseline characteristics of patients are presented in Table 1. Study participants were mostly White (86%) and male (61%), with an average age of the overall group at 34 years.

Primary Efficacy End Point

Disease Activity

The primary analysis of the primary efficacy end point of change from baseline to week 26 in disease activity in the elevated C5b-9 strata of the ITT population was not statistically significant. There was no significant difference in the LS mean difference in change from baseline (95% CI) between the avacopan group and the placebo group ($-0.0 [-1.9 \text{ to } 1.8]$) (Table 2). Secondary end points were not tested since the primary end point did not meet statistical significance. The primary efficacy analysis was subsequently rerun using complete data, including the

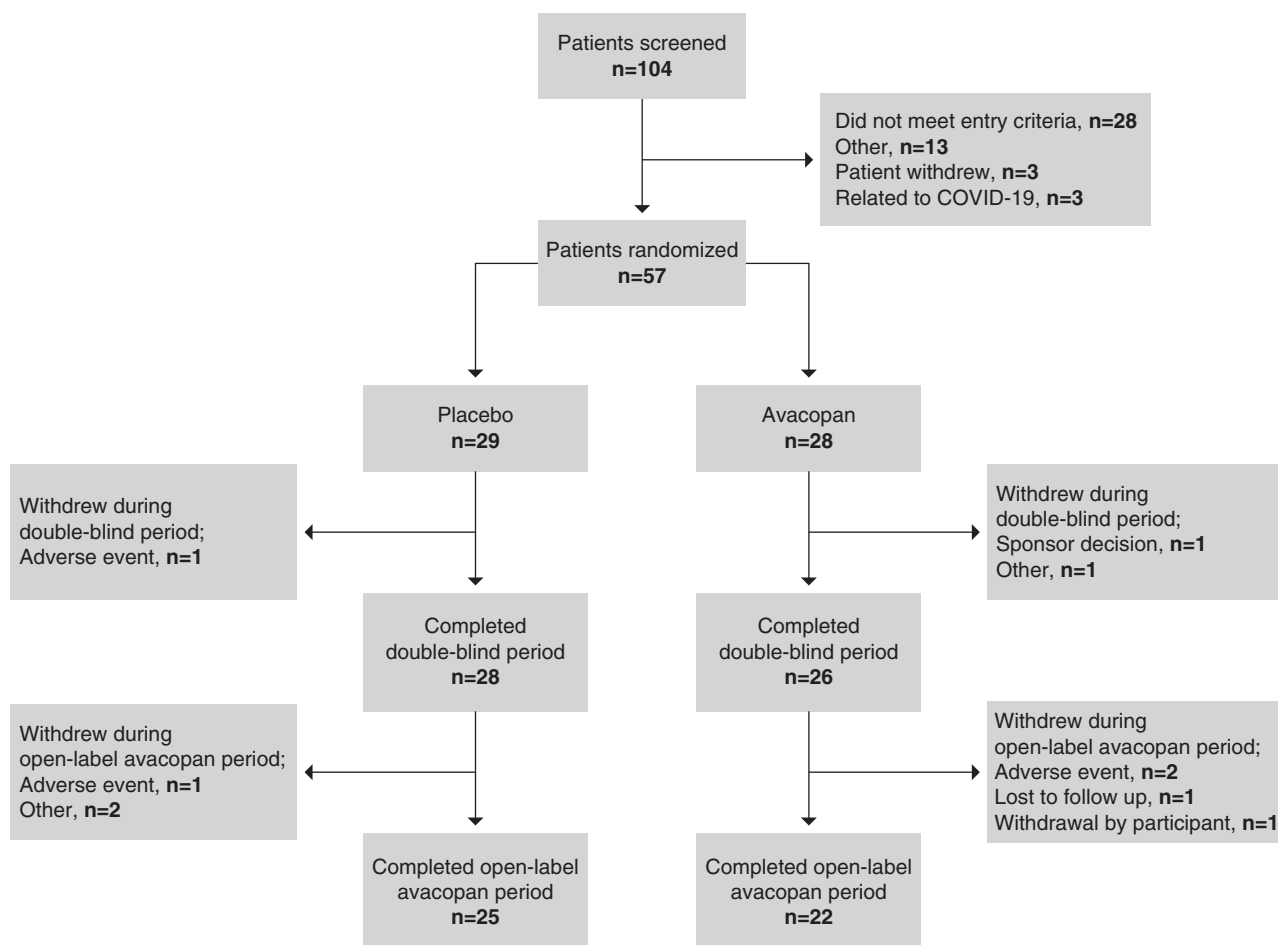


Figure 2. Study patient disposition. COVID-19, coronavirus disease 2019.

