FDA Briefing Document

Arthritis Advisory Committee Meeting
May 06, 2021

NDA# 214487
Drug name: avacopan

Proposed indication: treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA])

Applicant: ChemoCentryx, Inc.

Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the drug avacopan NDA 214487 for treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Introduction

Thank you for your participation in the Arthritis Advisory Committee (AAC) meeting to be held on May 6, 2021. As members of the AAC, you provide important expert scientific advice and recommendations to the U.S. Food and Drug Administration (the Agency) on the regulatory decision-making process related to the approval of a drug or biologic product for marketing in the United States. The upcoming meeting is to discuss New Drug Application (NDA) 214487 from the Applicant, ChemoCentryx, Inc., for the new molecular entity (NME) avacopan, an oral small molecule C5a receptor inhibitor, proposed for the treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]). The proposed dosing is 30 mg oral capsules twice daily.

ChemoCentryx, Inc. submitted the results of a single phase 3 study, CL010_168, and two phase 2 studies, CL002_168 and CL003_168. The focus of the AAC discussion will be data from Study CL010_168, also referred to as ADVOCATE, that compared avacopan to standard of care (protocol-specified 20-week prednisone taper) in patients with AAV; patients in both arms received a background of either rituximab or cyclophosphamide standard induction regimen. Study CL010_168 evaluated non-inferiority and superiority of avacopan compared to the control group at Week 26 and at Week 52. Complexities of the study design, as detailed in the briefing document, raise questions about the interpretability of the data to define a clinically meaningful benefit of avacopan and its role in the management of AAV. We ask for your input on the efficacy results, including their clinical meaningfulness, and the benefit-risk assessment of avacopan for the proposed indication. The Executive Summary provides a brief overview of the application and an introduction to the main issues for discussion, which are addressed in more detail in the review below.

Executive Summary

Background

ChemoCentryx has proposed avacopan, a new molecular entity C5a receptor antagonist, for treatment of adult patients with ANCA-associated vasculitis (GPA and MPA). The proposed dosing regimen is 30 mg twice daily orally. To support the NDA, the Applicant has provided data from Study CL010_168, a 60-week, phase 3, randomized, double-blind, double-dummy, active-controlled study, and two phase 2 studies, CL002_168 and CL003_168.

ANCA-associated vasculitides (AAV) are systemic vasculitides affecting small to medium-size vessels, associated with the presence of anti-neutrophil cytoplasmic antibody (ANCA), and include granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome). Treatment of severe AAV is generally initiated with induction therapy of glucocorticoids and either cyclophosphamide or rituximab, until remission is achieved. Maintenance therapy is utilized to prevent relapse and disease- and treatment-related morbidity and mortality.[1] Current treatment guidelines for

[1] Geetha D and Jefferson JA. ANCA-associated vasculitis: core curriculum 2020. *Am J Kidney Dis*. 2019; 75: 124-137.

maintenance therapy recommend low-dose glucocorticoids and either azathioprine, rituximab, methotrexate, or mycophenolate mofetil for at least 24 months after induction of sustained remission.[2] Rituximab is the only FDA-approved therapy for GPA and MPA in adult and pediatric patients 2 years of age and older in combination with glucocorticoids.[3]

Study Design

In Study CL010_168, 331 patients with ANCA-associated vasculitis were randomized to receive avacopan 30 mg twice daily (BID) for 52 weeks or a protocol-specified 20-week prednisone taper. Randomization was stratified based on three factors: 1) receiving IV rituximab, IV cyclophosphamide, or oral cyclophosphamide, 2) Proteinase-3 (PR3) or myeloperoxidase (MPO) ANCA-associated vasculitis, and 3) newly diagnosed or relapsing ANCA-associated vasculitis. Patients who received cyclophosphamide induction treatment received azathioprine as maintenance therapy, while patients who received rituximab induction treatment did not receive any maintenance therapy. Figure 1 presents the schematic of the study design.

The primary endpoints were the proportion of patients achieving disease remission at Week 26 and the proportion of patients achieving sustained remission at Week 52, each evaluated using the Birmingham Vasculitis Activity Score (BVAS)[4]. Disease remission was defined as a BVAS of 0 as determined by the Adjudication Committee and no glucocorticoids given for AAV within 4 weeks prior to assessment. Sustained remission required disease remission at Weeks 26 and 52 along with no relapses between Weeks 26 and 52. Detailed discussion of the definitions of these two endpoints and the planned analyses are located in the Background below. Each endpoint was tested for non-inferiority and superiority based on a pre-specified hierarchical multiple testing procedure. The study also evaluated multiple secondary endpoints; however, they were not adjusted for the multiplicity and thus should be considered purely exploratory. When there is more than one study endpoint, care must be taken to ensure that the evaluation of multiple hypotheses does not lead to inflation of the study's overall Type I error probability. The inflation of the Type I error rate can be quite substantial if there are many comparisons[5]. Hence, a nominal significance achieved by a secondary endpoint should be interpreted with caution.

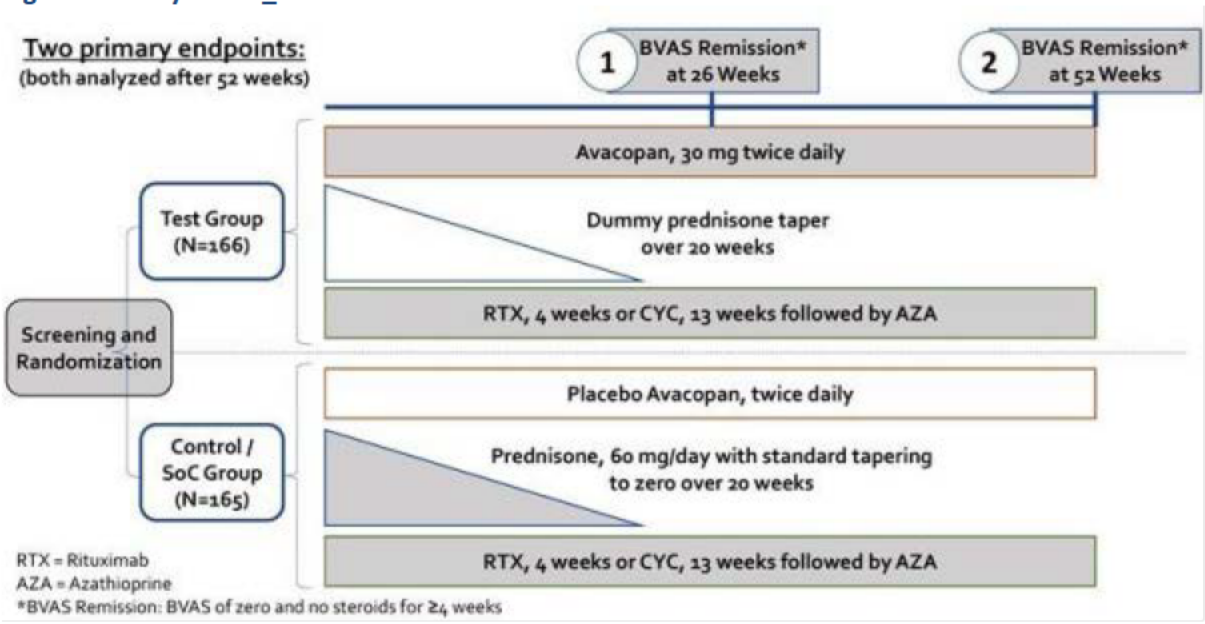
[2] Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis*. 2016; 75:1583-1594.

[3] FDA-approved rituximab labeling

[4] BVAS is a clinical scoring system of disease activity to identify active vasculitis in nine organ systems, including general, cutaneous, mucous membranes, ENT, chest, cardiovascular, abdominal, renal, and nervous system, and an "other" category. BVAS total scores can range from 0 to 63, with higher scores indicating higher disease activity. Scores are weighted based on the severity of signs and symptoms.

[5] See the FDA draft guidance *Multiple Endpoints in Clinical Trials Guidance for Industry* for further reference

Figure 1. Study CL010_168 Schematic



Source: NDA submission

Primary Endpoints: BVAS Remission at Week 26 and 52

In the phase 3 Study CL010_168, approximately 72% of the patients on the avacopan arm and 70% of the patients on the prednisone arm achieved remission at Week 26. The estimated difference in remission rate between avacopan and prednisone was 3.4%. A greater proportion of avacopan-treated patients (65.7%) compared to prednisone-treated patients (54.9%) achieved sustained remission at Week 52. According to the Applicant's sequential multiple testing procedure, noninferiority was first assessed at Week 26 and then at Week 52, followed by superiority tested at Week 52 and then Week 26. The first three tests were statistically significant, while the test of superiority at Week 26 was not statistically significant. The primary analyses of the study are summarized in Table 1.

Table 1. Primary Analysis of Remission at Week 26 and Sustained Remission at Week 52

	Avacopan (N=166)	Prednisone (N=164)	Difference	Non-inferiority p-value	Superiority p-value
Remission at Week 26	120 (72.3%)	115 (70.1%)	3.4%	<0.0001	0.48
95% CI	(64.8, 78.9)	(62.5, 77.0)	(-6.0, 12.8)		
Sustained Remission at Week 52	109 (65.7%)	90 (54.9%)	12.5%	<0.0001	0.0132
95% CI	(57.9, 72.9)	(46.9, 62.7)	(2.6, 22.3)		

Scores are based on the Adjudication Committee.
Abbreviations: N=the number of patients randomized who received at least one dose of drug; CI=confidence interval.
Counts and percentages relative to N.
Two-sided p-values from the Summary Score test adjusted for randomization strata were reported. Missing data at Week 26 and Week 52 were imputed as not achieving remission (Week 26) or sustained remission (Week 52), respectively.
For non-inferiority test, margin of 20% is used.
Source: Statistical Reviewer.

Although primary efficacy comparisons were statistically significant, the review team has identified several areas of concern, raising uncertainties about the interpretability of these data and the clinical meaningfulness of these results, as summarized below:

(1) At Week 26, the proportion of patients in disease remission in the avacopan group (72.3%) was non-inferior to the prednisone group (70.1%) according to the Applicant's testing plan. However, superiority was not met. In pre-submission communications, FDA stated that a non-inferiority comparison would not be sufficient to show that avacopan can replace glucocorticoids as it would be difficult to establish whether avacopan is effective or whether rituximab/cyclophosphamide was the primary driver of the efficacy in both treatment arms. In addition, the Agency expressed concerns about the ability to adequately justify an acceptable non-inferiority margin, given that there were no historical trials appropriate to estimate the contribution of glucocorticoids to the treatment effect of glucocorticoids and cyclophosphamide or rituximab in the control arm. As discussed below, the justification for the non-inferiority (NI) margin was based on studies of different types of vasculitides, with different concomitant therapies, and of various designs that would not be considered appropriate to inform a NI margin for the study.

(2) Interpretation of the non-inferiority at Week 26 is further limited by the large number of patients in the avacopan arm (86%) who received non-study supplied glucocorticoids from Week 0 to 26. While the mean cumulative glucocorticoid dose per patient over Week 0 to 26 was lower (1072.9 mg) in the avacopan-treated patients compared to the mean cumulative dose in the prednisone-treated patients (3192.5 mg), the non-inferiority assessment is not a comparison of avacopan vs. prednisone, but instead avacopan plus lower dose glucocorticoids vs. higher dose glucocorticoids. At this time, it is not clear how much reduction in glucocorticoids would be considered clinically meaningful and if the protocol-specified higher dose of glucocorticoids is required for control of disease activity. Therefore, the interpretability and meaningfulness of this comparison is challenging. This issue is further discussed below under Glucocorticoid Use.

(3) The clinical pharmacology program has identified avacopan as a CYP3A4 inhibitor that has the potential to increase exposures to systemic glucocorticoids which are CYP3A4 substrates, raising further uncertainties about the true difference in glucocorticoid exposures and its impact on the non-inferiority comparisons between the two groups at Week 26, and respectively the proposed role of avacopan as a steroid-sparing agent, as glucocorticoid exposures were not assessed in Study CL010_168.

(4) At Week 52, there was a disparity in observed treatment effects between the subgroups that received rituximab and cyclophosphamide (IV and oral) induction treatment. The estimated risk difference for disease remission at Week 52 was 15.0% (95% CI: [2.2%, 27.7%]) in the subgroup receiving induction with rituximab and 3.3% (95% CI: [-14.8%, 21.4%]) in the cyclophosphamide plus maintenance azathioprine subgroup (Table 10). Based on the data, there is no evidence of clinically meaningful treatment effect in the cyclophosphamide induction subgroup. Further, the

treatment comparison in the complementary rituximab induction subgroup may not be considered meaningful because these patients did not receive maintenance therapy, i.e., due to undertreating of patients, the effect observed in the rituximab subgroup may not represent a clinically meaningful treatment effect compared to standard of care. Thus, the observed superiority at Week 52 may be a result of the treatment difference in the subgroup receiving induction with rituximab. We note that, at the time the study was designed, repeat dosing with rituximab was not established as maintenance therapy; however, long-term immunosuppression had been demonstrated to reduce disease relapse and was standard-of-care. The result of the subgroup analysis suggests the possibility that avacopan was efficacious only in the population who did not receive standard-of-care maintenance immunosuppression therapy and may be considered undertreated, raising questions about the adequacy of the comparisons and clinical meaningfulness of the avacopan effect at Week 52.

(5) There were differences between the assessments performed by the Investigator and the Adjudication Committee, most frequently related to the attribution of persistent vasculitis which was not captured in the modified BVAS administered in the study. Discrepancies between the Investigator and Adjudication Committee occurred in 17 patients at Week 52. Statistical analyses of the primary endpoint using the Investigator assessment of BVAS remission resulted in more conservative estimates of treatment effect, e.g., statistical significance for superiority would no longer be demonstrated with these scores. While the pre-specified analysis used the Adjudicator assessments, the assessment based on the Investigators, experienced in management of vasculitis, may better reflect real-world use.

As detailed in the Section on Pertinent Regulatory History (Table 2), during the avacopan clinical development, including the phase 3 design stages, the Agency communicated many of the concerns with the design of Study CL010_168. To help address these concerns, the Agency has proposed to the Applicant several alternative trial designs that could more directly and reliably assess the efficacy of avacopan for the proposed indication and mitigate many of the uncertainties discussed above. Additional considerations on the alternative trial designs are discussed in Appendix 1: Alternative Trial Design Considerations. Assessment of glucocorticoids pharmacokinetics in any of the alternative study designs could also address the potential for clinically meaningful drug-drug interactions between avacopan and glucocorticoids where co-administration can result in increased systemic exposure to glucocorticoids, as detailed in the section on Clinical Pharmacology.

Secondary Endpoints and Other Assessments

Glucocorticoid Use

While only the prednisone group was intended to receive the protocol-specified prednisone taper, 87% of patients in the avacopan treatment group also received glucocorticoids during the study for vasculitis, adrenal insufficiency, and other clinical conditions (e.g., asthma, allergic reaction, arthritis, gout) at the Investigator's discretion. Although the protocol specified that glucocorticoids above the protocol-specified taper should be discontinued by Week 4, 86% of patients in the avacopan arm received

glucocorticoids from Week 0 to 26 (albeit at lower mean nominal doses compared to the prednisone arm). Further, glucocorticoid use from Week 26 to Week 52 was similar between the prednisone and avacopan groups. Therefore, the increased glucocorticoid use in the prednisone arm compared to the avacopan arm was limited to the period of the first 20 weeks of the study. The clinical relevance of the differences in the nominal glucocorticoid doses used from Week 0 to 26 between the prednisone and avacopan arms is uncertain, as it may be an artifact of the study design rather than a reflection of avacopan's control of disease activity.

To support the assessment of steroid-sparing effect of avacopan, the Applicant employed a novel instrument, Glucocorticoid Toxicity Index (GTI). The GTI is an instrument of weighted domains of labs, clinical measures, and symptoms/toxicities developed to assess toxicities associated with glucocorticoid use, with a Cumulative Worsening Score (CWS) intended to capture cumulative toxicity over time, and an Aggregate Improvement Score (AIS) intended to capture both improvement and worsening of toxicity over time. In CL010_168, at Weeks 13 and 26, the least squares mean of the GTI CWS and AIS were nominally significantly lower in the avacopan group than the prednisone group. However, differences in GTI between the treatment groups may reflect the study design which specified the prednisone doses to be used in the control group, rather than dosing glucocorticoids based on Investigator assessment of active disease. GTI was not assessed at later time points to assess the effects of glucocorticoids after completion of the pre-specified prednisone taper. In the case of Study CL010_168, where differences in glucocorticoid use were pre-specified in the protocol, the GTI does not provide information beyond that of the cumulative glucocorticoid doses to further inform the effect of avacopan. Further, GTI is a novel instrument for which there is no regulatory precedent, and a minimally clinically important difference (MCID) has not been established in AAV. Importantly, while the GTI is intended to evaluate the toxicities of glucocorticoids, avacopan does not impact the same mechanism of action, and may not be expected to have the same toxicities. Therefore, the assessment for only toxicities associated with the control treatment, in the absence of inclusion of assessment of toxicities of the investigational product, is biased as an assessment of overall safety.

Finally, interpretation of the differences in use of glucocorticoids are confounded by a potential drug-drug interaction (DDI) between avacopan and prednisone. In DDI study CL008_168, the systemic exposure of a CYP3A4 substrate increased up to 81% when co-administered with avacopan under fasted condition. Prednisone and non-study supplied glucocorticoids used in Study CL010_168 are all CYP3A4 substrates. While in Study CL003_168, prednisone concentrations could not be accurately quantified in most of the subjects, and prednisone exposure could not be adequately compared, limiting conclusions about a drug-drug interaction, the potential exposure increase of glucocorticoids when co-administered with avacopan due to DDI could not be ruled out. Therefore, while the cumulative glucocorticoid use was greater in the prednisone arm in Study CL010_168, the potential drug interaction between avacopan and prednisone raises questions about whether differences in glucocorticoid use between the avacopan and control arms based on the nominal doses of glucocorticoids used reflect true differences in glucocorticoid exposures and about the role of avacopan as a steroid-sparing agent.

The Agency acknowledges that reducing glucocorticoid use is an important goal in treatment of patients if it occurs in the context of a treatment that effectively controls disease activity. In that context,

reduced use of glucocorticoids has been described in product labels in other indications. Steroid-sparing has typically been used as supportive evidence of efficacy and not as the primary evidence of efficacy, as there is no universal definition of "steroid-sparing" effect or the magnitude of such effect on clinically meaningful outcomes. Importantly, sparing the use of glucocorticoids refers to sparing the toxicity of chronic non-physiologic/higher dose glucocorticoid treatment, i.e., safety, rather than efficacy. Respectively, such an assessment should also consider the overall safety of the investigational product, which in the case of avacopan is limited by the amount and extent of the safety database, as discussed in the section on Safety below.

Relapse

Relapse was defined as occurrence of at least one major item, at least 3 non-major items, or 1 or 2 non-major items for at least 2 consecutive visits on the BVAS after remission (BVAS=0) had been achieved.[6] There were more adjudicated relapses after remission in the prednisone group as compared to the avacopan group (33 relapses vs. 16 relapses, respectively, Table 17). Relapse was also assessed in a time-to-event analysis by the Applicant. However, the study was not designed to assess time to relapse or proportion of relapses. The time-to-relapse and proportion of relapse analyses based on the subset of patients who achieved remission condition on post-randomization variables, i.e., having first achieved remission and the timing of achieving remission. As a result, the subset of patients included in the analysis of these endpoints and the time those patients are at risk for relapse can no longer be assumed to be similar across treatment arms. The advantages of randomization are eliminated because the treatment arms are no longer balanced with respect to possible confounders, leading to biased comparisons between treatment arms and limiting the interpretability of these results. For example, remission may be achieved in different types of patients in the two treatment arms. Thus, when the treatment arms are compared with respect to relapse, differences cannot be attributed to the treatment, but rather to differences in the characteristics of the subset of patients included in the analysis. In addition, as noted earlier, the rituximab induction subgroup did not receive any maintenance therapy, raising the question of the adequacy of these comparisons and clinical meaningfulness of the avacopan effect between Weeks 26 and Week 52. The Agency has considered this analysis of relapse after remission to be exploratory, as detailed in the pertinent regulatory history section (Table 2).

Other Secondary Endpoints

The secondary endpoints also included, but are not limited to, Vasculitis Damage Index (VDI), renal assessments for change in eGFR and percent change in urinary albumin: creatinine ratio (UACR) in patients with renal disease at baseline, and quality of life measures. Similar mean increase in Vasculitis

[6] In Study CL010_168, a relapse was defined as worsening of disease, after having previously achieved remission (BVAS=0) at any time during the treatment period, whereas disease remission for the primary endpoint assessment was defined as achieving a BVAS of 0 and not taking glucocorticoids for AAV for 4 weeks prior to Week 26.

Damage Index, an instrument intended to assess cumulative organ damage as a result of ANCA-associated vasculitis, were observed between treatment groups from baseline to Week 52 (prednisone 1.13, avacopan 1.16, Table 18). Mean improvement in eGFR from baseline to Week 52 for patients meeting BVAS criteria for renal disease at baseline was greater in the avacopan group compared to the prednisone group (7.3 and 4.0 mL/min/1.73 m^2, respectively) with a model-based mean difference of 3.3 (95% CI: [-0.4, 6.9][7]). The clinical relevance of the small difference in change in eGFR over 52 weeks is uncertain. In addition, by 8 weeks post-treatment, the mean eGFR difference decreased to 0.6 mL/min/1.73 m^2. Percent change in UACR at Week 52 was similar in the avacopan and prednisone arms (-74% change from baseline and -77% change from baseline, respectively). Need for dialysis was also similar between groups (4 patients in the prednisone group vs. 3 patients in the avacopan group). Favorable trends towards improvement in general quality of life instruments, including SF-36 and EQ-5D-5L, were observed in the avacopan group as compared to the prednisone group at Weeks 26 and Week 52. However, (b) (4) , these are general quality of life instruments, not specific to vasculitis. Overall, the secondary endpoints do not provide additional support of a clinically meaningful treatment benefit for avacopan.