Table 1. Demographics and baseline characteristics of study population enrolled in ACCOLADE clinical trial

Characteristic Category	Elevated (>244 ng/ml) C5b-9		Normal (≤244 ng/ml) C5b-9		Combined Population	
	Placebo (N=22)	Avacopan (N=20)	Placebo (N=7)	Avacopan (N=7)	Placebo (N=29)	Avacopan (N=27)
Age at screening, yr						
Mean (SD)	34 (17)	31 (15)	48 (17)	33 (16)	37 (18)	32 (15)
Sex, n (%)						
Female	11 (50)	6 (30)	2 (29)	3 (43)	13 (45)	9 (33)
Male	11 (50)	14 (70)	5 (71)	4 (57)	16 (55)	18 (67)
Race, n (%)						
Asian	3 (14)	2 (10)	0 (0)	0 (0)	3 (10)	2 (7)
Black/African American	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	1 (4)
Other	1 (5)	1 (5)	0 (0)	0 (0)	1 (3)	1 (4)
White	18 (82)	16 (80)	7 (100)	7 (100)	25 (86)	23 (85)
Ethnicity, n (%)						
Hispanic/Latino	4 (18)	2 (10)	0 (0)	0 (0)	4 (14)	2 (7)
Not Hispanic/Latino	18 (82)	18 (90)	7 (100)	7 (100)	25 (86)	25 (93)
Disease type, n (%)						
C3 GN	20 (91)	19 (95)	5 (71)	4 (57)	25 (86)	23 (85)
DDD	2 (9)	0 (0)	2 (29)	3 (43)	4 (14)	3 (11)
Missing	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	1 (4)
History of kidney transplant, n (%)						
Yes	1 (5)	1 (5)	1 (14)	0 (0)	2 (7)	1 (4)
No	21 (96)	18 (90)	6 (86)	7 (100)	27 (93)	25 (93)
Missing	0 (0)	1 (5)	NA	NA	0 (0)	1 (4)
Duration of C3 glomerulopathy, mo						
Mean (SD)	50 (44)	50 (50)	36 (44)	51 (37)	47 (44)	50 (46)
eGFR, ml/min per 1.73 m²						
Mean (SD)	85 (43)	77 (43)	34 (16)	84 (34)	72 (44)	78 (40)
UPCR, g/g						
Mean (SD)	3 (3)	5 (4)	2 (1)	2 (2)	3 (2)	4 (3)
>1 g/g, n (%)	16 (73)	17 (85)	5 (71)	4 (57)	21 (72)	21 (78)
≤1 g/g, n (%)	6 (27)	3 (15)	2 (29)	3 (43)	8 (28)	6 (22)
Urine MCP1:creatinine ratio, pg/mg						
Mean (SD)	751 (519)	1430 (1470)	748 (439)	727 (620)	750 (492.5)	1241 (1323)
Body mass index, kg/m²						
Mean (SD)	24 (4)	25 (5)	26 (2)	30 (8)	25 (3)	26 (6)

ACCOLADE, Controlled Trial Evaluating Avacopan in C3 Glomerulopathy; C3, complement 3; C5b-9, membrane attack complex or terminal complement complex; DDD, dense deposit disease; MCP1, monocyte chemoattractant protein-1; NA, not applicable; UPCR, urine protein:creatinine ratio.

two patients whose week 26 visit had not been completed at the time of the primary analysis; the result was very similar (−0.0 [−1.8 to 1.8]).

A secondary analysis of the primary end point in the combined C5b-9 strata similarly showed no difference (0.1 [−1.4 to 1.7]) (Table 2). No differences between treatment groups in the change or percent change in disease activity were observed from week 26 to week 52 during the open-label period in the elevated or combined C5b-9 strata of the ITT population (Figure 3). In the elevated strata assigned to placebo, the mean percent change (SEM) in disease activity between baseline and week 26 was −19.5% (6.3), and between week 26 and week 52, the percent change (SEM) in the prior placebo group was 12.4% (12.8).

Secondary Efficacy End Points

Disease Chronicity

For the primary analysis of disease chronicity in the elevated C5b-9 strata, there was no difference in the change from baseline to week 26 between the avacopan

and placebo treatment groups—treatment difference (95% CI) = −0.5 (−1.5 to 0.5) (Figure 4 and Table 2).

In a secondary analysis of this end point in the combined C5b-9 strata participants assigned to avacopan, the change (95% CI) from baseline to week 26 was −0.6 (−1.5 to 0.2). In a subgroup analysis, estimates of change from baseline to week 26 in disease chronicity demonstrated greater increases (deterioration) in the placebo group compared with the avacopan group for those without a kidney transplant (treatment difference [95% CI] of −0.9 [−1.7 to −0.1]). No difference between treatment groups in the change or percent change in disease chronicity was observed from week 26 to week 52 during the avacopan treatment period in the elevated or combined C5b-9 strata (Figure 4). Analyses comparing disease chronicity during weeks 26 and 52 with values from baseline to week 26 within each treatment group demonstrated improvements (decreases) in the placebo group after 26 weeks of treatment with avacopan during the open-label period of the study. Differences in percent change (95% CI) and change (95% CI) between treatment periods of −47.5% (−85.2 to −9.7)

Table 2. Primary and secondary end points in intent-to-treat population (baseline to week 26)

Study End Point	Elevated (C5b-9 >244 ng/ml) Population (Primary Analysis)			Combined (Elevated and Normal C5b-9) Population (Secondary Analysis)		
	Avacopan (n=19)	Placebo (n=21)	Treatment Difference (95% CI)	Avacopan (n=27)	Placebo (n=29)	Treatment Difference (95% CI)
Primary end point—C3 Glomerulopathy Histological Index for disease activity						
LS mean change from baseline (95% CI)	−1.0 (−2.3 to 0.4)	−0.9 (−2.2 to 0.4)	−0.0 (−1.9 to 1.8)	−1.1 (−2.1 to 0.0)	−1.0 (−2.1 to 0.2)	0.1 (−1.4 to 1.7)
Secondary end points						
C3 Glomerulopathy Histological Index 1 for disease chronicity						
LS mean change from baseline (95% CI)	1.1 (0.3 to 1.8)	1.5 (0.9 to 2.2)	−0.5 (−1.5 to 0.5)	0.8 (0.2 to 1.4)	1.5 (0.9 to 2.0)	−0.6 (1.5 to 0.2)
UPCR, g/g						
LS mean ratio compared with baseline (95% CI)	0.84 (0.64 to 1.12)	0.86 (0.66 to 1.12)	0.98 (0.67 to 1.45)	0.73 (0.58 to 0.92)	0.90 (0.72 to 1.13)	0.81 (0.58 to 1.12)
LS mean percent change from baseline (95% CI) ^a	−16 (−36 to 12)	−14 (−34 to 12)		−27 (−42 to −8)	−10 (−28 to 13)	
eGFR, ml/min per 1.73 m ²						
LS mean change from baseline (95% CI)	0.4 (−4.7 to 5.6)	−3.6 (−8.4 to 1.3)	4.0 (−3.1 to 11.1)	−0.6 (−4.6 to 3.5)	−3.0 (−7.0 to 0.9)	2.5 (−3.2 to 8.1)
LS mean percent change from baseline (95% CI)	6.1 (−1.9 to 14.1)	−4.7 (−12.3 to 2.8)	10.8 (−0.2 to 21.9)	3.9 (−2.3 to 10.1)	−6.6 (−12.5 to −0.6)	10.4 (1.8 to 19.0)

C3, complement 3; C5b-9, membrane attack complex or terminal complement complex; CI, confidence interval; LS, least squares; MMRM, mixed effects model for repeated measures; UPCR, urine protein:creatinine ratio.

^aThe primary analysis of percent change from baseline in UPCR was carried out in participants in the intent-to-treat population with elevated membrane attack complex or terminal complement complex at baseline whose UPCR was abnormal (≥ 0.15 g/g) at baseline using a MMRM analysis to calculate the difference between the avacopan and placebo groups at week 26.

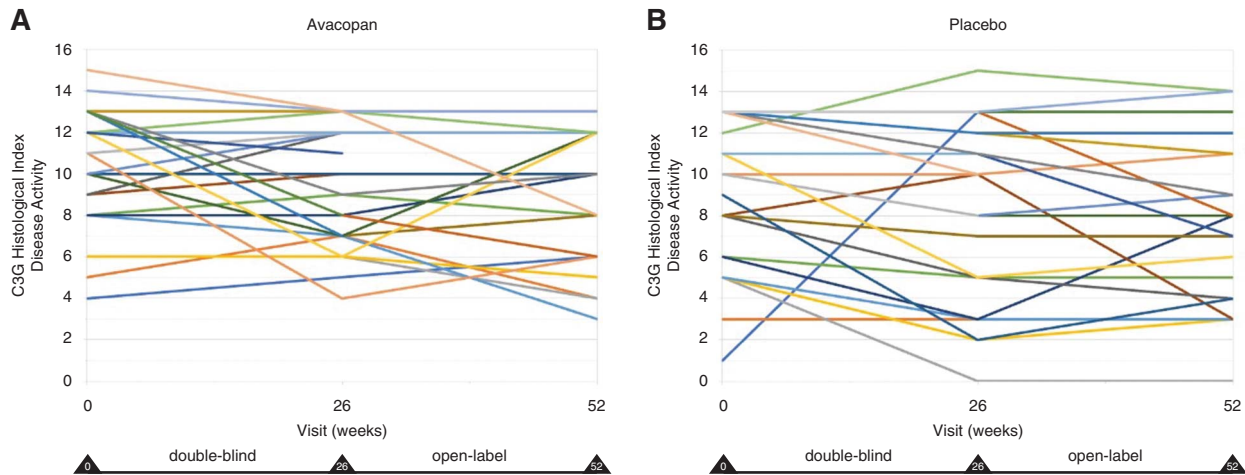


Figure 3. Individual C3 Glomerulopathy Histological Index of disease activity during double-blind and open-label periods. (A) Avacopan and (B) placebo groups. Patients in the placebo arm received avacopan from week 26 to week 52.

and -1.5 (-2.6 to -0.4), respectively, in the elevated C5b-9 strata and -38.2% (-66.7 to -9.7) and -1.3 (-2.2 to -0.4), respectively, in the combined C5b-9 strata. No differences between treatment periods were observed for the avacopan group.