SEE ATTACHED ERRATA

Safety

The safety database for avacopan in AAV is relatively small (n=239 including the phase 2 studies), particularly for the adequate assessment of rare and latent adverse events which could be associated with chronic immunosuppression. Only 166 patients were exposed to avacopan in the 52-week phase 3 study. In Study CL010_168, adverse events (AEs) were generally similar between the avacopan and prednisone groups. The proportion of patients with TEAEs (98.8% vs. 98.2%), severe AEs (23.5% vs. 25.0%), AEs leading to discontinuation of study medication (16.3% vs. 17.1%) and SAEs (42.2% vs. 45.1%) were similar between the avacopan and the prednisone treatment groups, respectively. Deaths were rare, 2 in the avacopan arm and 4 in the control arm. Treatment-emergent infections, serious infections, and opportunistic infections were similar or fewer in the avacopan group. No *Neisseria meningitidis* infections were reported. One avacopan-treated patient had life-threatening hepatitis B reactivation during the follow-up period after rituximab treatment. A greater proportion of avacopan-treated patients had AEs associated with hepatic abnormalities (13.3% vs. 11.6%), including hepatobiliary disorders (3.6% vs. 0.6%). The proportion of patients with AEs and SAEs within the hepatobiliary system organ class were also greater in the avacopan group (6.0% and 3.6 %, respectively) as compared to the prednisone group (1.8% and 0.6%, respectively). One patient had an SAE of hepatocellular injury with

[7] Derived from a mixed effects model for repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction as factors, and baseline as covariate. An unstructured covariance matrix was used to model the within-subject variance-covariance structure for the model errors. In the statistical analysis plan (SAP), the applicant proposed a Toeplitz covariance matrix. However, the SAP was submitted to the Agency after the data were unblinded, limiting the utility of Agency comments on pre-specified analyses. In this Backgrounder, the analysis results based this analysis model with an unstructured covariance matrix, which requires no assumption on the within-subject variance-covariance structure, are presented.

increase in liver enzymes upon rechallenge with avacopan. One patient had an SAE of hepatic function abnormal with improvement in liver enzymes after discontinuation of avacopan; this patient was also found to have a positive hepatitis B DNA assay was treated with entecavir and did not resume avacopan. The Investigator assessed the event as possibly related to avacopan, but attribution of the event is confounded by the subsequent diagnosis of hepatitis B. One patient had an SAE of severe hepatic function abnormal and met Hy's Law laboratory criteria with a liver biopsy that was suggestive of drug-induced hepatitis; however, this patient also received multiple other drugs associated with liver enzyme elevations. AEs associated with hepatic abnormalities led to drug discontinuation in 7 patients in the avacopan arm and 2 patients in the prednisone arm. In addition, there were 2 patients with angioedema (1 serious) in the avacopan group, compared to none in the prednisone group. Given the small safety database, conclusions are limited, however, imbalances in hepatotoxicity, liver enzyme elevations, and angioedema are observed despite the small sample size.

Phase 2 Studies

The Applicant submitted two randomized, double-blind, placebo-controlled phase 2 studies that provide limited supportive efficacy data. Both studies were of short duration (12 weeks) and evaluated a different primary endpoint than that assessed in the phase 3 study. This endpoint was based on a BVAS 50% response, defined as BVAS percent reduction from baseline of at least 50% plus no worsening in any body system component. At the end-of-phase 2 meeting, the Agency advised the Applicant that the clinical meaningfulness of BVAS 50% response is unknown and that the results were not supported by other important endpoints, such as BVAS remission, in either study. In CL002_168, BVAS 50% response was higher in the group that received avacopan plus reduced dose prednisone, compared to the avacopan plus no prednisone group or the full dose prednisone group. The study design that included two interventions, treatment with avacopan vs. placebo and the use of different prednisone regimens in each arm, as well as the endpoint assessment at a timepoint when patients continued to receive protocol-specified prednisone, limits a determination of a treatment effect of avacopan. In CL003_168, the phase 2 dose-ranging study, no dose-response was observed for avacopan; the greatest BVAS 50% response was reported in the 10 mg avacopan arm (91.7%), while lower response rates were reported in the 30 mg avacopan arm (80.0%) and control standard of care arm (84.6%). Similarly, BVAS remission, defined as BVAS of 0 at Week 12, was also lowest in the avacopan 30 mg plus standard of care group. All treatment groups received prednisone standard of care in this study, and a meaningful treatment effect of avacopan as add-on to glucocorticoids could not be concluded. Overall, the phase 2 data do not appear to provide support for the efficacy of avacopan over standard of care nor support for avacopan as a steroid-sparing agent, as proposed by the Applicant.

Benefit-Risk Considerations

AAV is a rare and serious disease associated with high morbidity and mortality. It is also a disease with high unmet need for new therapies. Given these considerations, in principle, a single adequate and well-controlled (AWC) study may be considered to establish substantial evidence of efficacy. However, in

CL010_168, there are substantial uncertainties around the phase 3 study design and results, raising questions about the adequacy of this single trial to inform the benefit-risk assessment.

Study CL010_168 demonstrated non-inferiority of avacopan to a pre-specified prednisone taper at Weeks 26 and 52 with both arms receiving background therapy and non-study specified glucocorticoids. However, throughout development, FDA reiterated that a non-inferiority comparison would not be sufficient to show that avacopan can replace glucocorticoids as it would be difficult to distinguish whether avacopan is effective or whether the induction treatment with rituximab/cyclophosphamide was the primary driver of the efficacy in both treatment arms. In addition, FDA expressed concerns about the ability to adequately justify a margin as the benefit of glucocorticoids when administered with rituximab or cyclophosphamide induction therapy is not well understood. As discussed in the *FDA Guidance for Industry Non-Inferiority Clinical Trials to Establish Effectiveness*, noninferiority designs are credible and appropriate only in situations in which the active control has shown a consistent effect (generally compared with placebo) in prior superiority trials conducted in a patient population similar to the population in the clinical investigation being planned.[8] The utility of a non-inferiority comparison is dependent on knowing that the active control had its expected effect in the non-inferiority study. However, the Applicant has not provided adequate data or information that would isolate the effect of prednisone to inform the margin of the non-inferiority comparison in this study.

Furthermore, non-protocol-specified glucocorticoids were used to control disease activity which resulted in glucocorticoid use in both treatment arms. Thus, the assessment of non-inferiority is a comparison of avacopan and lower dose glucocorticoids to higher dose glucocorticoids. In light of the uncertainties on the treatment effect of glucocorticoids in AAV and the emerging literature supporting the efficacy of lower doses of glucocorticoids in AAV, as described under Role of Glucocorticoids in AAV Treatment in the Background, the interpretation of the non-inferiority assessment is challenging. Additionally, data from the clinical pharmacology program has identified avacopan as a CYP3A4 inhibitor that has the potential to increase exposures to systemic glucocorticoids which are CYP3A4 substrates, raising further questions about the true difference in glucocorticoid exposures and its impact on the non-inferiority comparisons between the two groups, and respectively the proposed role of avacopan as a steroid-sparing agent.

The avacopan arm demonstrated superiority over the prednisone arm in achieving sustained remission at Week 52. The lack of maintenance therapy in the rituximab subgroup may have had an impact on the comparisons at Week 52. A treatment benefit was not observed in the cyclophosphamide subgroup. The result of the subgroup analysis suggests the possibility that avacopan was efficacious only in the population who did not receive standard-of-care maintenance immunosuppression therapy and may be considered undertreated. As a result, though statistical significance was observed for both non-inferiority and superiority at Week 52 for the primary endpoint, it is not clear if the comparisons

[8] FDA Guidance for Industry Demonstrating Substantial Evidence for Effectiveness for Human Drug and Biological Products. December 2019.

between the avacopan and prednisone arm beyond Week 26 are meaningful. Superiority of the avacopan arm over the prednisone arm was not achieved for remission at Week 26.

Beyond the assessment of remission in the primary endpoint, the secondary endpoints provide limited information to support a treatment benefit of avacopan, as discussed above.

A greater proportion of avacopan-treated patients had AEs and SAEs associated with hepatic abnormalities (i.e., liver enzymes abnormalities and hepatobiliary disorders). AEs associated with hepatic abnormalities led to drug discontinuation in 7 patients in the avacopan arm and 2 patients in the prednisone arm. Other safety events, including deaths, SAEs, AEs leading to discontinuation, and other AEs of special interest (e.g., infections) were generally similar or fewer in the avacopan group; however, the safety database is limited for the reliable assessment of rare or latent events.

We acknowledge that AAV is a rare and serious disease associated with high morbidity and increased mortality. It is also a disease with high unmet need for new therapies. However, FDA wants to ensure that new products have a defined context of use, i.e. how a product would be used, and a favorable benefit-risk assessment for patients. Given the concerns outlined above, the context of use and the benefit-risk of avacopan for the treatment of AAV are important to discuss with this Advisory Committee. We thank you for your participation in this Advisory Committee meeting and look forward to the discussion.

Draft Points for Consideration

The purpose of the AAC meeting is to discuss the New Drug Application (NDA) 214487 for avacopan, sponsored by ChemoCentryx, for the proposed indication of treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]). The Agency is seeking input from the Committee on whether the application provides substantial evidence of efficacy for the proposed indication and overall benefit-risk considerations in AAV as a rare and serious disease. The following are draft points to consider for discussion at the upcoming AC.

1. Discuss whether the results at Week 26 support a clinically meaningful benefit of avacopan. Include discussion of the following:
    - Appropriateness of a primary non-inferiority comparison against glucocorticoids to support the effectiveness of avacopan with rituximab/cyclophosphamide provided in both arms
    - The use of additional non-study supplied glucocorticoids
    - The noninferiority margin selection, considering the uncertainties about the effect size of glucocorticoids, when added to standard induction with cyclophosphamide or rituximab
    - The lack of statistically significant treatment effect in the superiority comparison at Week 26.
2. Discuss whether the results at Week 52 support a clinically meaningful benefit of avacopan. Include discussion of the following:
    - The impact of the lack of maintenance therapy in the rituximab subgroup
    - Discrepancies in results based on BVAS remission as determined by Adjudication Committee vs. Investigators.
3. Discuss whether the data support the use of avacopan as a steroid-sparing agent in AAV:
    - Include discussion of the impact of a potential drug-drug interaction with glucocorticoids in the assessment
    - The use of additional non-study supplied glucocorticoids.
4. Discuss how avacopan, if approved, should be used in the treatment approach to AAV based on the data from the clinical program.
5. Discuss whether the efficacy data are adequate to support approval of avacopan for treatment of AAV
    - If no, what additional data are needed?
6. Discuss whether the safety profile of avacopan is adequate to support approval of avacopan for the treatment of AAV
    - If no, what additional data are needed?
7. Discuss whether the benefit-risk profile is adequate to support approval of avacopan at the proposed dose of 30 mg twice daily for the treatment of AAV
    - If no, what additional data are needed?

Background

Avacopan

Avacopan (also known as CCX168) is a small molecule antagonist of C5a receptor (C5aR). C5a is an end product of the complement cascade (cleaved fragment of C5) and acts as a potent neutrophil chemoattractant and agonist. It has been proposed that C5a and C5aR may play a central role in the pathogenesis of AAV. One proposed mechanism involves the alternative complement pathway.[9] Cytokines prime neutrophils to express ANCA antigens at the cell surface.[10] Primed neutrophils adhere to the endothelium, and ANCAs interact with their antigens, resulting in further neutrophil activation.[11] ANCA-activated neutrophils release factors that can directly damage the endothelium but can also activate the alternative complement pathway, which, in turn, generates C5a.[12] C5a and C5aR on neutrophils then create an amplification loop for ANCA-mediated neutrophil activation, eventually culminating in severe necrotizing inflammation of the vessel wall.[13] It has also been noted that C5a may directly activate vascular endothelial cells, promoting retraction and increased permeability leading to tissue edema. Although C5a is a terminal component of the complement cascade, it is not part of the membrane attack complex (MAC). Avacopan, therefore, may block the deleterious effects mediated by C5a. The Applicant reports CCX168 inhibited C5a-induced neutropenia in cynomolgus monkeys. Additionally, in a hC5aR knock-in mouse, CCX168 blocked the development of glomerulonephritis in mice that received anti-MPO antibody (a mouse model of AAV).

ANCA-associated vasculitis

The presentation and natural history of AAV can be highly variable. The spectrum of disease may range from relatively mild and localized to the upper respiratory tract to life-threatening involvement of multiple organ systems (upper and lower respiratory tract, kidneys, etc.).[14] AAV is thus categorized into the localized or generalized disease, and then generalized disease can be further broken down into limited or severe disease. Localized disease refers to patients with symptoms restricted to the upper and/or lower airways without constitutional symptoms or systemic vasculitis.[15] Limited disease encompasses all non-life- or organ-threatening manifestations, including mild renal or pulmonary disease.[16] Severe disease, on the other hand, can be defined as life- or organ-threatening manifestations, including rapidly progressive glomerulonephritis (RPGN), diffuse alveolar hemorrhage (DAH), mesenteric ischemia, scleritis, and nervous system involvement.[17] If left untreated, AAV is a

[9] Kallenberg CGM and Heeringa P. Complement system activation in ANCA vasculitis: a translational success story? *Mol Immunol*. 2015; 68: 53-56.
[10] Kallenberg CGM and Heeringa P, 53-56.
[11] Kallenberg CGM and Heeringa P, 53-56.
[12] Kallenberg CGM and Heeringa P, 53-56.
[13] Kallenberg CGM and Heeringa P, 53-56.
[14] Malyak M. "Wegener's granulomatosis and other ANCA-associated diseases." *Rheumatology Secrets: Second Edition*. Ed. Sterling West. Philadelphia: Hanley and Belfus, Inc., 2002. 222-231. Print.
[15] Bosch X, Guilabert A, et al. Treatment of antineutrophil cytoplasmic antibody-associated vasculitis: a systematic review. *JAMA*. 2007; 298: 655-669.
[16] Lally L and Spiera R. Current landscape of antineutrophil cytoplasmic antibody-associated vasculitis: classification, diagnosis, and treatment. *Rheum Dis Clin N Am*. 2015; 41: 1-19.
[17] Lally L and Spiera R, 1-19.

uniformly fatal disorder with a mean survival time of < 1 year.[18] Patients frequently die from respiratory failure and renal failure. Availability of therapies, starting with glucocorticoids in 1948 and cyclophosphamide in the 1960s, has had a profound impact on the mortality. With currently available treatments, more recent remissions rates are as high as 90%, and mortality has decreased to 20% at 5 years.[19] In general, in the first year after diagnosis of AAV, the most frequent causes of death are therapy-related (59%) and then active vasculitis.[20] Therapy-related toxicities include infection, myelosuppression, infertility, and malignancy.[21] Despite high remission rates and improved mortality, over 50% of patients will relapse, particularly in the 12-18 months after immunosuppression is discontinued.[22] Several factors have been associated with a higher risk for relapse. These include the following: [23]

- Demographics: younger patients
- ANCA: PR3-antibody, persistence of ANCA after induction, increase in ANCA titers (more predictive of renal relapse)
- Clinical phenotype: GPA; lung, upper respiratory tract, or cardiac involvement; preserved renal function; prior relapse
- Therapy: discontinuation of immunosuppression, lower cumulative dose of cyclophosphamide during induction, discontinuation of prednisone, use of mycophenolate mofetil for maintenance, B-cell reconstitution after rituximab
- Other factors: chronic nasal carriage of *Staphylococcus aureus* and HLA-DP1*04 alleles

Available therapies

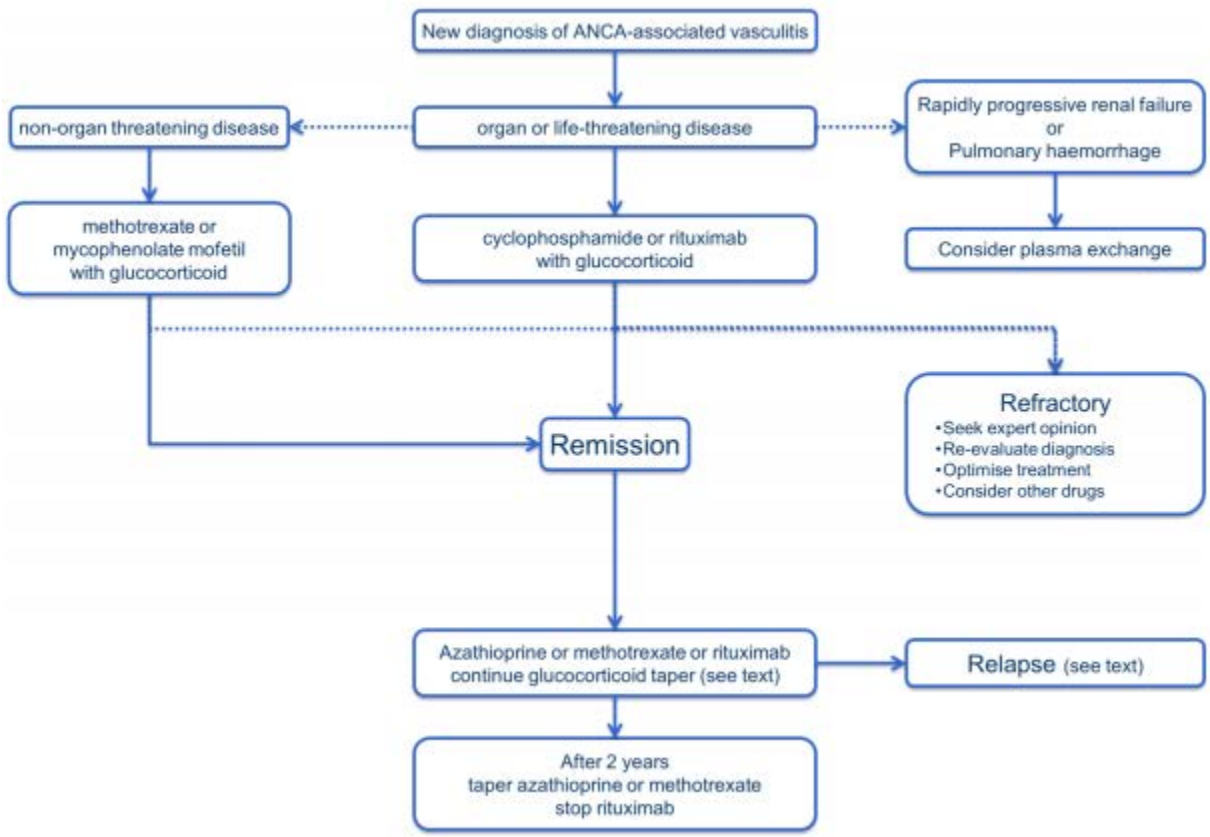
The treatment strategy of patients with AAV involves a few fundamental principles. First, the treatment paradigm is comprised of 2 phases: induction and maintenance treatment. This paradigm arose from the desire to minimize exposure of potent immunosuppressants (namely, cyclophosphamide).[24] Induction treatment typically lasts 3-6 months with the goal of establishing remission. Then, maintenance therapy is initiated to prevent relapse. The optimal duration of maintenance is unknown. The choice of therapy for induction and maintenance is tailored based on the severity of disease.

The 2015 update to the 2009 recommendations provided by the European League Against Rheumatism (EULAR) along with the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), as shown in Figure 2, reflects standard-of-care therapy.[25] For severe AAV, induction therapy involves a combination of glucocorticoids and either cyclophosphamide or rituximab. Induction

[18] Malyak M, 230.
[19] Emejuaiwe N. Treatment strategies in ANCA-associated vasculitis. *Curr Rheum Rep*. 2019; 21: 33.
[20] Little M, Nightingale P, et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. *Ann Rheum Dis*. 2010; 69: 1036-1043.
[21] Emejuaiwe N, 33.
[22] Geetha D and Jefferson JA. ANCA-associated vasculitis: core curriculum 2020. *Am J Kidney Dis*. 2019; 75: 124-137.
[23] Geetha D and Jefferson JA, 124-137.
[24] Emejuaiwe N, 33.
[25] Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis*. 2016; 75:1583-1594.

therapy should be continued until remission is achieved, typically 3-6 months.[26] Because relapse is so common in patients with AAV, maintenance therapy is utilized to prevent relapse and disease- and treatment-related morbidity and mortality.[27] For remission maintenance, the treatment guidelines recommend low-dose glucocorticoids and either azathioprine, rituximab, methotrexate, or mycophenolate mofetil.[28] As previously mentioned, the optimal duration of maintenance therapy is an area of debate, but there is a general sense that longer maintenance therapy will better prevent relapse as relapse rates tends to increase after discontinuation of immunosuppression.[29] The EULAR guidelines recommend at least 24 months of maintenance therapy.[30] Of the current treatment paradigm, only rituximab is FDA-approved for the treatment of AAV, while there are specific glucocorticoids approved for the broader indication of vasculitis.

Figure 2. Management of ANCA-associated Vasculitis



Source: Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis*. 2016; 75:1583-1594.

[26] Geetha D and Jefferson JA, 124-137.
[27] Geetha D and Jefferson JA, 124-137.
[28] Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations,1583-1594.
[29] Geetha D and Jefferson JA, 124-137.
[30] Yates M, Watts RA, Bajema IM, et al., 1583-1594.

Evolving Landscape of AAV Treatment

Rituximab

Rituximab (RTX) is a chimeric/human monoclonal antibody directed against the CD20 antigen. It was approved for treatment of GPA and MPA in combination with glucocorticoids on April 19, 2011, and the approval was based on data from the Rituximab in AAV (RAVE) trial. RAVE was a randomized, double-blind, active-controlled non-inferiority trial in 197 patients with GPA or MPA. All patients received a glucocorticoid taper and were randomized to either oral cyclophosphamide (CYC) 2 mg/kg daily for 3 to 6 months followed by azathioprine (AZA) for 12 to 15 months or RTX (375 mg/m^2 BSA administered once a week for 4 weeks) followed by placebo. Glucocorticoids were tapered over 20 weeks in both treatment arms. The primary endpoint in RAVE was achievement of complete remission at six months defined as a BVAS/WG[31] of zero and successful completion of the glucocorticoid taper six months after randomization. Patients discontinued glucocorticoids for one month prior to assessment of the primary endpoint. The data supported that RTX was not inferior to daily CYC for induction of remission in AAV.[32] A long-term assessment of efficacy at 12 and 18 months in RAVE showed no significant difference in complete remission at 12 and 18 months in these 2 treatment arms, suggesting that a single course of RTX may be as effective as CYC and azathioprine for 18 months.[33] However, these were tertiary endpoints in the RAVE trial, and rate of relapse remained high in both arms. Rituximab for maintenance therapy was formally evaluated in Maintenance of Remission using Rituximab in Systemic ANCA-associated Vasculitis (MAINRITSAN), a randomized controlled trial in 115 patients with AAV who achieved remission with CYC and then were randomized to maintenance treatment with either RTX (500 mg on Days 0 and 14 and then at a fixed dose interval at Months 6, 12, and 18) or AZA (2 mg/kg daily for 12 months, then 1.5 mg/kg daily for 6 months, then 1 mg/kg for 4 months).[34] Prednisone was continued for at least 18 months. More patients had sustained remission, defined as a BVAS of 0, at Month 28 in the RTX arm. Major relapse occurred in 5% of patients in the rituximab group and 29% in the azathioprine group. Based on the results of this trial, rituximab was approved for maintenance treatment on October 19, 2018.

Since MAINRITSAN, 2 other studies from the same investigator group evaluated the use of rituximab for maintenance therapy. MAINRITSAN2 was an open-label, randomized, controlled trial evaluating 2 rituximab infusion strategies for the maintenance of remission (N=162). Patients in the individually tailored treatment group received rituximab 500 mg on Day 0 after randomization and were then received additional infusions only if CD19+ lymphocytes or ANCA reappeared. The other treatment arms

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[31] BVAS/WG is a modification of the original BVAS comprised of 34 separate disease items categorized into 9 groups and an "other" section. Fifteen items are considered major. Items are classified as persistent, new/worse, or none. BVAS/WG score ranges from 0 to 64. Stone JH, Hoffman GS, et al. A disease-specific activity index for Wegener's granulomatosis – modification of the Birmingham Vasculitis Activity Score. *Arthritis Rheum*. 2001; 44: 912-920.

[32] Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. 2010; 363: 221-32.

[33] Specks U, Merkel P, Seo P, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med*. 2013; 369: 417-27.

[34] Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med*. 2014; 371:1771-80.

received a fixed infusion of rituximab on Days 0 and then every 6 months (Months 6, 12, and 18). The primary endpoint was the number of relapses (i.e., new or reappearing symptoms or worsening disease with BVAS >0) at Month 28. The investigators reported that there was no difference in relapse rates between the 2 treatment regimens, but the individually tailored arm received fewer infusions.[35] Patients who completed MAINRITSAN2 and were in complete remission could be rerandomized into MAINRITSAN3. MAINRITSAN3 was a multicenter, double-blind, randomized controlled trial comparing prolonged maintenance with IV rituximab 500 mg given every 6 months over 18 months with placebo (N=97). The primary endpoint was relapse-free survival at Month 28. Significantly more patients in the rituximab group (96%) achieved the primary endpoint compared to the placebo group (74%).[36] The investigators concluded that all 3 MAINRITSAN trials supported that (1) rituximab should become the new gold standard to maintain remission, (2) rituximab 500 mg per infusion is an adequate dose, (3) treatment should be prolonged, and (4) an individually tailored regimen may be prescribed.[37] In fact, the authors proposed that rituximab should be given over a prolonged period (specifically, 36 months after achieving remission) for any patients at high risk for relapse, namely, those with PR3 ANCAs and those who previously experienced a relapse.[38]

RITAZAREM was a randomized, controlled trial designed to assess whether rituximab is superior to azathioprine for the maintenance of remission following induction of remission with rituximab and glucocorticoids in patients with relapsing AAV. There were 3 phases to the trial: induction phase, maintenance phase, and follow-up phase. Data from the induction phase were published in 2020 and showed that 90% (i.e., 171 out of 188 patients) with relapsing disease achieved BVAS remission.[39] Patients in RITAZAREM had evidence of disease relapse at the time of enrollment (defined as 1 major or 3 minor disease activity items on the BVAS/WG) after previously achieving remission following at least 3 months of induction therapy. Induction therapy including RTX (375 mg/m^2/week for 4 weeks) and 2 glucocorticoid regimens (high dose starting at 60 mg daily and low dose starting at 30 mg daily, both tapered to 10 mg daily by month 4). BVAS remission was defined as BVAS/WG ≤ 1 with prednisone ≤ 10 mg by 4 months. One hundred seventy patients were then randomized to RTX or AZA for maintenance. Results from the maintenance phase showed that, 20 months after randomization, 11/85 (13%) patients in the RTX arm had experienced a relapse compared to 32/85 (38%) patients in the AZA arm.[40] The data from this trial appear to further support the role of RTX for induction and maintenance in patients with relapsing disease.

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[35] Charles P, Terrier B, Perrodeau E, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicenter, randomized, controlled, phase 3 trial (MAINRITSAN2). *Ann Rheum Dis*. 2018; 77; 1144-1150.

[36] Charles P, Perrodeau E, Samson M, et al. Long-term rituximab use to maintain remission of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. *Ann Intern Med.* 2020; 173:179-187.

[37] Charles P, Perrodeau E, Samson M, et al., Long-term rituximab use, 179-187.

[38] Charles P, Perrodeau E, Samson M, et al., Long-term rituximab use, 179-187.

[39] Smith RM, Jones RB, Specks U, et al. Rituximab as therapy to induce remission after relapse in ANCA-associated vasculitis. *Ann Rheum Dis*. 2020; 79: 1243-1249.

[40] Smith R, Jayne D, Merkel P. A randomized, controlled trial of rituximab versus azathioprine after induction of remission with rituximab for patients ANCA-associated vasculitis and relapsing disease [abstract]. *Arthritis Rheumatol*. 2019; 71 (suppl 10).

Role of Glucocorticoids in AAV Treatment

Glucocorticoids have been a mainstay of therapy in the treatment of AAV. As previously noted, glucocorticoid treatment led to a significant decrease in mortality in AAV when it was first introduced in the 1940s. Also, early glucocorticoid withdrawal appeared to be a strong predictor of relapse. However, "there is no consensus on the best tapering regimen or duration of glucocorticoid therapy for AAV."[41] In addition, there is concern that glucocorticoids may be responsible for much of the morbidity and mortality in AAV, such as infection and cardiovascular disease.[42] Various cohort studies seemed to show benefit with lower doses of glucocorticoids such as reduced duration of glucocorticoid therapy after RTX induction[43] and after a combined RTX and CYC induction[44]. However, this issue has recently been further highlighted because of the results of the PEXIVAS trial. The Plasma Exchange and Glucocorticoids for Treatment of Anti-neutrophil Cytoplasm Antibody-associated Vasculitis (PEXIVAS) was a randomized, controlled trial involving patients with severe, active AAV.[45] The trial was a 2-by-2 factorial design which allowed separate evaluations of initial treatment with plasma exchange as compared with no plasma exchange (with either cyclophosphamide or rituximab background therapy) and of 2 different regimens of oral glucocorticoids. Focusing on the glucocorticoid part of this trial, all patients were treated with daily IV methylprednisolone for 1 to 3 days for a maximum cumulative dose of 1 to 3 g. Then, patients received either a standard-dose regimen (based on regimens used in "a contemporary international trial") or a reduced-dose regimen (identical first week of treatment with dose reduction beginning in Week 2 and with 60% less cumulative glucocorticoids by Month 6).[46] (See Table 29 in the Appendix for details of the prednisone taper in PEXIVAS, as compared to RAVE and CLEAR [CL002_168, one of the phase 2 avacopan studies].) The investigators concluded that reduced dose regimen was noninferior to the standard dose regimen in terms of the primary outcome of composite death from any cause or end-stage kidney disease (ESKD). Therefore, current standard of care treatment with glucocorticoids (specifically, the dose and duration of therapy) may exceed what is necessary to treatment patients with AAV and remains an area for further consideration.

Pertinent Regulatory History

SEE ATTACHED ERRATA

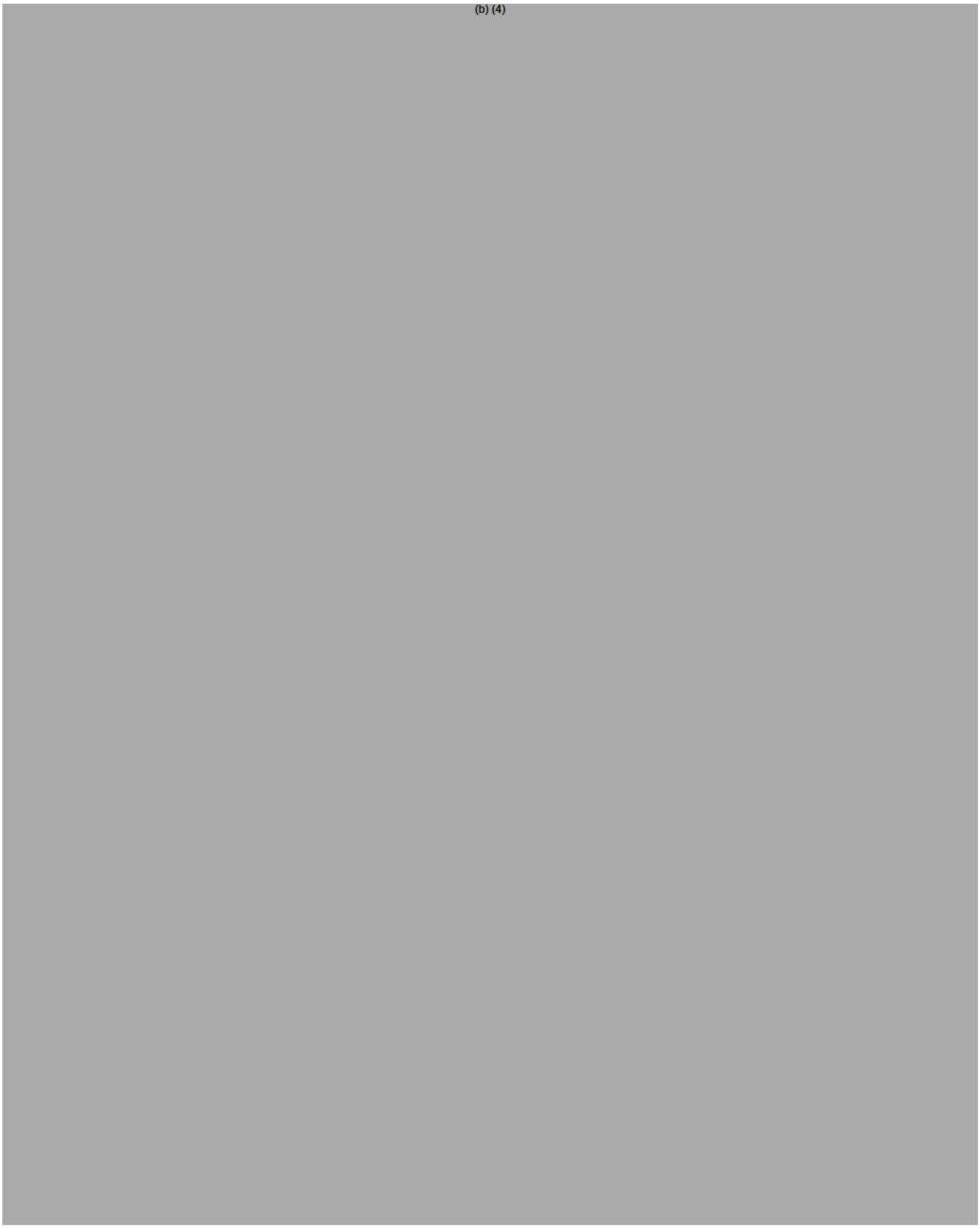
(b) (4)

[redacted]

[41] Geetha D and Jefferson JA, ANCA-associated vasculitis, 124-137.
[42] Miloslavsky EM, Niles JL, Wallace ZS, et al. Reducing glucocorticoid duration in ANCA-associated vasculitis: a pilot trial. *Sem Arthritis Rheum*. 2018; 48: 288-292.
[43] Miloslavsky EM, Niles JL, Wallace ZS, et al., 288-292.
[44] Pepper RJ, McAdoo SP, Moran SM, et al. A novel glucocorticoid-free maintenance regimen for anti-neutrophil cytoplasm antibody-associated vasculitis. *Rheumatology*. 2019; 58: 260-268.
[45] Walsh M, Merkel PA, Peh C-A, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med*. 2020; 382:622-631.
[46] Walsh M, Merkel PA, Peh C-A, et al.,622-631.

SEE ATTACHED ERRATA

(b) (4)



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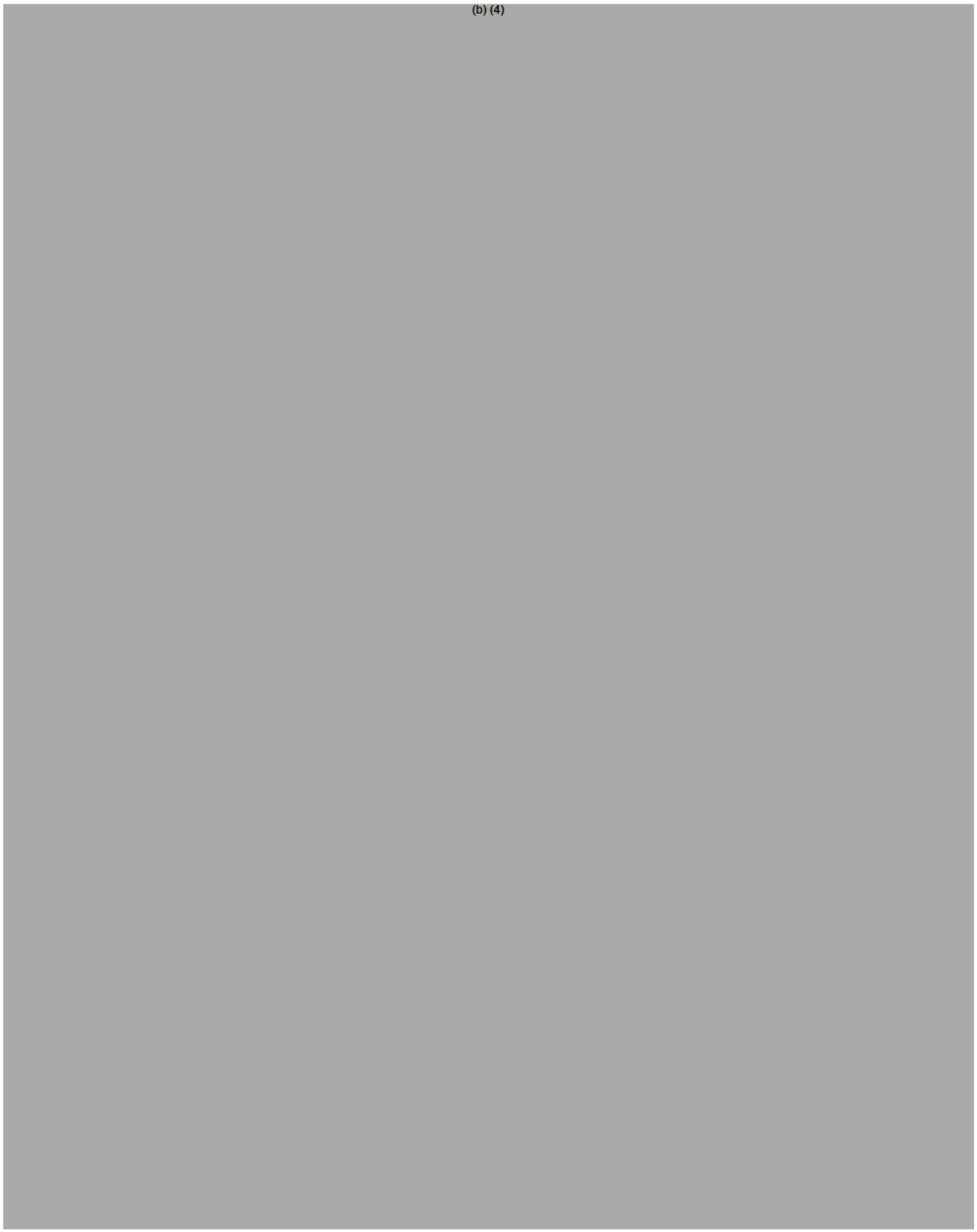

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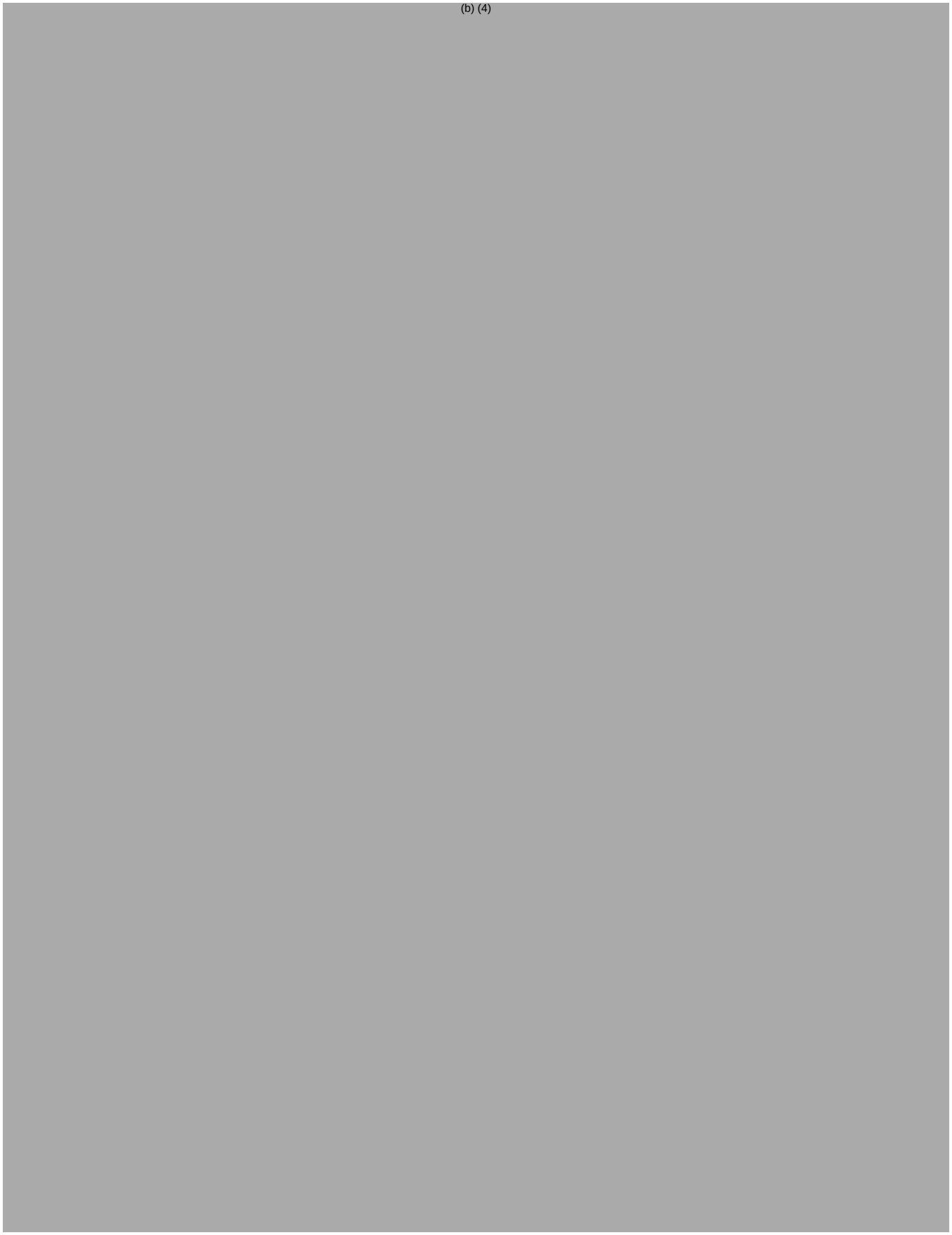