UPCR

The primary analysis of percent change from baseline in UPCR was performed in patients in the ITT population with elevated C5b-9 at baseline whose UPCR was abnormal (≥ 0.15 g/g) at baseline. There was no difference between treatment groups in the percent change from baseline to week 26 for UPCR in the elevated C5b-9 strata; LS mean (95% CI) percent change from baseline at week 26 was -16 (-36 to 12) in the avacopan group and -14 (-34 to 12) in the placebo group (Table 2).

The secondary analysis of this end point in the combined C5b-9 strata of the ITT population also showed

a larger decrease (improvement) in the percent change (95% CI) from baseline to week 26 in UPCR in the avacopan group (-27% [-42 to -8]) than in the placebo (-10% [-28 to 13]) group (Figure 5 and Table 2). In *post hoc* exploratory analysis, greater LS mean (95% CI) decreases (improvement) in UPCR from baseline to week 26 were observed in the patients in the combined C5b-9 strata with UPCR >1 g/g and eGFR <60 ml/min per 1.73 m² (-43% [-59 to -22]) in the avacopan compared with -7% [-31 to 25] in the placebo group). No differences in UPCR between treatment groups were observed from week 26 to week 52 during the open-label period in the elevated or combined C5b-9 strata.

eGFR

The primary analysis of percent change in eGFR from baseline to week 26 in the elevated C5b-9 strata demonstrated no statistically significant difference in the change in eGFR (LS mean percent change [95% CI] of 6.1% [-1.9 to

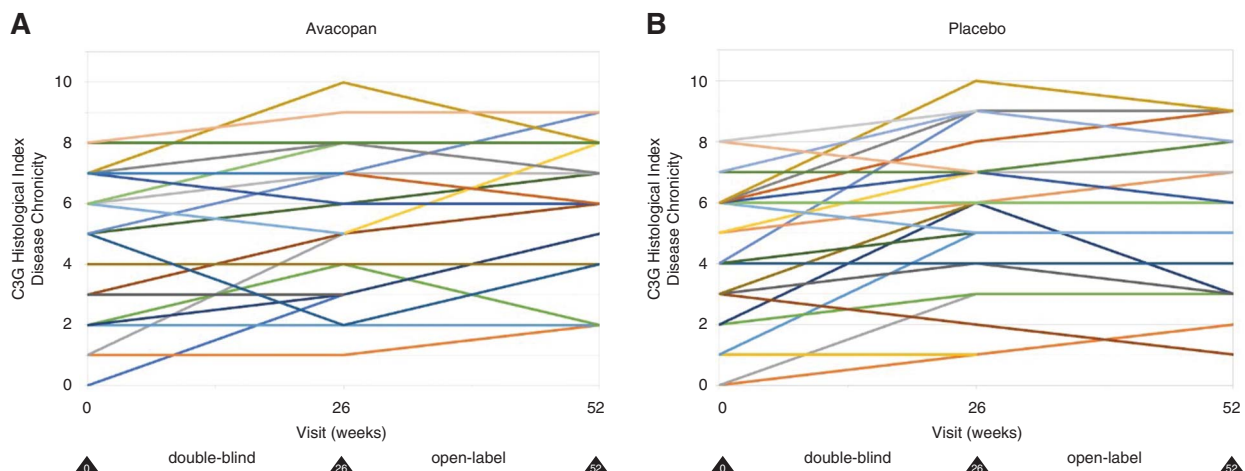


Figure 4. Individual C3 glomerulopathy Histological Index of disease chronicity during double-blind and open-label periods. (A) Avacopan and (B) placebo groups. Patients in the placebo arm received avacopan from week 26 to week 52. The color of lines may appear different if there is overlapping results from more than one participant.

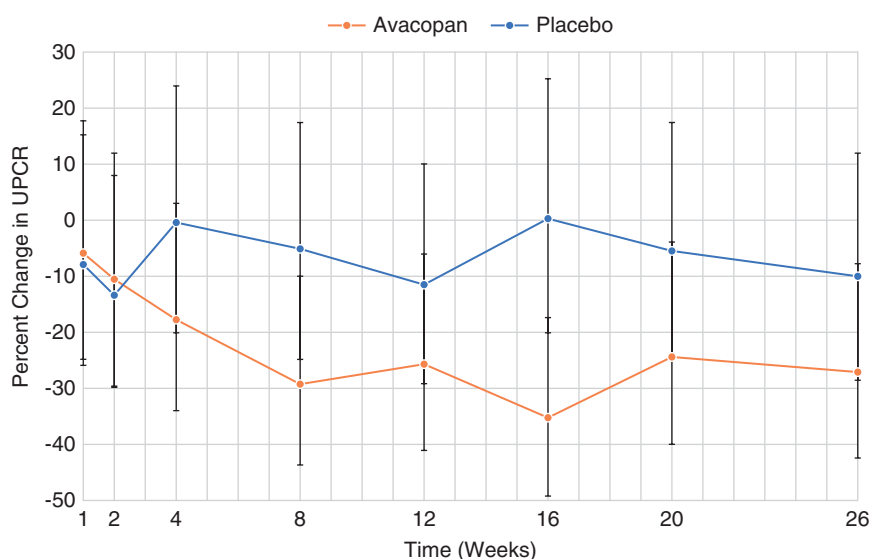


Figure 5. LS mean percent change from baseline (95% CI) in UPCR (g/g) in combined population. CI, confidence interval; LS, least squares; UPCR, urine protein:creatinine ratio.

14.1]) compared with in the placebo group (-4.7% [-12.3 to 2.8]). The corresponding LS mean change (95% CI) in eGFR from baseline to week 26 was 0.4 ml/min per 1.73 m 2 (-4.7 to 5.6) (avacopan group) and -3.6 ml/min per 1.73 m 2 (-8.4 to 1.3) (placebo group) (Table 2). In the subgroup of patients with eGFR <60 ml/min per 1.73 m 2 in the elevated C5b-9 stratum at baseline, the results were generally consistent with the primary analysis of this end point except for the change from baseline at week 26 (treatment difference of 8.0 ml/min per 1.73 m 2) was greater.

A secondary analysis of this end point in the combined C5b-9 strata showed that in participants treated with avacopan, the change in eGFR from baseline to week 26 was 3.9% (-2.3 to 10.1) (LS mean percent change [95% CI]) compared with a decrease of 6.6% (-12.5 to -0.6) in the placebo group (Figure 6 and Table 2). There was no difference between treatment groups in the LS mean change from baseline to week 26. In a subgroup analysis, the treatment effect of avacopan on eGFR between baseline and week 26 in the combined C5b-9 strata in patients with eGFR <60 ml/min per 1.73 m 2 was greater compared with placebo (treatment differences [95% CI] of 6.6 ml/min per 1.73 m 2 [1.2 to 12.1] and 20.7% [5.8 to 35.5]). During the open-label avacopan treatment period in the elevated C5b-9 strata, there were no differences between treatment groups during the avacopan treatment period in the percent change and change in eGFR from week 26 to week 52.

Histological Response

Analyses of the proportion of patients with a histological response, based on a decrease (improvement) in disease activity of at least 35%, showed no differences between the avacopan and placebo groups in either the elevated C5b-9 strata or the combined C5b-9 strata (Table 3). In the elevated C5b-9 strata, two (11%) patients in the avacopan group and four (20%) patients in the placebo group were responders. In the combined C5b-9 strata, four (15%)

patients in the avacopan group and seven (26%) patients in the placebo group met criteria for responders.

Additional Efficacy End Point

Changes in urine MCP1:creatinine ratio during the double-blind treatment period in this population were generally characterized by decreases from baseline in the avacopan group and stable values or increases from baseline in the placebo group (Supplemental Figure 1). During the open-label avacopan treatment period, the percent change from week 26 in urine MCP1:creatinine ratio was not different between treatment groups.

Safety

The mean (SD) duration of exposure to the investigational product (avacopan or placebo) was 46.5 (14.6) weeks in the avacopan group and 50.6 (9.3) weeks in the placebo group.

Overall Summary of AEs in the Double-Blind Treatment Period

The overall patient incidence of AEs was comparable in the avacopan (93%) and placebo (86%) groups. Most AEs reported in both groups were mild or moderate in severity. The most frequently reported AEs in the double-blind treatment period were diarrhea, headache, peripheral edema, and vomiting (Table 4). SAEs were reported during the double-blind treatment period in three patients each in the avacopan (11%) and placebo (10%) groups (Table 5). SAEs assessed by the investigator as possibly related to investigational product were reported in two patients each in the avacopan (7%) and placebo (7%) groups. All SAEs were single occurrences in each group, and all except two (Sjogren's syndrome and AKI) resolved during the study. No patient died during the double-blind treatment period.