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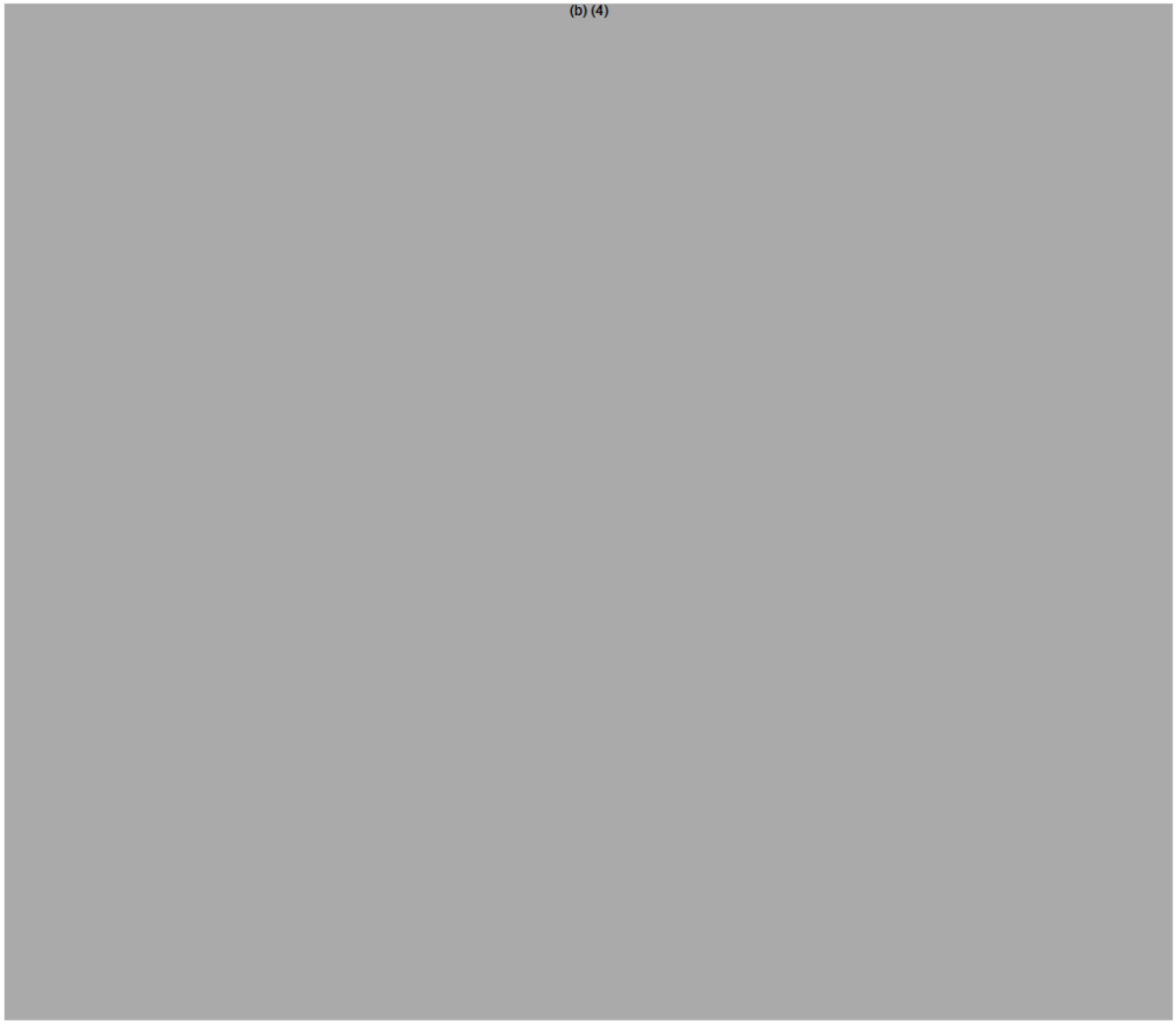
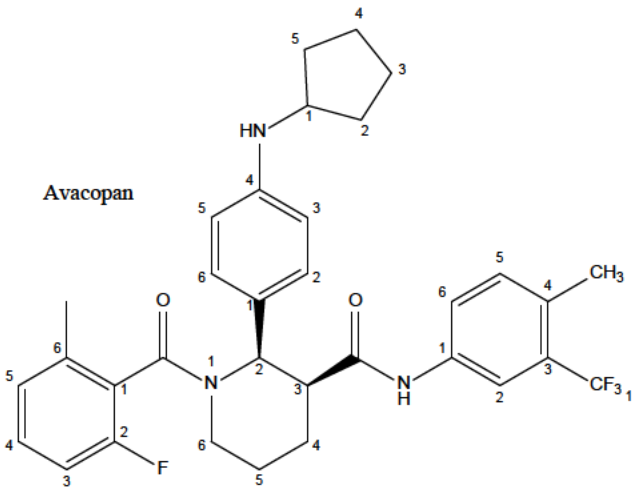


Product Quality Summary

Avacopan is a C5aR inhibitor. The avacopan molecule has a molecular formula of $C_{33}H_{35}F_4N_3O_2$ and a molecular weight of 582 g/mole. The structure and chemical name of avacopan are shown below:

Avacopan



(2*R*,3*S*)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-*N*-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide

Avacopan is a white to pale yellow crystalline solid that is practically insoluble in water. Avacopan is formulated as a 10 mg capsule (size 0) for oral administration with the following inactive ingredients: polyethylene glycol 4000, polyoxyl-40 hydrogenated castor oil. The hard gelatin capsules are light orange and yellow opaque bicolor with a clear gelatin sealing band. The top half of the capsule is printed with "CCX168" in black ink. The capsule shell contains gelatin, (b) (4) and the capsule sealing band contains gelatin and (b) (4) The avacopan drug product is supplied in bottles of 30 and 180 capsules with child-resistant (b) (4) seal closures which are to be stored at controlled room temperature.

Nonclinical Pharmacology-Toxicology Summary

Pharmacology studies demonstrated that CCX168 and its M1 metabolite were competitive antagonists of the complement component 5a receptor (C5aR) with comparable potency. In *in vitro* studies, CCX168 displaced human C5a from the C5a receptor with an average IC_{50} of 0.45 nM. In functional assays, pretreatment with CCX168 inhibited C5a-mediated chemotaxis of leukocytes with an A2 of 1.7 nM, inhibited of upregulation of the neutrophil surface CD11b adhesion molecule, and inhibited C5aR-mediated calcium mobilization in neutrophils and monocytes in response to stimulation with hC5a. In a murine ANCA disease model, using human C5aR knock-in transgenic mice injected with anti-myeloperoxidase (MPO) antibody, treatment with CCX168 at 5 mg/kg BID and 37.5 mg/kg QD significantly reduced the incidence of glomerular crescent formation and necrosis in the kidneys and reduced urinary leukocytes, erythrocytes, and total protein.

In GLP-compliant pivotal toxicology studies conducted with CCX168 for 13-weeks in hamster, 26-weeks in rats, and 44-weeks in monkey, no CCX168-related adverse findings were identified at exposures up to 5.8-, 10.5-, and 4.2-fold greater than the exposure achieved with the proposed clinical dose of 30 mg BID, respectively.

Avacopan was negative for genotoxicity in a standard battery of in vitro and in vivo genetic toxicology tests. No treatment-related tumors were identified in 2-year oral studies with SD rats and hamsters that were conducted to assess the carcinogenic potential of avacopan.

Avacopan did not affect fertility, reproductive performance, or embryofetal development in male and female hamsters treated with oral doses of avacopan up to 1000 mg/kg/day. In a pre- and postnatal development study, avacopan and the CCX168-M1 metabolite were detected in plasma of the offspring of lactating hamsters.

Clinical Pharmacology Summary

Pharmacokinetics

Avacopan capsules (10 mg) are proposed to be orally administered twice daily with food. The pharmacokinetics of avacopan has been evaluated in healthy subjects and patients with ANCA-associated vasculitis. A mono-hydroxylated product of avacopan, M1, is the major circulating metabolite, presenting approximately 12% of the total drug-related exposure in plasma, and has approximately the same activity as avacopan on the C5aR.

Following a single dose of 30 mg avacopan, a high-fat, high-calorie meal increased avacopan AUC by approximately 72%. The high fat meal did not affect Cmax, and delayed the median Tmax from 2.0 hours to 6.0 hours as compared to fasted condition. For the active metabolite M1, a high-fat, high-calorie meal did not affect the AUC, but reduced Cmax by 51% as compared to fasted condition. The plasma protein binding of avacopan and metabolite M1 is greater than 99.9%. Avacopan is mainly metabolized by CYP3A4. The main route of clearance of avacopan is metabolism followed by biliary excretion of the metabolites into feces. Following oral administration of radiolabeled avacopan, about 77% and 10% of the radioactivity was recovered in feces and urine, respectively, and 7% and <0.1% of the radioactive dose was recovered as unchanged avacopan in feces and urine, respectively. Based on population pharmacokinetic analysis, the median effective half-life of avacopan is 36.8 hours (1.5 days).

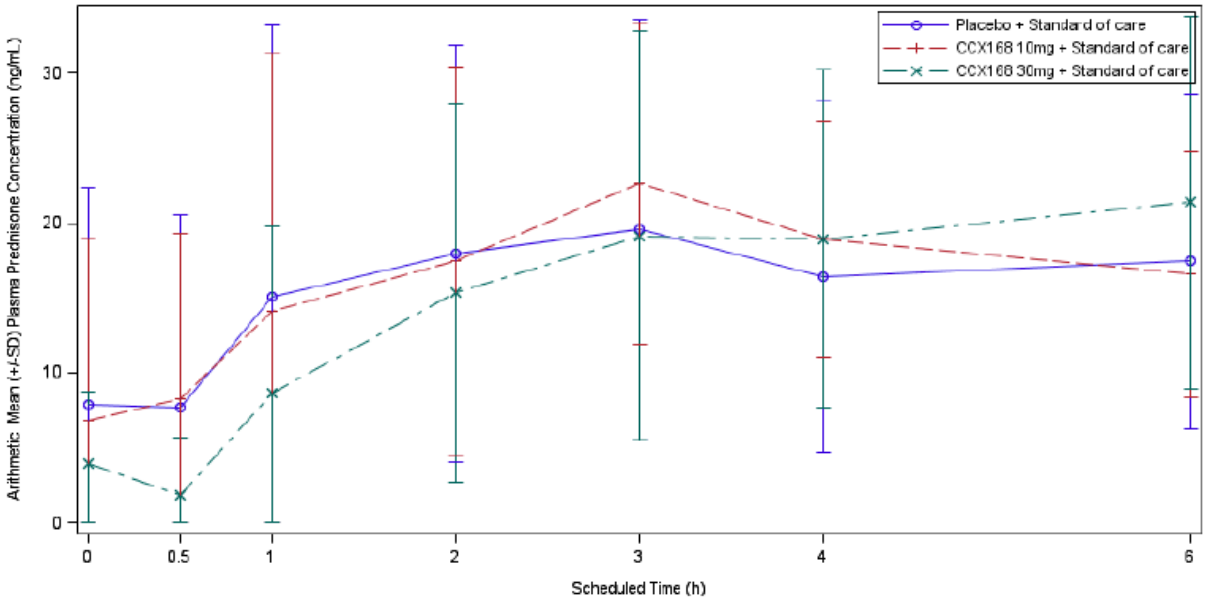
Drug-drug interactions

In-vitro drug interaction studies indicated that avacopan and its metabolite M1 showed time-dependent inhibition on CYP3A4. The inhibition potential of avacopan on a sensitive CYP3A4 substrate (midazolam) has been evaluated in Study CL008_168. It is a phase 1, open-label study with 2 parallel cohorts in 32 healthy subjects. In cohort A, 16 subjects received a single dose of 2 mg midazolam on Days 1 and 13. Thirty mg avacopan was administered twice daily under fasted condition from Day 3 to 13. Midazolam PK comparison between Day 1 and Day 13 indicated that when co-administered with avacopan under fasted condition, midazolam AUC and Cmax increased by 81% and 55%, respectively. Note that avacopan capsules are proposed to be given with food and a high-fat, high-calorie meal may increase avacopan AUC by approximately 72%. The impact of avacopan on CYP3A4 substrates under fed condition has not been studied.

Prednisone is a CYP3A4 substrate, and a CYP3A4 inhibitor such as avacopan may increase the exposure of prednisone. In the phase 2 study CL003_168, all treatment groups (avacopan 10 mg, 30 mg, vs. placebo) received a prednisone taper regimen starting at 60 mg daily. While prednisone concentrations were comparable among treatment arms on Day 1, the CYP3A4 inhibitory effect of avacopan may not be reflected at this early timepoint (Figure 3). During Days 15-85, since prednisone concentrations in most of subjects could not be accurately quantified (below the lower limit of quantification (LLOQ)), prednisone exposure could not be adequately compared among treatment groups (Figure 3 and Figure 4, Table 3). Overall, the potential exposure increase of prednisone when co-administered with avacopan cannot be ruled out based on Study CL003-168.

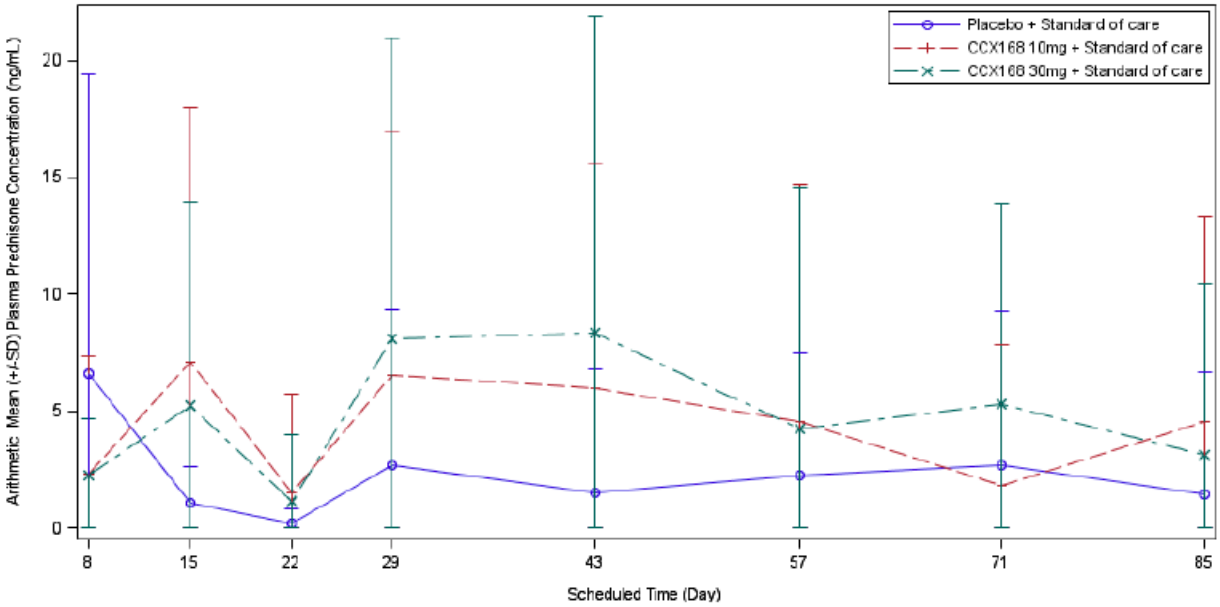
In addition, the non-study supplied glucocorticoids used in the phase 3 study CL010_168 are all identified to be CYP3A4 substrates (Table 4). However, the pharmacokinetics of systemic glucocorticoids were not assessed in the phase 3 study CL010_168. Therefore, while the impact of avacopan coadministration on prednisone exposure is inconclusive based on the information in the avacopan clinical pharmacology program, the potential exposure increase of glucocorticoids used in the phase 3 study CL010_168 when co-administered with avacopan due to drug-drug interactions could not be reliably ruled out. This potential drug-drug interaction between avacopan and glucocorticoids raises questions whether differences in glucocorticoid use between the avacopan and control arms based on the nominal doses of glucocorticoids used reflect true differences in glucocorticoid exposures and about the role of avacopan as a steroid-sparing agent.

Figure 3. Concentration (Mean ± SD) – Time Profile of Prednisone on Day 1 (Linear Scales)



Source: Final Report of PK Analysis in Support of ChemoCentryx Clinical Trial CL003_168, Figure 7, page 23.

Figure 4. Concentration (Mean ± SD) – Time Profile of Prednisone on Days 8-85 (Linear Scales)



Source: Final Report of PK Analysis in Support of ChemoCentryx Clinical Trial CL003_168, Figure 7, page 23.

Table 3. The number of subjects with prednisone concentration below the LLOQ (2 ng/mL) during Days 8-85 in Study CL003_168

Treatment arm	Day 8	Day 15	Day 22	Day 29	Day 43	Day 57	Day 71	Day 85
10 mg BID	8/12	7/13	11/13	9/13	9/13	9/12	10/11	8/11
30 mg BID	7/16	6/16	13/16	10/16	8/14	11/15	9/14	13/16
Placebo	6/13	7/11	11/12	11/13	12/13	10/13	11/13	12/13

Source: Clinical Pharmacology Reviewer

Table 4. Summary of non-Study supplied glucocorticoid use in Study 010_168

Prednisone arm	Avacopan arm	CYP3A4 substrate (Yes or No)
Dexamethasone		Yes
Hydrocortisone		Yes
Hydrocortisone sodium succinate		Yes
Methylprednisolone		Yes
Methylprednisolone sodium succinate		Yes
Prednisolone		Yes
Prednisolone sodium succinate		Yes
Prednisone		Yes
--	Betamethasone	Yes
--	Betamethasone sodium phosphate	Yes
--	Cortisone	Yes
--	Hydrocortisone sodium phosphate	Yes

Note: the summary is based on the reported Standardized Medication Name
Source: Clinical Pharmacology Reviewer

Avacopan Clinical Development Program

Study CL010_168 (ADVOCATE)

Study Design

Study CL010_168 was a randomized, double-blind, double-dummy, active-controlled, multicenter international clinical study. Patients with ANCA-associated vasculitis who met eligibility criteria (see below) were stratified by the following criteria to ensure balance across treatment arms:

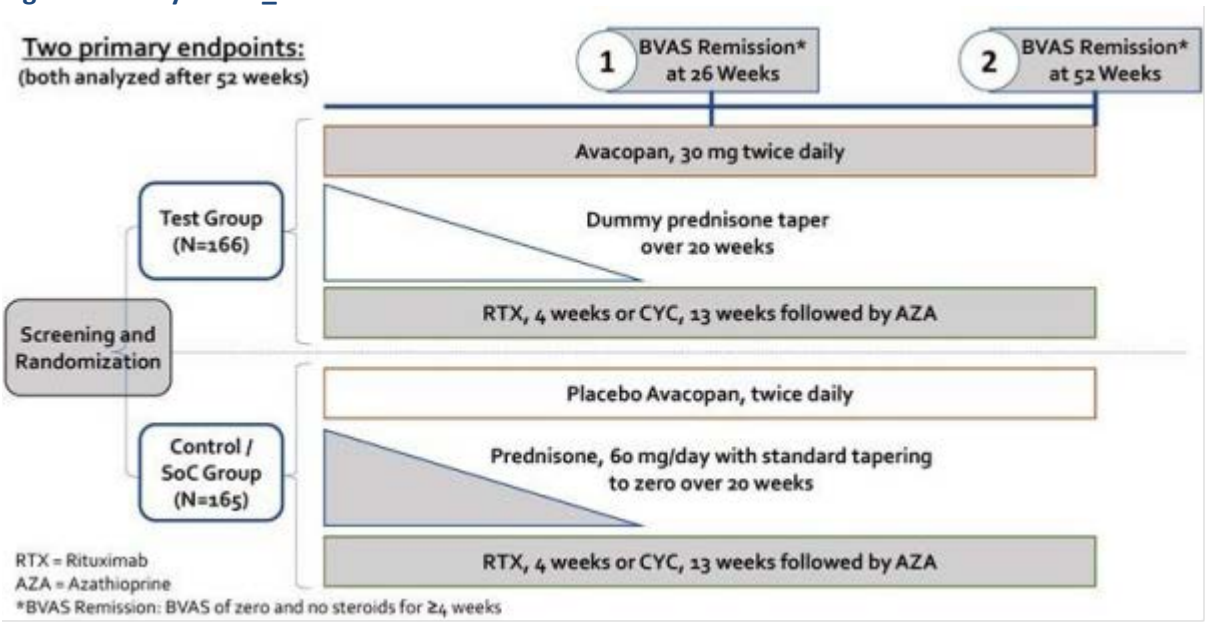
- One of the following 3 standard-of-care immunosuppressant treatment regimens
    - IV rituximab once weekly for 4 weeks
    - IV cyclophosphamide for 13 weeks followed by oral azathioprine (or mycophenolate if AZA contraindicated) from Week 15 onwards
    - Oral cyclophosphamide for 14 weeks followed by oral azathioprine (or mycophenolate if AZA contraindicated) from Week 15 onwards
- Positive test for PR3 versus MPO ANCA at diagnosis
- Newly diagnosed versus relapsed ANCA-associated vasculitis

Following stratification, patients were randomized in a 1:1 ratio to the following treatment arms:

- Group A ("prednisone group") received the following:
    - avacopan-matching placebo
    - cyclophosphamide (CYC) for induction/ AZA for maintenance or rituximab (RTX) for induction/no maintenance
    - full starting dose of prednisone
- Group B ("avacopan group") received the following:
    - avacopan 30 mg BID
    - CYC for induction/AZA for maintenance or RTX for induction/no maintenance
    - prednisone-matching placebo

The study included 3 periods: screening (up to 2 weeks), double-blind treatment (up to 52 weeks), and follow-up (8 weeks). Thus, the last scheduled visit could potentially be at Week 60. Figure 5. shows the study schematic.

Figure 5. Study CL010_168 Schematic



Sources: Pre-NDA Meeting package.