The patient incidence of AE leading to discontinuation of investigational product in the double-blind

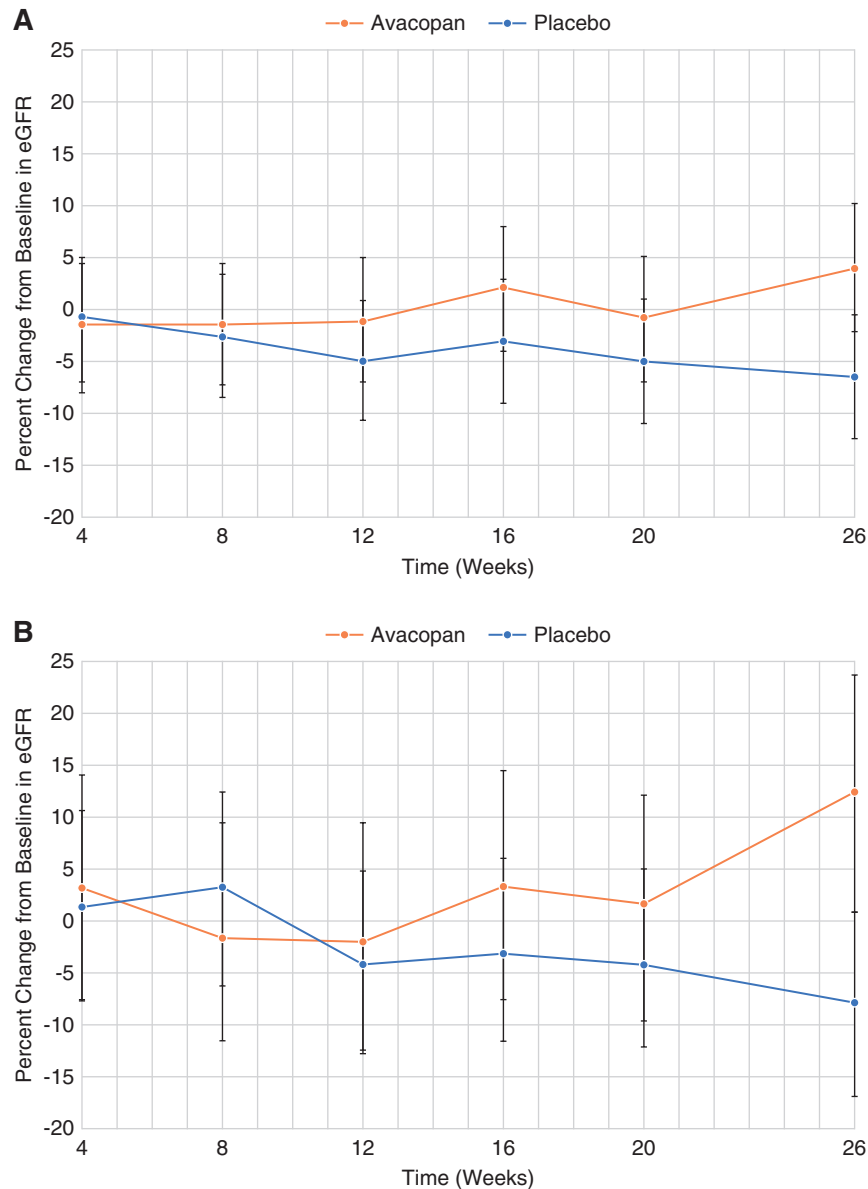


Figure 6. LS mean percent changes from baseline (95% CI). (A) eGFR and (B) subgroup of patients with baseline eGFR <60 ml/min per 1.73 m² in combined population.

treatment period was comparable between treatment groups (one patient in each group). In both cases, the AEs were nonserious.

Reports of AEs and SAEs during the open-label treatment period were comparable with those observed during the double-blind phase (Supplemental Section 4 and Supplemental Tables 1 and 2).

No new safety risks with avacopan were identified from evaluating events of interest. The patient incidence of AEs of interest, including infections, liver and muscle events, hypersensitivity events, and events of decreased white blood cells, were overall similar between the avacopan and placebo groups during both study treatment periods.

No notable differences between treatment groups were observed in chemistry, hematology, and urinalysis laboratory parameters, vital signs, weight, body

mass index, and electrocardiogram findings during the study.

Discussion

ACCOLADE, a double-blind, placebo-controlled, phase 2 study designed to evaluate the efficacy and safety of avacopan 30 mg BID in patients with C3 glomerulopathy, was the largest randomized clinical trial of complement inhibition in this patient population. The primary efficacy end point in this study was kidney histological assessment using a novel disease activity score determined by summing the scores of seven defined components that affect kidney function (*e.g.*, mesangial hypercellularity, endocapillary proliferation, leukocyte infiltration).¹ The primary end point was not met in this study because the percent change from

Table 3. Histologic response in the intent-to-treat population (baseline to week 26)

Response Status	Placebo	Avacopan
Elevated C5b-9 stratum (primary analysis)		
N	20	18
Responder, n (%)	4 (20)	2 (11)
Nonresponder, n (%)	16 (80)	16 (89)
Absolute response rate difference		−8.9%
Relative response rate		0.56
Combined C5b-9 stratum (secondary analysis)		
N	27	26
Responder, n (%)	7 (26)	4 (15)
Nonresponder, n (%)	20 (74)	22 (85)
Absolute response rate difference		−10.5%
Relative response rate		0.59