Patient Population

Patients were at least 18 years of age. In countries where it was approved, patients could be enrolled as adolescents (ages 12 to 17 years). Patients had a diagnosis of GPA or MPA, consistent with the Chapel-Hill Consensus Conference definitions. Additionally, patients had to have positive anti-PR3 or anti-MPO antibodies (historic or current) and evidence of active disease defined by at least 1 major item or at least 3 minor items or at least 2 renal items of proteinuria and hematuria (due to vasculitis) in the BVAS. Patients had to have a eGFR ≥ 15 mL/minute/1.73m^2. Other significant exclusion criteria include the following:

- Alveolar hemorrhage requiring invasive pulmonary ventilation support anticipated to last beyond the screening period
- Requirement of dialysis or plasma exchange within 12 weeks prior to screening
- Kidney transplant
- Any other multi-systemic autoimmune disease, e.g., eosinophilic granulomatosis with polyangiitis, systemic lupus erythematosus (SLE), IgA vasculitis, rheumatoid vasculitis, Sjogren's syndrome, anti-glomerular basement membrane disease, or cryoglobulinemic vasculitis

Patients could not be enrolled if they received the following therapy:

- Cyclophosphamide (CYC) within 12 weeks prior to screening
- Azathioprine (AZA), mycophenolate (MMF), or methotrexate (MTX) must be withdrawn prior to Day 1
- IV glucocorticoids (> 3000 mg methylprednisolone or equivalent) within 4 weeks prior to screening

- Continuous oral glucocorticoids (> 10 mg prednisone or equivalent) for more than 6 weeks prior to screening
- Rituximab or other B-cell antibody within 52 weeks of screening or 26 weeks if there is evidence of B-cell reconstitution
- Other biologics (e.g., anti-TNFs, abatacept, alemtuzumab, IVIg, belimumab, tocilizumab, or eculizumab) within 12 weeks prior to screening

Concomitant therapy

Use of mycophenolate (unless used instead of azathioprine for maintenance therapy), methotrexate, anti-TNF treatments, abatacept, alemtuzumab, IVIg, belimumab, tocilizumab, eculizumab, or other experimental or immunosuppressive drugs were prohibited over the course of the study.

(b) (4)

(b) (4)

SEE ATTACHED ERRATA

Glucocorticoids

Glucocorticoids were allowed prior to and during the screening period. Patients with severe AAV were allowed to receive (1) IV glucocorticoids at a cumulative dose equivalent to methylprednisolone 3 g in the 4-week period prior to screening and (2) oral glucocorticoids at any dose for the 6-week period prior to screening. However, patients were ineligible for participation if they received continuous treatment of > 10 mg prednisone-equivalent daily for more than 6 weeks prior to screening. During the screening period of the study, patients with severe AAV could also receive IV or oral glucocorticoids. The cumulative dose of IV glucocorticoids prior to screening and during screening should not have exceeded methylprednisolone 3 g or equivalent. Oral glucocorticoids should be tapered to a dose that does not exceed prednisone 20 mg or equivalent on Day 1.

The Applicant considered "study-supplied prednisone" as that received by the patients in the control group who received a standardized tapering schedule over the course of the study. The tapering schedule differed slightly based on body weight. Patients with a body weight ≥ 55 kg started on prednisone 60 mg per day and tapered to zero over 20 weeks. Adult patients with a body weight < 55 kg and adolescent patients with a body weight > 37 kg started on prednisone 45 mg per day and tapered to zero over 20 weeks. Adolescent patients with body weight ≤ 37 kg started on prednisone 30 mg and tapered to zero over 20 weeks. (See Table 28 in the Appendix for details of the prednisone taper.)

The protocol provided instructions on non-study supplied glucocorticoid use. Additional glucocorticoids (i.e., non-study supplied glucocorticoids) was to be avoided as much as possible during the study. If a patient was still taking a dose of non-study-supplied prednisone ≤ 20 mg on Day 1, the glucocorticoids should be tapered to zero over a 4-week period.

Subjects were allowed to receive glucocorticoids for the following reasons related to AAV.

- Relapse of AAV during the study: Subjects could be treated with IV glucocorticoids (0.5 to 1 g methylprednisolone per day for 3 days) and/or oral glucocorticoids, tapered according to the subject's condition.
- Worsening of disease that involved a major item in the BVAS: Subjects could be treated with IV glucocorticoids (0.5 to 1 g methylprednisolone per day for 3 days) and/or oral glucocorticoids, tapered according to the subject's condition.
- Worsening of disease not involving a major item in the BVAS: Subjects could be treated with a short burst (i.e., not more than 2 weeks) of oral glucocorticoids at a maximum dose of prednisone 20 mg or equivalent.

Patients experiencing a relapse or worsening of disease could continue study drug treatment and remain in the study.

Efficacy Endpoints and Analysis Plan

There were two primary endpoints prespecified in the protocol, each assessed for non-inferiority and superiority.

(1) The proportion of subjects achieving disease remission at Week 26
Disease remission at Week 26 was defined by the following criteria:
- Achieving BVAS 0 as determined by the adjudication committee (AC)
- No administration of glucocorticoids given for AAV within 4 weeks prior to Week 26
- No BVAS >0 during the 4 weeks prior to Week 26

(2) The proportion of subjects achieving sustained disease remission at Week 52
Sustained disease remission at Week 52 was defined by the following criteria:
- Disease remission at Week 26
- Disease remission at Week 52
    - BVAS 0 as determined by the AC
    - No administration of glucocorticoids given for AAV within 4 weeks prior to Week 52
- No disease relapse between Week 26 and Week 52 as determined by the AC

The protocol defined that "glucocorticoid use" refers to both prednisone study medication and other glucocorticoids that may have been given for AAV for the 4 weeks prior to BVAS assessment at Weeks 26 and 52. Subjects were permitted to receive low doses of oral glucocorticoids (≤ 10 mg/day) for treatment of adrenal insufficiency or other conditions. These subjects were to be considered responders if all other requirements for meeting the endpoints were met.

The two primary endpoints were to be tested sequentially using a gatekeeping procedure (i.e. fixed sequence procedure) to preserve the overall Type I error rate at 5% level. The sequence of testing was as follows: (1) test for non-inferiority regarding remission at Week 26, (2) test for non-inferiority regarding sustained remission at Week 52, (3) test for superiority regarding sustained remission at Week 52, and (4) test for superiority regarding remission at Week 26.

In a non-inferiority comparison, the goal is to demonstrate that the test drug has an effect by showing that its effect is sufficiently close to the effect of an active control. Because there is no placebo arm in the non-inferiority study, the effect of the active control is not measured in the study itself but must be assumed based on past performance of the active control. The validity of any conclusion from a non-inferiority comparison depends on the estimated effect of the active control and its relevance to the current non-inferiority study. The study should be designed to show that the effect of the test drug, i.e., avacopan, is not inferior to the effect of the active control, i.e., prednisone, by a specified amount, called the non-inferiority margin, or M. It is important to choose a margin that is smaller than the treatment effect of the active control compared to placebo, estimated from historical studies, such that ruling out the margin establishes that the new treatment is effective. A common approach is to choose the margin to be some percentage of a conservative estimate of the effect of the active control, e.g., the lower bound of the confidence interval for the estimated treatment effect of the active control from previous placebo-controlled studies[47].

The Applicant's justification for the non-inferiority margin was based on meta-analyses of 20 published studies to assess the historical disease remission rate at Week 26. Notably, there were not any placebo-controlled historical studies of the active control regimen used in the current study.

(1) The lower bound of the 95% confidence interval for the disease remission rate when receiving cyclophosphamide plus glucocorticoid treatment was 67.5% based on a meta-analysis of 19 studies. The lower bound of the 95% confidence interval for the disease remission rate at Week 26 when receiving rituximab plus glucocorticoid treatment was 54.2% based on a meta-analysis of 3 studies. At the design stage, the Applicant expected that 50% of patients would receive either cyclophosphamide or rituximab in the phase 3 study, thus the average was used. Therefore, the Applicant used the average of the lower bounds, 60.9%, as a conservative estimate of disease remission rates for a clinical trial of patients receiving cyclophosphamide plus glucocorticoids or rituximab plus glucocorticoids.

(2) The disease remission rate with glucocorticoids alone was estimated to be 45.5% (95% CI: 28.7%, 62.3%) based on the meta-analysis of 3 published studies.[48,49,50] The study by Hoffman et al., 1992, included 10 patients with granulomatosis with polyangiitis (GPA, Wegener granulomatosis) who received only glucocorticoids as treatment; the study by Ribi et al., 2010, included 66 patients with microscopic polyangiitis (MPA) who received only glucocorticoids; the study by Nachman et al., 2010, included patients with MPA (67%) or with necrotizing crescentic

[47] See the *FDA Guidance for Industry Non-Inferiority Clinical Trials to Establish Effectiveness* for additional discussion.
[48] Hoffman GS, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116(6):488–498.
[49] Nachman PH, et al. Treatment response and relapse in antineutrophil cytoplasmic autoantibody-associates microscopic polyangiitis and glomerulonephritis. J Am Soc Nephrol 1996;7(1):33–39.
[50] Ribi C, et al. Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: a prospective randomized study of one hundred twenty-four patients. Arthritis Rheum 2010; 62(4):1186–1197.

glomerulonephritis (33%). None of the studies were randomized; for Ribi et al., 2010, patients were to be randomized at the time of treatment failure with glucocorticoids only regimen.

(3) To estimate the contribution of glucocorticoids to the remission rate of the cyclophosphamide/rituximab plus glucocorticoid, the Applicant noted the following:
    a. Assuming that the contribution of glucocorticoids to the remission rate is at least half of the combined cyclophosphamide/rituximab plus glucocorticoid remission rate, the Applicant estimated treatment of effect of glucocorticoids is 30.5% (half of 60.9%).
    b. Using the lower limit of the 95% CI of the remission rate from the meta-analysis of studies with glucocorticoids alone as treatment, a conservative estimated treatment effect is 28.7%.

    By further discounting these treatment effect estimates by one-third, a 20% margin was derived as the non-inferiority margin at Week 26 for the proposed avacopan phase 3 clinical trial.

There are several issues with the Applicant's proposed method to derive the non-inferiority margin. First, there are no historical placebo-controlled trials evaluating the efficacy of glucocorticoids as an add-on therapy to CYC or RTX. Thus, the Applicant relied on single arm results from various different studies. Second, the relevance of many of the historical studies cited for the setting of the proposed NI study is questionable because of potential differences in important factors such as the patient population (e.g., several studies included patients with necrotizing crescentic glomerulonephritis, polyarteritis nodosa), standard of medical care, and treatment regimen (e.g., rate and amount of glucocorticoid tapering). Even the definition of 'remission' and the time point of endpoint assessment were not consistent. Third, the determination of the extent of the contribution of glucocorticoids to the historical estimated remission rate on glucocorticoids + CYC or RTX is based on key, implausible, and unverifiable assumptions; it is unlikely that the efficacy of glucocorticoids alone is similar to that of glucocorticoids when added on to CYC or RTX. Therefore, with the proposed NI margin of -20%, it would be very difficult to determine if a finding of similar remission rates on the proposed comparator arms was due to the efficacy of avacopan or to the fact that the remission rates on both arms were primarily driven by the induction treatment with cyclophosphamide or rituximab (with little to no benefit provided from avacopan).

<u>Birmingham Vasculitis Activity Score (BVAS)</u>

BVAS version 3 was used in this study. BVAS is a standardized measure of disease activity, including 57 clinical features, grouped into 9 organ systems plus an "other" category. Only symptoms/signs attributed to the presence of active AAV were to be reported. Items are scored as "persistent" or "new/worse." Scores can range from 0 to 63. For this study, the following modifications were implemented.

- The BVAS version 3 considers the presence of disease activity within the 28 days prior to assessment. This is what was done in study CL010_168 for all study visits except for Week 4. For the Week 4 BVAS assessment, disease activity with the 7 days prior to visit was to be recorded, in order to avoid inclusion of the baseline visit.

- The “persistent” disease aspect of the BVAS version 3 was not used. Rather, only the presence or absence of disease activity was assessed.

All BVAS data entered by the Investigators were adjudicated by an adjudication committee (AC) to ensure consistency in scoring across all study centers. The AC consisted of AAV disease experts who adjudicated the data according to a charter.

Secondary endpoints, as defined by the Applicant, included the following:

(1) Glucocorticoid-induced toxicity as measured by a change over the first 26 weeks in the GTI
Glucocorticoid Toxicity Index (GTI)
The GTI is a tool intended to quantify toxicity associated with glucocorticoid use. The GTI version 2.0 quantifies changes in glucocorticoid toxicity with 2 scores, the Cumulative Worsening Score (GTI-CWS) and the Aggregate Improvement Score (GTI-AIS).
   - GTI-CWS assesses cumulative glucocorticoid toxicity, regardless of whether the toxicity has lasting effects or is transient. New toxicities that occur are added, but toxicities that resolve on follow-up are not removed. GTI-CWS may increase or remain the same over time but does not decrease. If an investigational agent is effective at decreasing glucocorticoid toxicity over time, the score will be lower in the investigational treatment arm compared to the comparison arms.
   - GTI-AIS is intended to assess whether a therapy is effective at diminishing any glucocorticoid toxicity over time. Toxicities are removed if improvement occurs but can also be added if a new toxicity occurs or if worsening in any item occurs. Therefore, if an investigational agent is effective at decreasing glucocorticoid toxicity over time, the GTI-AIS will decrease over the course of the study in that arm.

(2) BVAS of 0 at Week 4, regardless of whether the subjects received glucocorticoids during this period
This secondary endpoint is not further discussed in this document. The clinical meaningfulness of early remission without sustained remission is unknown.

(3) Change from baseline over 52 weeks in health-related quality of life as measured by the domains and component scores of the SF-36v2 and EQ-5D-5L Visual Analogue Scale (VAS) and Index

(4) Proportion of subjects with relapse and time to experiencing a relapse
Relapse was defined as occurrence of at least one major item in the BVAS or ≥ 3 minor items in the BVAS or 1 or 2 minor items in the BVAS recorded at 2 consecutive visits after having achieved BVAS=0 at any time during the treatment period.

Renal assessments in subjects with renal disease at baseline (based on the BVAS renal component)

(5) Change in eGFR from baseline over 52 weeks
(6) In subjects with albuminuria at baseline, the percent change in urine albumin: creatinine ratio (UACR) from baseline over 52 weeks
(7) Percent change in urinary MCP-1: creatinine ratio from baseline over 52 weeks

Urinary MCP-1:creatinine ratio is a biomarker without established clinical relevance. It is not further discussed in this document.

(8) Change in the VDI from baseline over 52 weeks, including the Week 26 and Week 52 time points

Vasculitis Damage Index (VDI)

The VDI is intended to assess organ damage that occurred in all patients since the onset of vasculitis. It includes 64 items in 11 organ systems (including an "other" category). Damage is defined as the presence of non-healing scars and does not give any indication of current disease activity. Damage items in the VDI are often the direct result of previous disease activity (captured in the BVAS), and damage is defined as having been present or currently present for at least 3 months. Thus, damage would be counted even if it is not currently present. Each item of damage is marked "yes" or "no," and all the positive items (i.e., marked "yes") are totaled. Newly diagnosed patients with less than 3 months since disease onset will have a VDI total score of 0. The VDI score can deteriorate or remain stable, but damage is defined as being irreversible and, thus, cannot decrease over time.

There are limitations to the results of the secondary endpoints. No secondary endpoints were adjusted for multiplicity. Furthermore, the primary time point for the majority of the secondary endpoints was not pre-specified. When there is more than one study endpoint, care must be taken to ensure that the evaluation of multiple hypotheses does not lead to inflation of the study's overall Type I error probability. The inflation of the Type I error rate can be quite substantial if there are many comparisons[51]. Hence, a nominal significance achieved by a secondary endpoint should be interpreted with caution.

Results and Discussion

Patient Disposition

Three hundred thirty-one patients were enrolled in the study and randomized to treatment. One hundred sixty-five patients were randomized to the prednisone arm. Of these, 164 received at least 1 dose of study medication, as the Investigator determined that the renal biopsy for 1 patient did not indicate the presence of vasculitis. One hundred sixty-six patients were randomized to the avacopan arm, and all received at least 1 dose of study medication. As shown in Table 5, 86.0% of patients in the prednisone arm and 80.7% of patients in the avacopan completed treatment through Week 26, and 79.7% of patients in the prednisone arm and 77.7% of patients in the avacopan arm completed treatment through Week 52. Thus, over the course of the study, the proportion of patients who discontinued treatment were similar in each arm, 20.7% in the prednisone arm and 22.3% in the avacopan arm. The most common reason for discontinuation was adverse events for both time periods and reported by a similar proportion of patients in each treatment arm. Patients who discontinued study drug treatment or who initiated medication changes (including those prohibited by the protocol) were not automatically withdrawn from the study, but efforts were made to continue to follow the patients for all regularly scheduled visits. Of the patients who discontinued treatment, 22 out of 34 in the

[51] See the FDA draft guidance *Multiple Endpoints in Clinical Trials Guidance for Industry* for further reference

prednisone arm and 22 out of 37 in the avacopan arm completed the study through the Week 52 assessment.

Table 5. Patient Disposition for Study Treatment at Weeks 26 and 52

	Prednisone (N=164)	Avacopan (N=166)
Completed Week 26 Treatment	**141 (86.0%)**	**134 (80.7%)**
Discontinued Treatment prior to Week 26	23 (14.0%)	32 (19.3%)
Withdrawal by subject	1 (0.6%)	3 (1.8%)
Withdrawal by guardian	-	-
Lost to follow-up	-	1 (0.6%)
Lack of efficacy	-	-
Adverse event	20 (12.2%)	21 (12.7%)
Physician decision	2 (1.2%)	4 (2.4%)
Sponsor decision	-	2 (1.2%)
Other	-	1 (0.6%)
Completed Week 52 Treatment	**130 (79.3%)**	**129 (77.7%)**
Discontinued Treatment prior to Week 52	34 (20.7%)	37 (22.3%)
Withdrawal by subject	1 (0.6%)	3 (1.8%)
Withdrawal by guardian	-	-
Lost to follow-up	-	1 (0.6%)
Lack of efficacy	-	-
Adverse event	29 (17.7%)	26 (15.7%)
Physician decision	3 (1.8%)	4 (2.4%)
Sponsor decision	-	2 (1.2%)
Other	1 (0.6%)	1 (0.6%)

Abbreviations: N=the number of patients randomized who received at least one dose of drug.
Counts and percentages relative to N.
Source: Statistical Reviewer.

Analysis population

The patients randomized in Study CL010_168 had similar baseline demographics across treatment arms. There were more males (56.5%), and patients were generally between the ages of 51 and 75 years (67.6%). More patients had newly diagnosed disease (69.4%), a diagnosis of GPA (54.8%), and MPO positivity (57.0%). Based on BVAS components, most patients had clinical manifestations that fell within the renal component (81.2%), general component (68.2%), ear/nose/throat component (43.6%), and chest component (43.0%); these clinical manifestations were similar across treatment arms. For induction treatment, more patient received RTX (64.8%). Of the 116 patients who received CYC, 96 patients received azathioprine, and 30 patients received mycophenolate as maintenance treatment. Twenty-four patients received both azathioprine and mycophenolate (n=14 in the prednisone arm and n=10 in the avacopan arm). Table 6 and Table 7 present the baseline patient demographics and disease characteristics of the patient population for each treatment arm.

Table 6. Baseline Demographics of Patients in CL010_168

Demographic Parameters	Prednisone (N= 164)	Avacopan (N= 166)
Sex		
Male	88 (53.7%)	98 (59.0%)
Female	76 (46.3%)	68 (41.0%)
Age		
Mean years (SD)	60.5 (14.5)	61.2 (14.6)
Min-max (years)	15-88	13-83
Race		
White	140 (85.4%)	138 (83.1%)
Black or African American	2 (1.2%)	3 (1.8%)
Asian	15 (9.1%)	17 (10.2%)
Other	7 (4.3%)	8 (4.8%)
Ethnicity		
Hispanic or Latino	5 (3.0%)	7 (4.2%)
Not Hispanic or Latino	157 (95.7%)	151 (91.0%)
Not reported/unknown	2 (1.2%)	8 (4.8%)
Region		
North America	25 (15.2%)	34 (20.5%)
Europe and rest of world except Japan	129 (78.7%)	121 (72.9%)
Japan	10 (6.1%)	11 (6.6%)
Height		
Mean cm (SD)	170.0 (11.2)	168.4 (10.7)
Min-max (cm)	141-197	139-188
Weight		
Mean kg (SD)	77.8 (19.3)	76.4 (20.3)
Min-max (kg)	41.9-133.6	40.3-138
BMI		
Mean kg/m^2 (SD)	26.8 (5.2)	26.7 (6.0)
Min-max (kg/m^2)	17.0-41.7	16.5-46.6

Abbreviations: N=the number of patients randomized who received at least one dose of drug; SD=standard deviation; min=minimum; max=maximum.
Counts and percentages relative to N.
Source: Statistical Reviewer.

Table 7. Baseline Disease Characteristics of Patients in CL010_168

	Prednisone (N=164)	Avacopan (N=166)
AAV status		
Newly diagnosed	114 (69.5%)	115 (69.3%)
Relapsed	50 (30.5%)	51 (30.7%)
Age at Diagnosis of AAV		
Mean (SD)	59.4 (15.2)	59.8 (15.6)
Min-Max	12.8-87.7	8.3-83.9
n	164	166
Type of AAV		
Granulomatosis with Polyangiitis (Wegener's)	90 (54.9%)	91 (54.8%)
Microscopic Polyangiitis	74 (45.1%)	75 (45.2%)
Duration of AAV (months)		
Mean (SD)	20.1 (40.5)	22.9 (52.5)
Min-Max	0-212.5	0-362.3
n	164	166
ANCA Positivity		
MPO	94 (57.3%)	94 (56.6%)
PR3	70 (42.7%)	72 (43.4%)
BVAS (adjudicated)		
Mean (SD)	16.2 (5.69)	16.3 (5.87)
Min-Max	5-33	5-37
n	164	166

Abbreviations: N=the number of patients randomized who received at least one dose of drug; SD=standard deviation; min=minimum; max=maximum; n=number of patients with non-missing baseline characteristics; AAV=anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis; BVAS=Birmingham Vasculitis Activity Score.
Counts and percentages relative to N.
Source: Statistical Reviewer.

Primary endpoints

Approximately 72% of the patients on avacopan arm and 70% of the patients on prednisone arm achieved remission at Week 26 (Table 8). The estimated difference in remission rate between avacopan and prednisone was approximately 3%. At Week 26, the non-inferiority comparison was statistically significant (based on the non-inferiority margin proposed by Applicant), but superiority was not demonstrated. Avacopan was superior to prednisone in achieving sustained remission at Week 52 (two-sided p-value=0.0132). The estimated treatment difference in sustained remission rate between avacopan and prednisone was 12.5%.

Table 8. Remission at Week 26 and Sustained Remission at Week 52

	Avacopan (N=166)	Prednisone (N=164)	Difference	Non-inferiority p-value	Superiority p-value
Remission at Week 26	120 (72.3%)	115 (70.1%)	3.4%	<0.0001	0.48
95% CI	(64.8, 78.9)	(62.5, 77.0)	(-6.0, 12.8)		
Sustained Remission at Week 52	109 (65.7%)	90 (54.9%)	12.5%	<0.0001	0.0132
95% CI	(57.9, 72.9)	(46.9, 62.7)	(2.6, 22.3)		

Abbreviations: N=the number of patients randomized who received at least one dose of drug; CI=confidence interval.
Counts and percentages relative to N.
Two-sided p-values from the Summary Score test adjusted for randomization strata were reported. Missing data at Week 26 and Week 52 were imputed as not achieving remission (Week 26) or sustained remission (Week 52), respectively.
Source: Statistical Reviewer.

Discrepancy between Investigator and Adjudication Committee

Analyses of the primary endpoints based on Investigator BVAS assessments were conducted and presented in Table 9. Remission rates and sustained remission rates on both arms were lower using the Investigator assessments compared to the Adjudication Committee assessments. Of note, avacopan was no longer statistically significant in the superiority comparison of sustained remission at Week 52.

Table 9 Analyses Based on Investigator Assessments

	Avacopan (N=166)	Prednisone (N=164)	Difference	Non-Inferiority p-value	Superiority p-value
Remission at Week 26	104 (62.7%)	102 (62.2%)	1.3%	<0.0001	0.79
95% CI	(54.8, 70.0)	(54.3, 69.6)	(-8.7, 11.4)		
Sustained Remission at Week 52	91 (54.8%)	77 (47.0%)	8.5%	<0.0001	0.1026
95% CI	(46.9, 62.5)	(39.1, 54.9)	(-1.7, 18.6)		

Abbreviations: N=the number of patients randomized who received at least one dose of drug; CI=confidence interval.
Counts and percentages relative to N.
Two-sided p-values from the Summary Score test adjusted for randomization strata were reported. Missing data at Week 26 and Week 52 were imputed as not achieving remission (Week 26) or sustained remission (Week 52), respectively.
Source: Statistical Reviewer.

The Applicant explained that "the reason for discrepancies between Investigator and Adjudicator assessments is that Investigators tended to score items that did not show evidence of new or worsening active disease after the baseline assessment." Many of the discrepancies can be attributed to scoring of persistent activity and whether or not it is considered "active." Of the 56 times the Adjudicator changed an Investigator response at Weeks 26 and 52, most of the changes were related to differences in the renal assessment (n=34). The other organ system with the most discrepancies was ENT (n=8).

Subgroup analysis

An analysis of remission at Week 26 and Week 52 by background induction therapy is presented in Table 10. At Week 26, the difference in response rate in the two treatment arms by induction background therapy was similar. However, at Week 52, the magnitude of treatment difference between avacopan and prednisone arms was greater in the patients who received rituximab for induction compared to

patients who received cyclophosphamide induction and azathioprine maintenance therapy. The rituximab-treated patients did not receive standard-of-care maintenance therapy between Weeks 26 and 52, raising questions about the adequacy of comparisons at Week 52.

Table 10 Remission at Week 26 and Sustained Remission at Week 52 by Background Induction Therapy

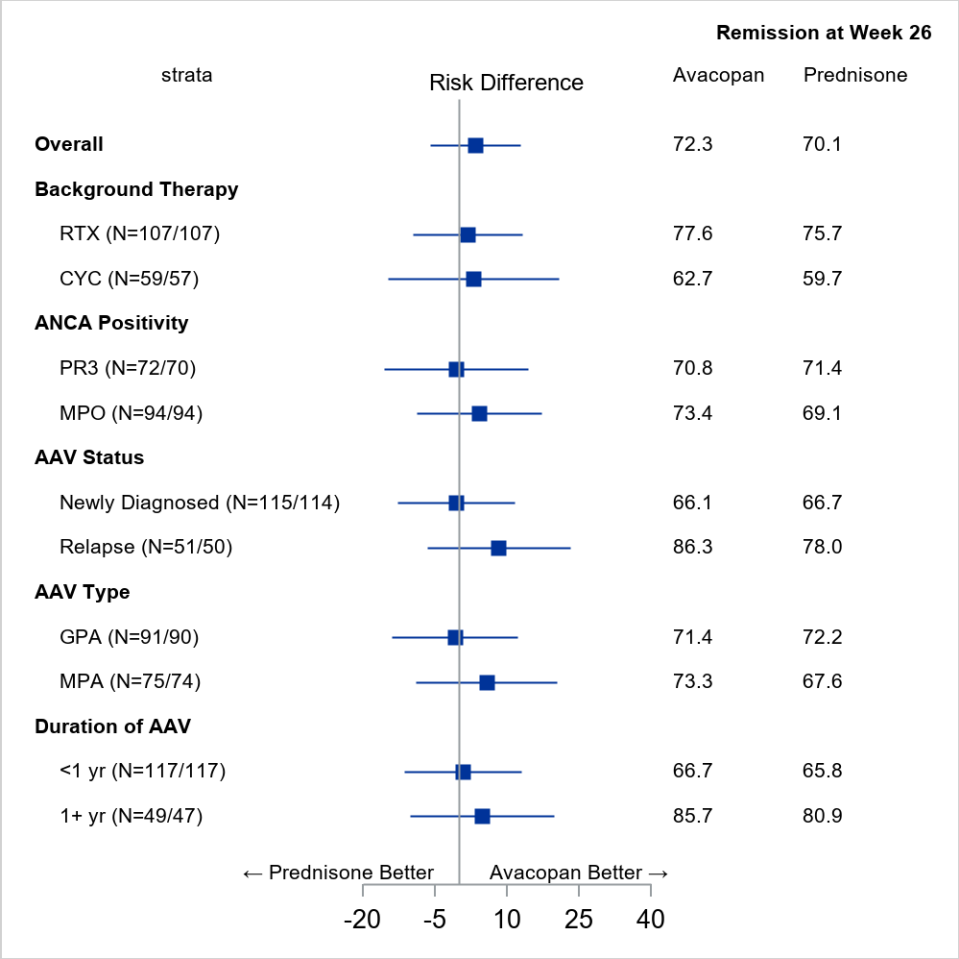
Endpoint	Background Induction Therapy	Treatment	N	Responder Count (%)	Response Rate (95% CI)	Response Rate Difference 95% CI
Remission at Week 26	RTX	Prednisone	107	81 (75.7)	(66.5, 83.5)	1.9% (-9.5%, 13.2%)
		Avacopan	107	83 (77.6)	(68.5, 85.1)	
	CYC	Prednisone	57	34 (59.6)	(45.8, 72.4)	3.1% (-14.7%, 20.8%)
		Avacopan	59	37 (62.7)	(49.1, 75.0)	
Sustained Remission at Week 52	RTX	Prednisone	107	60 (56.1)	(46.1, 65.7)	15.0% (2.2%, 27.7%)
		Avacopan	107	76 (71.0)	(61.5, 79.4)	
	CYC	Prednisone	57	30 (52.6)	(39.0, 66.0)	3.3% (-14.8%, 21.4%)
		Avacopan	59	33 (55.9)	(42.4, 68.8)	

Abbreviations: N=the number of patients randomized who received at least one dose of drug; CI=confidence interval.
Counts and percentages relative to N.
Point estimate and 95% confidence interval using normal approximation were reported.
Source: Statistical Reviewer.

Analyses of the two primary endpoints by baseline disease characteristic subgroups, including background induction therapy, are further presented in the forest plots in Figure 6 (remission at Week 26) and Figure 7 (sustained remission at Week 52). Though these subgroups were pre-specified, there are limitations with such subgroup analyses, as these are exploratory analyses which are not controlled for multiplicity and consist of a smaller number of patients.

Figure 6 shows that, at Week 26, results from subgroup analyses were generally consistent with findings in the overall population.

Figure 6 Remission at Week 26 by Randomization Strata or Baseline Characteristics



The notation N=XXX/YYY indicates the number of patients randomized who received at least one dose of drug in avacopan and prednisone arm, respectively.
Source: Statistical Reviewer.

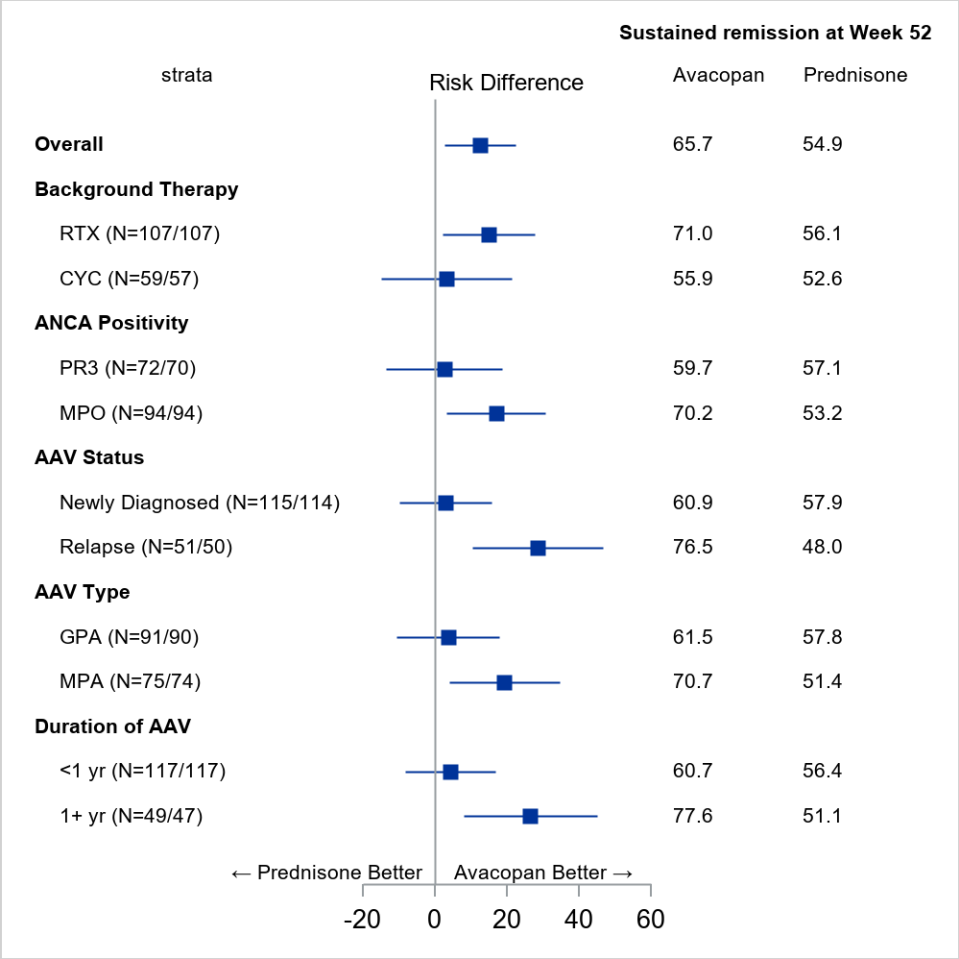
At Week 52 (Figure 7), multiple subgroups (RTX induction therapy, MPO positivity, baseline relapsing disease, underlying MPA, and disease duration of > 1 year) appeared to have larger magnitude of treatment effect. The larger treatment effect in patients who are MPO positive and those with MPA may be expected based on clinical experience in these populations. PR3-positivity and GPA are associated with increased risk relapse, treatment failure, and more organ involvement.[52,53,54] The baseline disease characteristic that seemed to have the greatest influence on treatment effect was relapsing disease, the proportion of patients who achieved sustained remission in patients with relapsing disease was 76.5% in the avacopan arm compared to 48% in the prednisone arm. However, for newly diagnosed

[52] Geetha D and Jefferson JA. ANCA-associated vasculitis: core curriculum 2020. *Am J Kidney Dis*. 2019; 75: 124-137.
[53] Hilhorst M, van Paassen P, Tervaert JWC. Proteinase 3-ANCA vasculitis versus Myeloperoxidase ANCA vasculitis. *J Am Soc Nephrol*. 2015; 26: 2314-2327.
[54] Wallace ZS and Miloslavsky EM. Management of ANCA associated vasculitis. *BMJ.* 2020; 368: m421.

disease, responses were similar between the two treatment arms, 60.9% in the avacopan arm and 57.9% in the prednisone arm.

Based on background induction therapy, the proportion of patients who received RTX induction and achieved sustained remission at Week 52 was 71.0% in the avacopan arm vs. 56.1% in the prednisone arm. Responses were similar in patients who received CYC induction, 55.9% in the avacopan arm and 52.6% in the prednisone arm. In this study, the RTX subgroup did not receive maintenance therapy between Weeks 26 and 52. The lack of maintenance therapy in this subgroup of patients may have resulted in this greater treatment difference at Week 52.

Figure 7 Sustained Remission at Week 52 by Randomization Strata or Baseline Characteristics



The notation N=XXX/YYY indicates the number of patients randomized who received at least one dose of drug in avacopan and prednisone arm, respectively.
Source: Statistical Reviewer.

A similar subgroup analysis of the primary endpoint was performed utilizing baseline demographics (Figure 12. [Remission at Week 26] and Figure 13. [Sustained Remission at Week 52] in Appendix). Results from subgroup analyses by baseline demographics were consistent with findings in the overall

population, with some variability from the smaller subgroups, such as the adolescent subgroup with age 12-17 years.

Secondary endpoints

Glucocorticoids

Glucocorticoid use and the potential decrease in toxicities from glucocorticoids in the avacopan arm were an important objective of the avacopan program, intended to support a steroid-sparing benefit of avacopan.

Glucocorticoid Toxicity Index (GTI)

GTI was developed to quantitatively capture glucocorticoid toxicity and the glucocorticoid-sparing ability of therapies. The index is composed of the broad categories of body mass index (BMI), glucose tolerance, blood pressure, lipids, steroid myopathy, skin toxicity, neuropsychiatric toxicity, and infection. Observed changes in these broad categories are weighted and can result in an increase or decrease in points; for example, an increase in blood pressure or the diagnosis of oral/vaginal candidiasis or uncomplicated zoster are each associated with an increase of 19 points. As described above, higher scores are reflective of greater toxicity. The GTI was assessed while patients in the standard of care arm received protocol-specified prednisone (i.e., through Week 20) with the last assessment of GTI performed at Week 26. Although non-study supplied glucocorticoids were administered in both arms throughout the treatment duration (discussed in detail below), there is no assessment of GTI at any of the later time points.

The Applicant assessed steroid toxicity based on the GTI-CWS and GTI-AIS. Table 11 shows the GTI-CWS at Weeks 13 and 26. At both time points, the GTI-CWS increased compared to baseline, consistent with greater toxicity. The increase in the GTI-CWS was nominally significantly lower in the avacopan arm.

Table 11. Glucocorticoid Toxicity Index-Cumulative Worsening Score (GTI-CWS) at Weeks 13 and 26

Treatment Arm	Change from Baseline		
	LS Mean[1] (95% CI)	Diff (95% CI)	P-value
Week 13			
Prednisone	36.9 (31.3, 42.6)		
Avacopan	26.0 (20.4, 31.6)	-10.9 (-18.2, -3.7)	0.0033
Week 26			
Prednisone	57.0 (49.4, 64.6)		
Avacopan	40.2 (32.7, 47.8)	-16.8 (-27.0, -6.5)	0.0014

1: Least square (LS) means and p-values were derived from a mixed effects model for repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction, and randomization strata as factors. An unstructured covariance matrix was used to model the within-subject variance-covariance structure for the model errors.
If a Visit after Week 13 (e.g., early termination visit) also falls within the Week 13 analysis visit window (Day 2-137) and no Week 26 exist, using the Last Observation Carried Forward, this Visit was assigned to Week 26 Analysis VISIT.
Abbreviations: LS=least square; CI=confidence interval; Diff=difference.
Source: Statistical Reviewer.

Unlike GTI-CWS which only scores worsening, GTI-AIS measures both worsening and improvement in the different body systems. GTI-AIS is presented in Table 12 and again shows an increase from baseline in

both treatment arms, consistent with greater toxicity. The increase in GTI-AIS is lower in the avacopan arm, and the difference as compared to the prednisone arm is nominally significant at Weeks 13 and 26.

Table 12. Glucocorticoid Toxicity Index-Aggregate Improvement Score (GTI-AIS) at Weeks 13 and 26

Treatment Arm	Change from Baseline		
	LS Mean[1] (95% CI)	Diff (95% CI)	P-value
Week 13			
Prednisone	23.3 (16.7, 29.9)		
Avacopan	10.0 (3.4, 16.5)	-13.3 (-21.8, -4.8)	0.0024
Week 26			
Prednisone	23.5 (16.4, 30.6)		
Avacopan	11.4 (4.3, 18.5)	-12.1 (-21.5, -2.7)	0.0114

1: Derived from a mixed effects model for repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction, and randomization strata as factors. An unstructured covariance matrix was used to model the within-subject variance-covariance structure for the model errors.
If a Visit after Week 13 (e.g., early termination visit) also falls within the Week 13 analysis visit window (Day 2-137) and no Week 26 exist, using the Last Observation Carried Forward, this Visit was assigned to Week 26 Analysis VISIT.
Abbreviations: LS=least square; CI=confidence interval; Diff=difference.
Source: Statistical Reviewer.

There are limitations to the interpretation of the GTI-CWS and GTI-AIS. The GTI is a clinician-reported instrument and is not considered a direct measure of how a patient feels, functions, or survives. The GTI does not include the patients' perspectives, rather it is a measure of clinician-reported outcomes and biomarkers. The clinically meaningful within-patient change is not known. Certain rare but serious events (in the domains of "endocrine," "gastrointestinal," "musculoskeletal," and "ocular") are omitted from the GTI score. (b) (4) . Lastly, the clinical meaningfulness of a measure of glucocorticoid toxicity is unclear when one arm required glucocorticoids (protocol-specified prednisone) and one did not. There was no comparable measure of the potential toxicities associated with avacopan (i.e., hepatotoxicity). Thus, this could lead to an inherently biased assessment in this study.

SEE ATTACHED ERRATA

Glucocorticoid Use

Another approach to assessing glucocorticoid use in study CL010_168 was to analyze the actual glucocorticoid use and to calculate the doses administered in both treatment arms. In this section, "cumulative glucocorticoid use" refers to all glucocorticoids used in both treatment arms, i.e., the protocol-specified, 20-week prednisone taper in the prednisone arm, as well as the non-study supplied glucocorticoids in both treatment arms. Also, of interest, is an evaluation of only non-study supplied glucocorticoids (i.e., use beyond what was prespecified), and this is discussed separately below.

The mean cumulative glucocorticoid use per patient over 52 weeks was 3654.5 mg in the prednisone arm compared to 1348.9 mg in the avacopan arm. Table 13 presents the cumulative glucocorticoid use in both treatment arms by induction therapy and by treatment period. As the protocol-specified taper allowed for prednisone through Week 20, it is expected that patients in the prednisone arm received more glucocorticoids during the first half of the study. Although glucocorticoids were not protocol-specified for the avacopan arm, 86% of patients in the avacopan arm still received glucocorticoids in the

first half of the study. The mean cumulative glucocorticoid use at Week 26 was 1072.9 mg in the avacopan arm and 3192.5 mg in the prednisone arm. In the second half of the study, glucocorticoid use was not protocol-specified but could be administered for reasons as previously described (vasculitis, adrenal insufficiency, and other conditions). (b) (4)

In the prednisone arm, the mean cumulative dose was 580.0 mg and 399.2 mg in patients who received CYC and RTX, respectively; in the avacopan arm, the mean cumulative dose was 270.3 mg and 279.1 mg in patients on CYC and RTX respectively.