Histological response is defined as a decrease (improvement) in the C3 Glomerulopathy Histological Index for disease activity of at least 35% from baseline to week 26. C5b-9, membrane attack complex or terminal complement complex.

baseline at week 26 in disease activity was not different between avacopan and placebo groups in the elevated C5b-9 strata, as well as the combined ITT groups. During the double-blind period, change from baseline at week 26 between treatment groups was also similar in the elevated or combined strata for secondary measures of efficacy, including UPCR, eGFR, disease chronicity (*i.e.*,

Table 4. Adverse events ≥10% in either treatment group during double-blind treatment period

Preferred Term	Placebo (N=29), n (%)	Avacopan (N=28), n (%)
Any AE	25 (86)	26 (93)
Edema peripheral	1 (3)	5 (18)
Headache	2 (7)	5 (18)
Vomiting	2 (7)	4 (14)
Diarrhea	4 (14)	3 (11)
Fatigue	0 (0)	3 (11)
Blood creatine phosphokinase increased	1 (3)	3 (11)
Blood creatinine increased	0 (0)	3 (11)
Weight decreased	0 (0)	3 (11)
Anemia	3 (10)	3 (11)
Lymphopenia	0 (0)	3 (11)
Decreased appetite	0 (0)	3 (11)
Hypertension	3 (10)	3 (11)
Upper respiratory tract infection	3 (10)	2 (7)
Abdominal pain	3 (10)	2 (7)
Nasopharyngitis	3 (10)	1 (4)
Nausea	3 (10)	1 (4)
Back pain	3 (10)	1 (4)
Muscle spasms	3 (10)	0 (0)

N=number of patients randomized to treatment group in the safety population in the specified group during the double-blind treatment period; n=number of patients in specified category. AE, adverse event.

Table 5. Serious adverse events during double-blind treatment period

Preferred Term	Placebo (N=29), n (%)	Avacopan (N=28), n (%)
Any SAE	3 (10)	3 (11)
Gastroenteritis salmonella	0 (0)	1 (4)
Neutropenic sepsis	0 (0)	1 (4)
Pneumonia	1 (3)	1 (4)
Bacterial parotitis	1 (3)	0 (0)
Bronchitis	1 (3)	0 (0)
Neutrophil count decreased	0 (0)	1 (4)
Sjogren's syndrome	0 (0)	1 (4)
AKI	0 (0)	1 (4)
Alcohol withdrawal syndrome	1 (3)	0 (0)

The safety population in the double-blind treatment period was defined as all patients who received at least one dose of investigational product in the double-blind treatment period. N=number of patients randomized to treatment group in the safety population in double-blind treatment period in specified group; n=number of patients in specified category; %=100×n/N. SAE, serious adverse event.

measure of kidney damage), histological response, and urine MCP1:creatinine ratio.

Despite the robustness of disease activity in determining ongoing glomerular injury, it is a snapshot of kidney function at week 26. The disease chronicity is an equally meaningful measure because it evaluates accumulated kidney damage over the course of disease. In this study, the changes from baseline at week 26 for disease chronicity were no different between the placebo and the avacopan group. During the open-label avacopan treatment period, the change from week 26 to week 52 in disease chronicity was different from the change from baseline at week 26 for the combined group. This finding may indicate that patients who continued to receive avacopan up to week 52, as well as those randomized to placebo and then switched to avacopan at week 26, experienced less kidney damage accumulation over time. The implications of this finding are uncertain and should be further explored in future studies. However, there may be a role of C5aR blockade in slowing progression of C3 glomerulopathy, particularly in patients who have already accrued some degree of chronic injury.

Traditional clinical parameters may not fully capture the progression of C3 glomerulopathy, which is why this study based its primary outcome on histology; however, these data provide important information about the extent of kidney function changes. In this study, the changes from baseline at week 26 for both UPCR and eGFR end points were slightly improved in the avacopan group compared with placebo in the combined group. These improvements in UPCR appeared larger in the exploratory *post hoc* analyses in subgroup of patients with UPCR >1 g/g and eGFR <60 ml/min per 1.73 m². Similarly, larger improvements in eGFR from baseline to week 26 were shown in the avacopan group compared with the placebo group in the exploratory *post hoc* analyses in subgroup of patients with eGFR <60 ml/min per 1.73 m².