SEE ATTACHED ERRATA

Table 13. Cumulative Glucocorticoid Use (Prednisone or Prednisone Equivalent in mg) in Study CL010_168 (Week 0-26, Week 26-52, and Week 0-52) by Background Therapy

Induction Therapy	CYC		RTX	
	Prednisone + CYC N=57	Avacopan + CYC N=59	Prednisone + RTX N=107	Avacopan + RTX N=107
Glucocorticoid Use Weeks 0-26				
Number of subjects[1]	57 (100%)	40 (67.8%)	107 (100%)	103 (96.3%)
Mean dose[2]	3373.1	1092.3	3096.1	1062.2
Median dose[2]	2785	280	2870	400
Range of dose	760-8543	0-8555	1385-10465	0-8337
Glucocorticoid Use Weeks 27-52				
Number of subjects	21 (36.8%)	16 (27.1%)	42 (39.3%)	28 (26.2%)
Mean dose	580.0	270.3	399.2	279.1
Median dose	0	0	0	0
Range of dose	0-4263	0-2980	0-5208	0-3890
Glucocorticoid Use Weeks 0-52				
Number of subjects	57 (100%)	42 (71.2%)	107 (100%)	103 (96.3%)
Mean dose	3953.1	1362.6	3495.3	1341.3
Median dose	2838	285	2950	430
Range of dose	760-10203	0-9575	1385-12033	0-9612

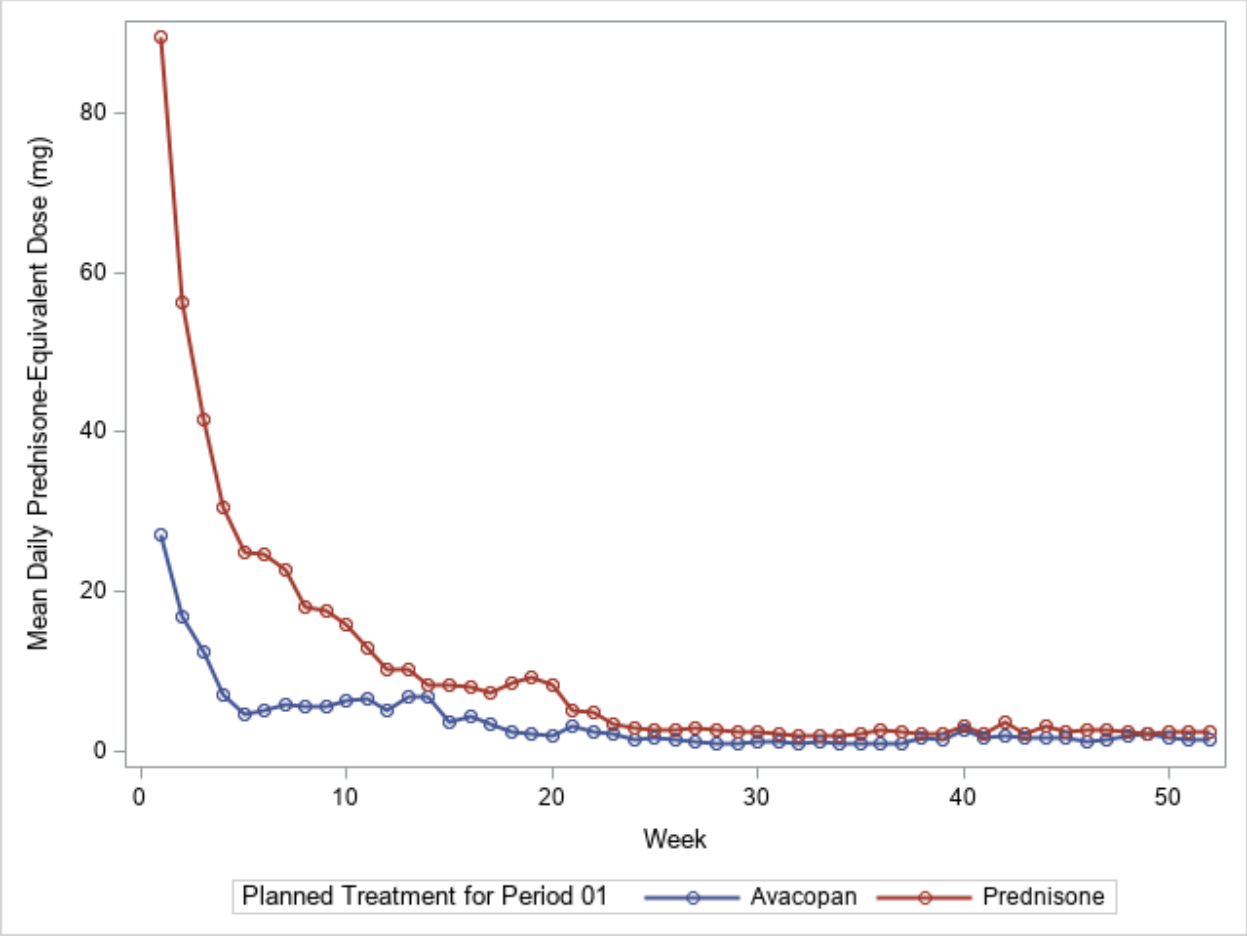
Abbreviations: N=number of all patients randomized who received at least one dose of drug; CYC=cyclophosphamide; RTX=rituximab.

1. Counts and percentages relative to N.
2. Mean and median based on all patients randomized who received at least one dose of drug.

Source: Statistical Reviewer

Figure 8 is a graphical representation of the cumulative glucocorticoid use, including protocol-specified prednisone and non-study supplied glucocorticoids, by mean daily dose in each treatment arm. As previously stated, both treatment arms received glucocorticoids throughout the study. In the initial portion of the study, because of the protocol-specified prednisone taper, there is a large difference in the mean daily dose between the two arms. After completion of the 20-week prednisone taper, the mean daily dose is essentially the same during the second half of the study. The clinical relevance of the differences in the glucocorticoid doses used from Week 0 to 26 between the prednisone and avacopan arms is uncertain, as it may be an artifact of the study design rather than a reflection of avacopan's control of disease activity.

Figure 8. Mean Daily Dose of Cumulative Glucocorticoid Use (Prednisone Equivalent Dose)



Mean daily dose is calculated by dividing the total use in a week by (7 times the total number of subjects in each arm).
Source: Statistical Reviewer.

Because glucocorticoid use was specified for only the prednisone arm, there is an interest in comparing the amount of glucocorticoids used beyond the protocol-specified amount, i.e., non-study supplied glucocorticoid use, provided at the Investigator's discretion. An analysis of non-study supplied glucocorticoid use showed that similar numbers of patients in both treatment arms required glucocorticoids (Table 14).

Table 14. Number of Patients Who Received Non-Study Supplied Steroids (Week 0 to 52)

	Glucocorticoid Use	No Glucocorticoid Use	Total
Avacopan	145 (87.3%)	21 (12.7%)	166
Prednisone	149 (90.9%)	15 (9.1%)	164

Source: Statistical Reviewer.

The mean dose of cumulative non-study supplied glucocorticoid use was also similar across treatment arms through the 52-week study duration, 1265.3 mg in the prednisone arm and even greater at 1348.9 mg in the avacopan arm. Table 15 presents the cumulative non-study supplied glucocorticoid use by treatment periods and by background induction therapy. More non-study supplied glucocorticoids were

used in the first half of the study in both treatment arms. More patients who received induction therapy with RTX (96.3% in the avacopan arm and 97.2% in the prednisone arm) required non-study supplied glucocorticoids compared to those who received induction therapy with CYC (67.8% in the avacopan arm and 78.9% in the prednisone arm) in the first half of the study. Mean dose of non-study supplied glucocorticoids in the first half of the study was greater in the avacopan arm than in the prednisone arm, regardless of background induction therapy. In the second half of the study, the proportion of patients requiring non-study supplied steroids was similar across treatment arms and background induction therapy. Mean dose of non-study supplied glucocorticoids in the second half of the study was numerically lower in the avacopan arm than in the prednisone arm, regardless of background induction therapy, although differences between treatment arms were relatively small.

Table 15. Cumulative Non-Study Supplied Steroid Use (Prednisone or Prednisone-Equivalent in mg) in Study CL010_168 (Week 0-26, Week 26-52, Week 0-52) by Background Therapy

Induction Therapy	CYC		RTX	
	Prednisone + CYC N=57	Avacopan + CYC N=59	Prednisone + RTX N=107	Avacopan + RTX N=107
Glucocorticoid Use Weeks 0-26				
Number of subjects[1]	45 (78.9%)	40 (67.8%)	104 (97.2%)	103 (96.3%)
Mean dose[2]	1031.2	1092.3	681.7	1062.2
Median dose[2]	290	280	415	400
Range of dose	0-6098	0-8555	0-4160	0-8337
Glucocorticoid Use Weeks 27-52				
Number of subjects	21 (36.8%)	16 (27.1%)	42 (39.3%)	28 (26.2%)
Mean dose	580.0	270.3	399.2	279.1
Median dose	0	0	0	0
Range of dose	0-4263	0-2980	0-5208	0-3890
Glucocorticoid Use Weeks 0-52				
Number of subjects	45 (78.9%)	42 (71.2%)	104 (97.2%)	103 (96.3%)
Mean dose	1611.2	1362.6	1080.8	1341.3
Median dose	345	285	495	430
Range of dose	0-8488	0-9575	0-5528	0-9612

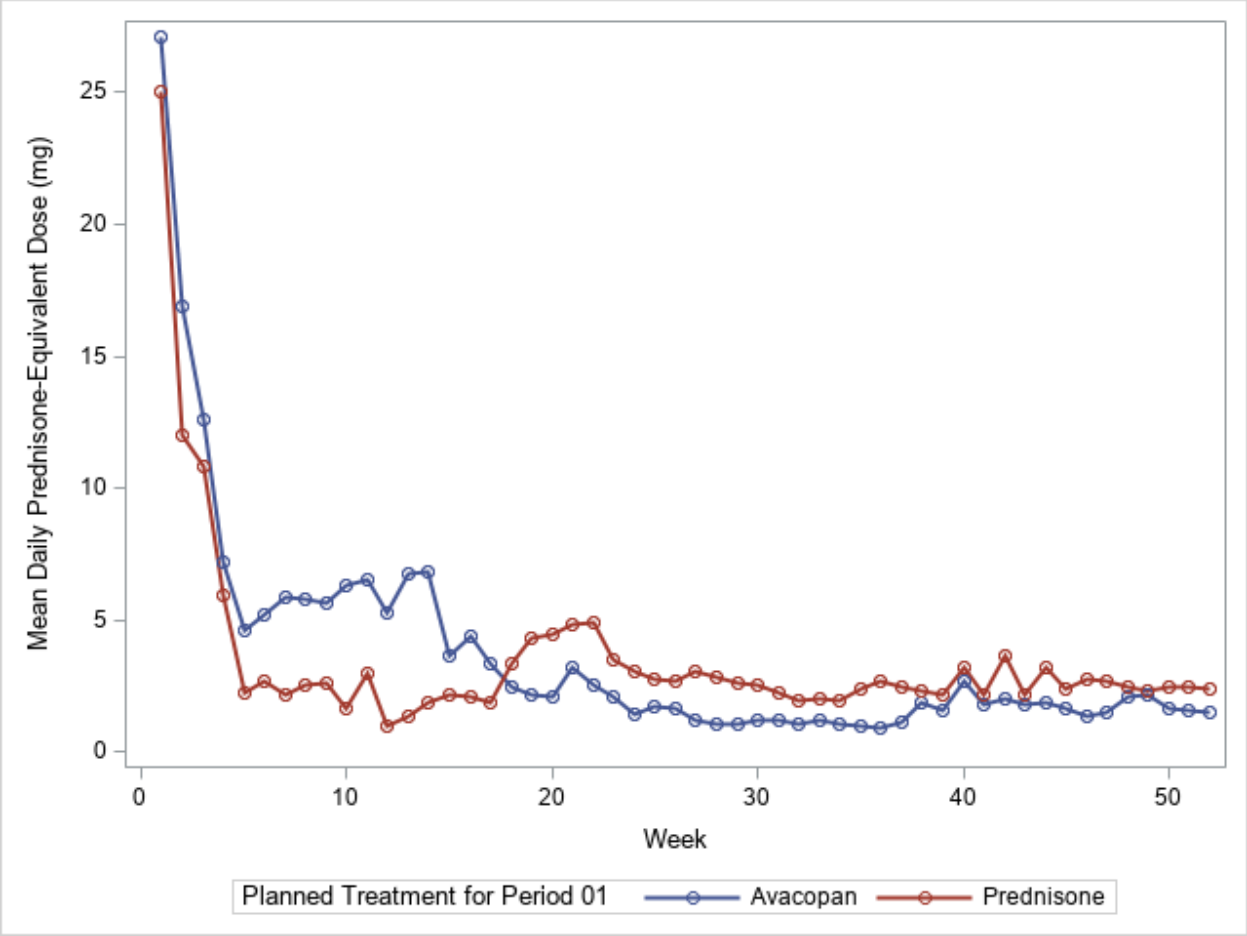
Abbreviations: N=number of all patients randomized who received at least one dose of drug; CYC=cyclophosphamide; RTX=rituximab.

1. Counts and percentages relative to N.
2. Mean and median based on all patients randomized who received at least one dose of drug.

Source: Statistical Reviewer

Figure 9 is a graphical representation of this same information by mean daily dose of non-study supplied glucocorticoids by treatment arm. It is clear that both treatment arms required non-study supplied glucocorticoids. During the induction period, the avacopan arm required more non-study supplied glucocorticoids. Following induction, all glucocorticoid use was non-study supplied, and the amount of use was similar across treatment arms.

Figure 9. Mean Daily Dose of Cumulative Non-Study Supplied Glucocorticoids (Prednisone Equivalent Dose)



Mean daily dose is calculated by dividing the total use in a week by (7 times the total number of subjects in each arm).
Source: Statistical Reviewer.

Reasons for Non-Study Supplied Glucocorticoid Use

Investigators could treat study subjects with non-study supplied glucocorticoids for a variety of reasons. Specifically, for the treatment of AAV non-study supplied glucocorticoids were used to treat persistent vasculitis, worsening vasculitis, and relapse. Worsening vasculitis and relapse are defined above in the description of the protocol. Patients had persistent vasculitis if they had one or more major items in the BVAS before study entry and did not show improvement or stabilization of these major items within the first 4 weeks of the study. Glucocorticoids for maintenance of remission were to be avoided as much as possible, but patients were included in this category if they had achieved a BVAS of 0 but still required glucocorticoids. Over the 52-week study period, 117 patients (71.3%) in the prednisone arm received glucocorticoids for vasculitis, and 106 patients (63.9%) in the avacopan arm received glucocorticoids for vasculitis. A similar number of patients in each treatment arm received glucocorticoids for persistent vasculitis (n=85 [51.8%] in the prednisone arm, n=80 [48.2%] in the avacopan arm), worsening vasculitis (n=29 [17.7%] in the prednisone arm, n=31 [18.7%] in the avacopan arm), and maintenance of remission (n=26 [15.9%] in the prednisone arm, n=32 [19.3%] in the avacopan arm). However, more patients in the

prednisone arm (n=38 [23.2%]) received glucocorticoids to treat a relapse compared to patient in the avacopan arm (n=17 [10.2%]).

Table 16 presents a summary of the reasons why patients received non-study supplied glucocorticoids by background induction therapy and by treatment periods (Week 0 to 26 and 27 to 52). Focusing on patients who received glucocorticoids for vasculitis, in the first half of the study, the greatest proportion of patients in both treatment arms received glucocorticoids for persistent vasculitis. In the second half of the study, the proportion of patients who received non-study supplied glucocorticoids for vasculitis was lower. In both parts of the study, across treatment arms, the proportion of patients requiring non-study supplied glucocorticoids was similar for treatment of worsening vasculitis, persistent vasculitis, and remission. There was, however, a numerical difference between the avacopan and prednisone groups in the treatment of relapse with more patients in the prednisone group requiring non-study supplied glucocorticoids for relapse. From Week 0 to 26, 6.6% of patients in the avacopan arm (n=11) received non-study supplied glucocorticoids for relapse compared to 17.7% of patients in the prednisone arm (n=29). From Week 27-52, 4.8% of patients in the avacopan arm (n=8) received non-study supplied glucocorticoids for relapse compared to 15.2% in the prednisone arm (n=25). As shown in Table 16, over the course of the study, a greater proportion of patients in the rituximab subgroup on both arms received non-study supplied glucocorticoids for the treatment of relapse (prednisone 28.0%, avacopan 11.2%) as compared to the cyclophosphamide group (prednisone 14.0%, avacopan 8.5%).

Table 16. Reasons for Use of Non-Study Supplied Glucocorticoids in Study CL010_168 by Background Therapy (Week 0 to 26 and Week 27 to 52)

	Avacopan (N=166)		Prednisone (N=164)	
	RTX (N=107)	CYC (N=59)	RTX (N=107)	CYC (N=57)
Week 0 to 26				
Treatment of AAV	**65 (60.7%)**	**38 (64.4%)**	**71 (66.4%)**	**42 (73.7%)**
Treatment of worsening vasculitis	17 (15.9%)	10 (16.9%)	9 (8.4%)	13 (22.8%)
Treatment of relapse	9 (8.4%)	2 (3.4%)	24 (22.4%)	5 (8.8%)
Treatment of persistent vasculitis	47 (43.9%)	30 (50.8%)	46 (43.0%)	37 (64.9%)
Maintenance of remission	14 (13.1%)	13 (22.0%)	13 (12.1%)	7 (12.3%)
Treatment of other disorder, not vasculitis†	15 (14.0%)	5 (8.5%)	11 (10.3%)	6 (10.5%)
Treatment of adrenal insufficiency	2 (1.9%)	1 (1.7%)	7 (6.5%)	1 (1.8%)
Pre-medication for rituximab	96 (89.7%)	4 (6.8%)	95 (88.8%)	4 (7.0%)
Pre-medication for other agent	1 (0.9%)	4 (6.8%)	1 (0.9%)	7 (12.3%)
Week 27 to 52				
Treatment of AAV	**19 (17.8%)**	**14 (23.7%)**	**29 (27.1%)**	**21 (36.8%)**
Treatment of worsening vasculitis	6 (5.6%)	4 (6.8%)	4 (3.7%)	10 (17.5%)
Treatment of relapse	5 (4.7%)	3 (5.1%)	18 (16.8%)	7 (12.3%)
Treatment of persistent vasculitis	6 (5.6%)	4 (6.8%)	5 (4.7%)	9 (15.8%)
Maintenance of remission	6 (5.6%)	7 (11.9%)	10 (9.3%)	6 (10.5%)
Treatment of other disorder, not vasculitis	7 (6.5%)	3 (5.1%)	7 (6.5%)	1 (1.8%)
Treatment of adrenal insufficiency	-	-	5 (4.7%)	-
Pre-medication for rituximab	9 (8.4%)	1 (1.7%)	12 (11.2%)	4 (7.0%)
Pre-medication for other agent	-	-	-	-

† Other disorders (not vasculitis) does not include adrenal insufficiency or pre-medication, which are analyzed separately.
Patients were non-responders if relapse occurred after Week 26.
Patients who experienced relapse before Week 26 or the other reasons for AAV (in red) could still be responders as long as glucocorticoids were not administered within 4 weeks of assessment.
Glucocorticoids for any of the reasons shaded in blue at any time did not preclude a patient from being a responder.
Abbreviations: N=the number of patients randomized who received at least one dose of drug; AAV=ANCA-associated vasculitis.
Counts and percentages relative to N.
Source: Statistical Reviewer.

In summary, based on these exploratory analyses, a smaller proportion of patients in the avacopan arm required glucocorticoids for relapse than in the prednisone arm, while similar proportions of patients required non-study supplied glucocorticoids to control increased disease activity, based on worsening vasculitis, persistent vasculitis, and maintenance of remission. The assessment of relapses is discussed further in the next section.

It is important to recognize that the requirement for glucocorticoids did not necessarily preclude patients from being categorized as responders. Patients who experienced a relapse after achieving remission at Week 26 and patents who were treated with glucocorticoids for vasculitis within 4 weeks of the endpoint assessment (at Week 26 or 52) were considered non-responders. Otherwise, patients could receive glucocorticoids for vasculitis and were still considered responders. Selected examples of patients who received glucocorticoids for vasculitis or a clinical finding potentially concerning for vasculitis but who were still considered responders are described in the Table 30. Examples of patients who were considered responders despite non-study supplied glucocorticoids include patients who

received multiple courses of prednisone for vasculitis, who received IV glucocorticoids for pulmonary hemorrhage, and who received multiple doses of IV glucocorticoids for vasculitis and lung nodules. These cases highlight how challenging it is to interpret the glucocorticoid use and the contribution to therapeutic benefit in this study.

Relapse

The Applicant evaluated relapse, i.e., proportion of patients with relapse and time to relapse based on the subset of patients who achieved remission, as secondary endpoints. As previously noted, relapse was defined as worsening of disease after having previously achieved remission (BVAS=0) as defined by ≥ 1 major item in the BVAS or ≥ 3 minor items in the BVAS or 1-2 minor items in the BVAS at 2 consecutive study visits. The Applicant's analysis of relapse, however, is limited, as it depends on post-randomization variables, i.e., having first achieved remission and the timing of the remission. As a result, the subset of subjects included in this analysis and the time those subjects are at risk for relapse can no longer be assumed to be similar across treatment arms. The advantages of randomization are eliminated because the treatment arms are no longer balanced with respect to possible confounders, leading to potentially biased comparisons between treatment arms and limiting the interpretability of these results. For example, remission may be achieved in different types of patients in the two treatment arms. Thus, when the treatment arms are compared with respect to relapse, differences cannot be attributed to the treatment, but rather to differences in the characteristics of the subset of patients included in the analysis. For these reasons, these results are considered exploratory only.