Avacopan is a selective C5aR antagonist that inhibits the interaction of C5aR and anaphylatoxin C5a.^{11,14} Avacopan does not seem to affect C5b-9 production, thereby not affecting the membrane attack complex.¹⁰ Furthermore, owing to its selective mode of action, avacopan may not interfere with the upstream components of the complement cascade and preserves the beneficial, anti-inflammatory functions of the C5L2 pathway.^{14,15} Evidence from animal models suggests that inhibition of C5a may be more important than inhibition of C5b-9 in C3 glomerulopathy because deletion of complement 6, which is part of the C5b-9 complex, in complement factor H knockout mice failed to protect the mice from developing symptoms of C3 glomerulopathy.⁶ These preclinical data, in conjunction with supportive clinical and kidney outcome observed in patients with GPA or MPA, suggested that the mode of action of avacopan could provide anti-inflammatory effects and improve kidney function in patients with C3 glomerulopathy. Despite no statistical differences in primary efficacy end points between avacopan and placebo, some of the data, along with subgroup analyses, show positive trends in the kidney effects of avacopan in these patients. The effects of avacopan on mitigating chronicity changes compared with placebo suggest a potential role for this agent as a disease-stabilizing therapy, which may be particularly beneficial in mild to moderate disease, and when used early in the disease course. Despite not affecting C3 deposition, the ability to reduce the inflammatory response elicited by C5a and the ensuing risk of accumulated chronicity from unchecked anaphylatoxin effect suggests a potential rationale for avacopan.

The safety data from this study collected over a 52-week treatment period and the 8-week follow-up period did not identify significant safety concerns, and avacopan was generally well tolerated in patients with C3 glomerulopathy. The incidence, type, and severity of AEs and SAEs and those leading to discontinuation of investigational treatment were comparable with those reported in the placebo group. More specifically, infection, liver and muscle events, hypersensitivity events, and decreases in white blood cells were similar between the treatment groups. Exposure to avacopan did not show any trends indicative of treatment-related laboratory abnormalities, as well as no effects on vital signs, including BP, electrocardiogram, or body mass index.

This trial had some limitations, most notably the small sample size ($N=57$), which may have contributed to the observed study results, despite this being the largest randomized clinical trial in C3 glomerulopathy to date. The patient population in the study was mostly a prevalent disease population, with most patients being enrolled at approximately 4 years after their initial diagnosis. Conceivably, a benefit of avacopan on disease activity, not seen in this study, may have been apparent in a study limited to incident disease when the disease is at its most active and before any disease chronicity has ensued. In addition, the ACCOLADE study population had elevated and normal C5b-9 values; however, it is possible that the selection of another biomarker for stratification, like C5a, would have been more meaningful and sensitive for this trial. Finally, considering the complexity of C3 glomerulopathy disease

and trial design requirements, the duration of treatment may not have been optimal, as a longer study period could have been more appropriate to assess kidney function and damage, especially if changes in chronicity indices (both histologically and by eGFR) are to be used.

In conclusion, ACCOLADE was a randomized, double-blind, placebo-controlled, phase 2 global study in 57 patients that evaluated the safety and efficacy of avacopan 30 mg BID compared with placebo in improving kidney function in patients with the rare disease of C3 glomerulopathy. The primary end point for the study was not met; other clinical effects of avacopan to improve certain key kidney function parameters and slow disease progression were variable and require further evaluation. Safety data from this study, collected over a 52-week treatment period and an 8-week follow-up period, did not identify any safety concerns with avacopan, which was well tolerated in this patient population.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at <http://links.lww.com/JSN/E901>.

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Data Sharing Statement

There is a plan to share clinical study data. This may include deidentified individual patient data for variables necessary to address the specific research question in an approved data sharing request; also related data dictionaries, study protocol, statistical analysis plan, informed consent form, and/or clinical study report. Data sharing requests relating to data in this manuscript will be considered after the publication date and (1) this product and indication (or other new use) have been granted marketing authorization in both the US and Europe, or (2) clinical

development discontinues, and the data will not be submitted to regulatory authorities. There is no end date for eligibility to submit a data sharing request for these data. Qualified researchers may submit a request containing the research objectives, the Amgen product(s) and Amgen study/studies in scope, end points/outcomes of interest, statistical analysis plan, data requirements, publication plan, and qualifications of the researcher(s). In general, Amgen does not grant external requests for individual patient data for the purpose of reevaluating safety and efficacy issues already addressed in the product labeling. A committee of internal advisors reviews the requests. If not approved, requests may be further arbitrated by a Data Sharing Independent Review Panel. Requests that pose a potential conflict of interest or an actual or potential competitive risk may be declined at Amgen's sole discretion and without further arbitration. Upon approval, information necessary to address the research question will be provided under the terms of a data sharing agreement. This may include anonymized individual patient data and/or available supporting documents, containing fragments of analysis code were provided in analysis specifications. Further details are available at the following: <https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request>.

Supplemental Material

This article contains the following supplemental material online at <http://links.lww.com/JSN/E900>.

Supplemental Listing 1. List of study principal investigators.

Supplemental Section 1. Complete list of study inclusion and exclusion criteria.

Supplemental Section 2. Prior and concomitant treatment.

Supplemental Section 3. Description of statistical analysis methods of primary and secondary end points.

Supplemental Section 4. Summary of safety findings during open-label period.

Supplemental Table 1. Adverse events $\geq 10\%$ in either treatment group during open-label treatment period.

Supplemental Table 2. Serious adverse events during open-label treatment period.

Supplemental Figure 1. LS mean percent change from baseline (95% CI) in urine MCP1:creatinine ratio in combined population.

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