The Agency performed an alternative exploratory analysis to assess relapse that instead incorporates all patients and addresses the concerns of conditioning on a post-randomization variable. Table 17 presents patients who did not achieve remission in both treatment arms, as well as patients who relapsed after achieving remission (before or after Week 26). In the primary endpoints, patients who achieved remission after Week 26 (e.g., Week 39) would have been considered non-responders at both Week 26 and Week 52. In contrast to the primary endpoint assessment, patients who achieved remission after Week 26 but did not suffer a relapse before the Week 52 assessment are considered responders in this analysis. Thus, this exploratory analysis attempts to evaluate the patients with refractory and/or relapsing disease based on the overall population.

The overwhelming majority of randomized patients in Study CL010_168 achieved remission (i.e., BVAS=0) during the 52-week double-blind treatment period. The number of patients in each treatment arm who never achieved remission was similar in each treatment arm (4.8% in the avacopan arm and 4.3% in the prednisone arm). However, more patients in the prednisone arm (20.1%) experienced a relapse compared to patients in the avacopan arm (9.6%). Hence, the proportion of patients who never achieved remission or achieved remission but had a relapse was larger in the prednisone group (24.4% vs 14.5%, difference: -9.9% with 95% CI: [-18.4%, -1.5%][55]). These post-hoc analyses are exploratory and

[55] Point estimate and 95% confidence interval using normal approximation were reported.

do not on their own support a determination that avacopan decreases relapses or helps to achieve remission.

Table 17. Proportion of Patients Who Did Not Achieve Remission (BVAS=0) or Relapsed after Remission (BVAS=0)

Summary by Treatment Arms				
	Prednisone (N=164)		**Avacopan (N=166)**	
Did not achieve BVAS=0	7 (4.3%)		8 (4.8%)	
Achieved BVAS=0	157 (95.7%)		158 (95.2%)	
Relapse	33 (20.1%)		16 (9.6%)	
Between Week 0-Week 26[1]	16 (9.8%)		3 (1.8%)	
Between Week 27-Week 52[2]	17 (10.4%)		13 (7.8%)	
Did not achieve BVAS=0 or Relapsed	40 (24.4%)		24 (14.5%)	
Summary by Treatment Arms and Background Induction Therapy				
	Prednisone (N=164)		**Avacopan (N=166)**	
	RTX (N=107)	**CYC (N=57)**	**RTX (N=107)**	**CYC (N=59)**
Did not achieve BVAS=0	3 (2.8%)	4 (7.0%)	3 (2.8%)	5 (8.5%)
Achieved BVAS=0	104 (97.2%)	53 (93.0%)	104 (97.2%)	54 (91.5%)
Relapse	21 (19.6%)	12 (21.1%)	9 (8.4%)	7 (11.9%)
Between Week 0-Week 26[1]	8 (7.5%)	8 (14.0%)	1 (0.9%)	2 (3.4%)
Between Week 27-Week 52[2]	13 (12.1%)	4 (7.0%)	8 (7.5%)	5 (8.5%)
Did not achieve BVAS=0 or Relapsed	24 (22.4%)	16 (28.1%)	12 (11.2%)	12 (20.3%)

1. Day 1 to Day 183
2. Day 184 to End of treatment

Abbreviations: N=the number of patients randomized who received at least one dose of drug; BVAS=Birmingham Vasculitis Activity Score.

Counts and percentages relative to N.

Source: Statistical Reviewer.

Vasculitis Damage Index (VDI)

Vasculitis items that were persistent for at least 3 months and "did not show evidence of worsening disease" were not scored on the BVAS, as modified in this study. Instead, the Applicant noted that the Vasculitis Damage Index (VDI) would capture "persistent disease." The VDI was one of the secondary endpoints. As previously described, it captures any vasculitis activity that has been present or is currently present for 3 months.

Table 18 shows the change from baseline in VDI in both treatment arms after induction (Week 26) and maintenance (Week 52). The change from baseline in VDI was similar between treatment arms at both timepoints.

Table 18. Change from Baseline in Vasculitis Damage Index (VDI) at Weeks 26 and 52

Treatment Arm	Change from Baseline		
	LS Mean[1] (95% CI)	Diff (95% CI)	P-value
Week 26			
Prednisone	0.95 (0.77, 1.13)		
Avacopan	1.04 (0.87, 1.22)	0.10 (-0.13, 0.33)	0.3888
Week 52			
Prednisone	1.13 (0.94, 1.32)		
Avacopan	1.16 (0.97, 1.34)	0.03 (-0.21, 0.27)	0.7969

1: Derived from a mixed effects model for repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction, and randomization strata as factors. An unstructured covariance matrix was used to model the within-subject variance-covariance structure for the model errors.
Abbreviations: LS=least square; CI=confidence interval; Diff=difference.
Source: Statistical Reviewer.

As the VDI is a measure of both past and present disease that is persistent for at least 3 months, these results suggest that patients had similar levels of persistent disease or damage over time with either avacopan or prednisone. Although the Applicant states that the persistent active disease that would normally have been captured by the BVAS Version 3 would be captured instead with the VDI, it would be very difficult to distinguish how much of the "persistent" disease activity is active disease and, therefore, potentially responsive to treatment versus chronic damage, which may not be expected to respond to treatment. Assessment of a change in persistently active disease would be important in assessing the therapeutic benefit of avacopan.

Quality of Life Measures

Quality of life was assessed based on the SF-36 and EQ-5D-5L, both general quality of life instruments, not specific to the assessment of vasculitis. Favorable trends towards improvement were observed in the avacopan group as compared to the prednisone group. On the SF-36, the point estimate for the mean change from baseline in PCS and MCS at Week 52 trended toward greater improvement in the avacopan group across the 8 domains although the confidence intervals did not rule out zero effect in most of the domains. EQ-5D-5L, is based on a Visual Analogue Scale and a population norm-based Index. The EQ-5D-5L showed improvement in the avacopan group compared to the prednisone group for the VAS score (13.1 vs. 7.0, respectively) and greater change from baseline in the Index score (0.0481 vs. -0.0027, respectively) at Week 52[56], indicating the patients in the avacopan group generally felt better about their overall health compared to the prednisone group. Smaller differences between treatment groups were observed at Week 26. The clinical meaningfulness of these improvements and differences between the avacopan and prednisone arms are unclear.

[56] Derived from a mixed effects model for repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction, and randomization strata as factors. An unstructured covariance matrix was used to model the within-subject variance-covariance structure for the model errors.

Secondary endpoint: Renal assessment

The Division of Cardiology and Nephrology (DCN) was consulted to assist with determining the clinical meaningfulness of the renal endpoints.

Baseline renal disease

Patients were categorized as having baseline renal disease by meeting criteria for the BVAS renal component. Specifically, Investigators assessed the following:

- Hypertension (HTN): Diastolic blood pressure (DBP) was > 95 mmHg and if HTN was considered related to AAV SEE ATTACHED ERRATA
- Proteinuria: Proteinuria is > 1+ on urinalysis or > 0.2 g protein: g creatinine on urine sample
- Hematuria: (b) (4)
- Elevated serum creatinine (SCr) at first assessment at the following levels:
    - Serum creatinine 1.41-2.82 mg/dL
    - Serum creatinine 2.83-5.64 mg/dL
    - Serum creatinine ≥ 5.65 mg/dL
- Score >30% increase in creatinine or >25% fall in creatinine clearance

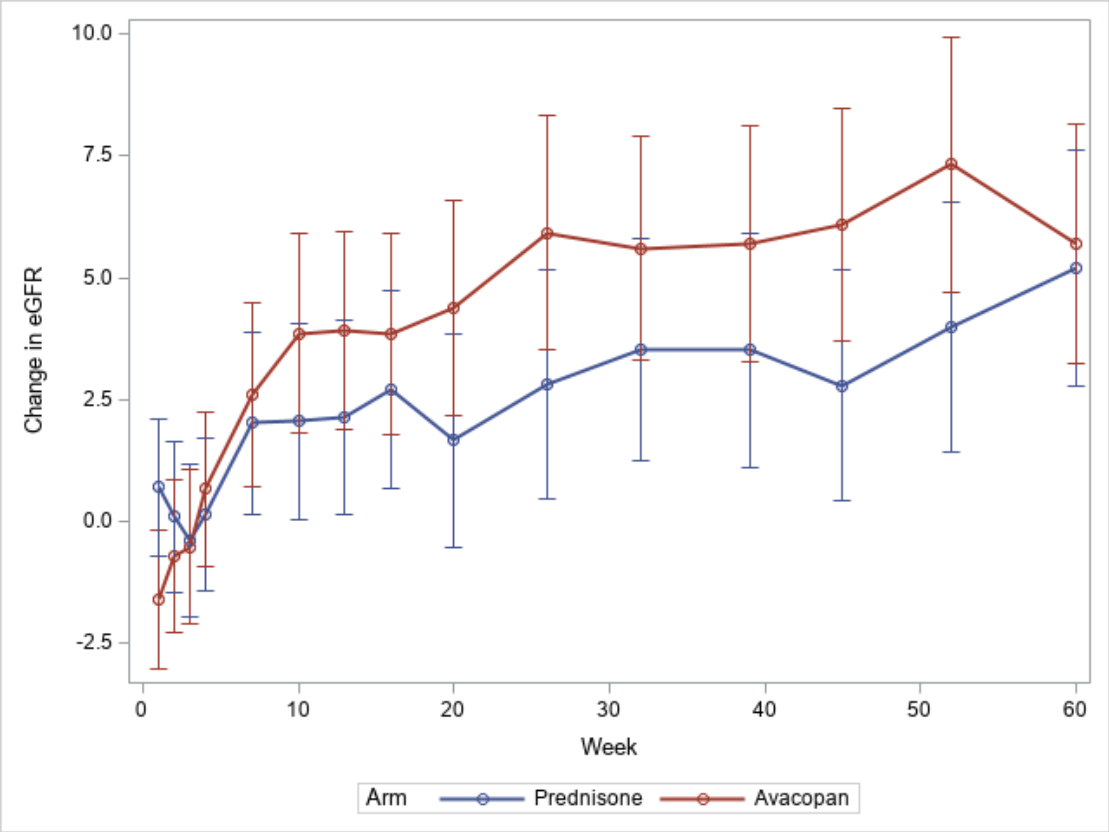
The most commonly observed renal criterion was proteinuria (65.2% in the prednisone arm and 66.3% in the avacopan arm). The other renal criteria observed in the study patient population included hematuria (41.5% prednisone arm vs. 46.4% avacopan arm), increase in serum creatinine (49.4% prednisone arm vs. 52.4% avacopan arm), and RBC casts/glomerulonephritis (36.0% prednisone arm vs. 36.1% avacopan arm). Patients in each treatment arm met a similar mean number of criteria (2.7 in the prednisone group and 2.8 in the avacopan group). Identifying baseline glomerulonephritis with BVAS criteria only may have limitations. Concerns include only using DBP in the assessment of HTN, (b) (4) inability to differentiate acute versus chronic kidney disease in the elevated SCr criterion, and a lack of guidance on time course for change to determine an increase in creatinine or fall in creatinine clearance. For example, it is not clear whether patients had evidence of chronic kidney disease before the current diagnosis or flare of vasculitis. Together, these make it challenging to understand the type and degree of renal disease attributed to AAV at baseline and makes it difficult to understand the nature of the benefit and the clinical importance of the trial's renal assessments.

eGFR

The change in eGFR from baseline was evaluated for all patients with baseline renal disease. 10 shows the change from baseline in eGFR over the 52-week treatment period and the 8-week follow-up period (off therapy). There is a trend toward a greater improvement in eGFR over time in the avacopan arm. At Week 52, the change in eGFR was 7.3 mL/min/1.73 m^2 in the avacopan arm compared to 4.0 mL/min/1.73 m^2 in the prednisone arm. This treatment difference, however, is lost after avacopan is discontinued at Week 52, as assessed at Week 60. The Applicant also performed a (b) (4) subgroup analysis in patients with stages of kidney disease based on GFR (i.e., eGFR < 30 mL/min/1.73 m^2, 30 to 59 mL/min/1.73 m^2, and > 59 mL/min/1.73 m^2) and noted that the greatest change from baseline

occurred in patients with < 30 mL/min/1.73 m^2 at baseline. This post-hoc analysis is considered exploratory; in addition, the treatment difference in patients with baseline GFR < 30 mg/min/1.73 m^2 was small (5.7 mL/min/m^2 at Week 52) and decreased at Week 60, similar to the analysis in the overall population of patients with baseline renal disease.

Figure 10. Change from Baseline in eGFR in all Patients with Renal Disease at Baseline (60-week Study Period)



Least Squares (LS) means with 95% confidence intervals. Derived from a mixed effects model for repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction as factors, and baseline as covariate. An unstructured covariance matrix was used to model the within-subject variance-covariance structure for the model errors.
Sources: Statistical reviewer.

SEE ATTACHED ERRATA

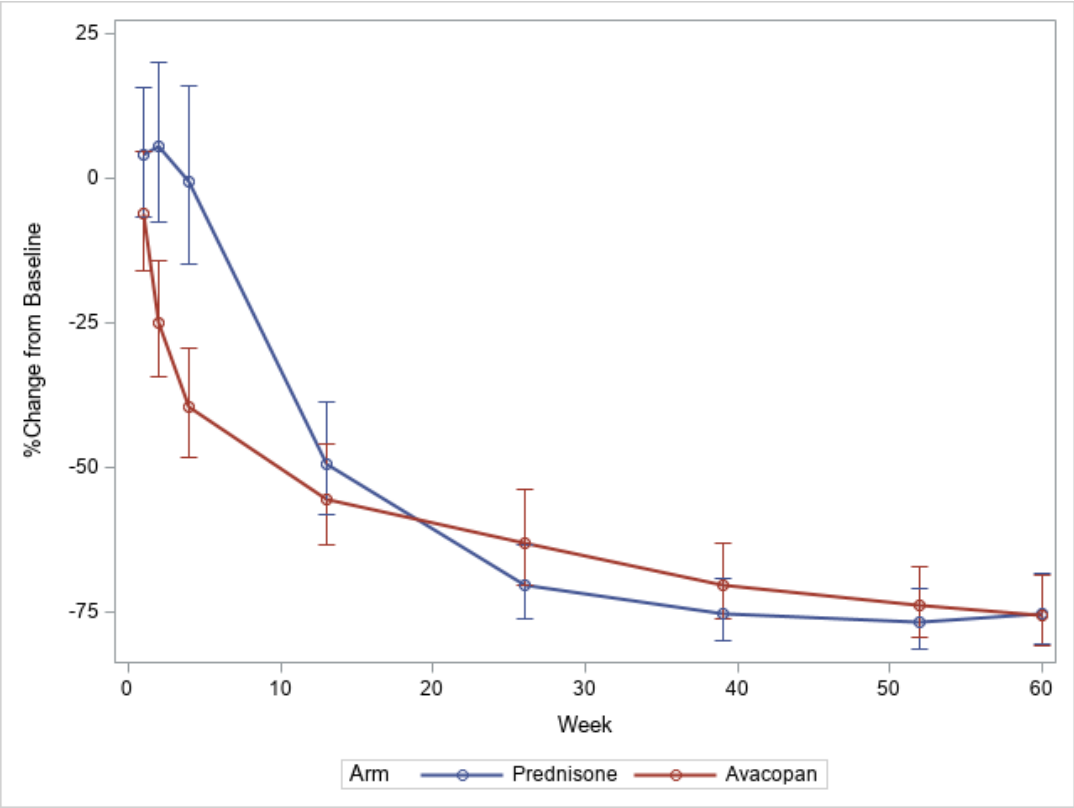
The mean difference between treatment arms on eGFR was small at 3.3 mL/min/1.73m^2, and the clinical meaningfulness is unclear. Additionally, the fact that the treatment benefit appears to be lost within 8 weeks after study drug discontinuation further questions the clinical importance of the results.

Urine Albumin:Creatinine Ratio (UACR)

The urine albumin:creatinine ratio (UACR) analysis was only performed in patients who met BVAS criteria for renal disease at baseline who also had a UACR ≥ 10 mg/g creatinine, a value that is generally considered to be in the normal range. 11 shows the percent change from baseline in the UACR in this subset of patients. There is an improvement observed in both treatment arms. The improvement appears to occur more quickly in the avacopan arm with a 40% decrease in UACR at Week 4 compared

to no change in the prednisone arm. However, the improvement in UACR becomes more similar after Week 13 in both treatment arms without a major difference over time, as seen in 11. It is challenging to interpret the clinical significance of percent change in albuminuria in a population that includes patients with near-normal albuminuria levels at baseline. In addition, the Applicant did not provide data supporting the use of UACR as a surrogate for clinical outcomes in ANCA-associated vasculitis; however, it seems unlikely that the difference seen at Week 4 but not at later timepoints would predict a meaningful clinical benefit of avacopan over prednisone.

Figure 11. Percent Change from Baseline in Urinary Albumin:Creatinine Ratio (UACR) in Patients with Baseline Renal Disease and Baseline UACR ≥ 10 mg/g



Least Squares (LS) means with 95% confidence intervals. Derived from a mixed effects model for repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction as factors, and baseline as covariate. An unstructured covariance matrix was used to model the within-subject variance-covariance structure for the model errors.
Sources: Statistical reviewer.

Dialysis

Few patients required dialysis during the study, balanced by treatment arms. Overall, 4 patients in the prednisone group required dialysis and 3 patients in the avacopan arm required dialysis.

Safety

Exposure

The safety population included all patients who were randomized and received at least 1 dose of study drug. One hundred thirty-four patients (80.7%) received at least 184-365 days of avacopan. In the prednisone arm, 157 patients (95.7%) received 30-183 days of therapy. Thus, the safety population in patients who received approximately 1 year of avacopan is small, and conclusions on safety are limited.

An additional 73 patients received avacopan through the two phase 2 studies, but the treatment periods in these studies were much shorter at 12 weeks. The safety of the phase 2 studies will be discussed separately under each phase 2 study.

Overview

An overview of safety is presented in Table 19. An adverse event was considered treatment-emergent if it occurred on or after the date/time of first dose of study drug through the end of study (Week 60). Most patients in both arms experienced at least 1 TEAE (98.2% in the prednisone arm and 98.8% in the avacopan arm). Overall, a similar proportion of patients in both treatment arms experienced adverse events, including serious adverse events (SAEs) and adverse events leading to discontinuation. SAEs are described in more detail below.

In the first half of the study through Week 20 (the duration of the pre-specified prednisone taper), the proportion of patients with SAEs (n=49 [29.5%] in the avacopan arm and n=54 [32.9%] in the prednisone arm) and discontinuations due to AEs was similar between treatment arms (n=11 [13.3%] in the avacopan arm and n=19 [11.6%] in the prednisone arm). After Week 20 (when the pre-specified prednisone taper was completed), the proportion of patients with SAEs (n=32 [19.3%] in the avacopan arm and n=44 [26.8%] in the prednisone arm) and discontinuations due to AEs (n=5 [3.0%] in the avacopan arm and n=9 [5.5%] in the prednisone arm) was lower than the first half of the study in both arms with a smaller number in the avacopan arm (data not shown).

Table 19. Overview of Treatment Emergent Adverse Events (TEAEs) in Study CL010_168

Number of patients with ≥ 1	Prednisone N=164 n (%)	Avacopan N=166 n (%)	Avacopan vs. Prednisone Diff (95% CI)
TEAEs	161 (98.2%)	164 (98.8%)	0.6% (-2.0, 3.3)
Deaths	4 (2.4%)	2 (1.2%)	-1.2% (-4.1, 1.7)
Serious TEAEs (SAEs)	74 (45.1%)	70 (42.2%)	-3.0% (-13.7, 7.7)
Severe TEAEs	41 (25.0%)	39 (23.5%)	-1.5% (-10.8, 7.7)
Life-Threatening TEAEs	14 (8.5%)	8 (4.8%)	-3.7% (-9.1, 1.7)
TEAEs Leading to Treatment Discontinuations [57]	28 (17.1%)	27 (16.3%)	-0.8% (-8.9, 7.2)

[57] In Table 5, the main reason for early discontinuation of study medication recorded by the Investigators is summarized. Here, a summary of the actions taken for study medication by the Investigators as a result of a TEAE is presented. Table 5 also includes discontinuation of treatment of two patients (one in each arm) attributed to death, which occurred before the action of drug withdrawal could be taken. Table 19 includes two additional patients in the avacopan arm withdrawn from the treatment by the Investigator; these were attributed to 'other' and 'sponsor decision' in Table 5.

Abbreviations: N=number of patients randomized who received at least one dose of drug; n=number of subjects with at least one event; Diff=difference; CI=confidence interval; TEAE=treatment-emergent adverse event; SAE=serious adverse event.
Source: CL010_168 CSR Table 22; ISS

TEAEs

The most common System Organ Class (SOC) in which TEAEs were reported in both treatment arms was Infections and infestations (n=113 [68.1%] in the avacopan arm and n=124 [75.6%] in the prednisone arm). Infections are discussed in detail in the AESI section below.

The most frequently reported TEAEs by preferred term (PT) in the avacopan arm were nausea (n=39 [23.5%], 54 events), peripheral edema (n=35 [21.1%], 39 events), headache (n=34 [20.5%], 43 events), arthralgia (n=31 [18.7%], 42 events), and hypertension (n=30 [18.1%], 36 events). Of the more common AEs (i.e., ≥ 5% of patients in either treatment arm), the ones that occurred with greater than 2% higher difference in the avacopan arm were nausea (23.5% in the avacopan arm vs. 20.7% in the prednisone arm), headache (20.5% in the avacopan arm vs. 14.0% in the prednisone arm), vomiting (15.1% in the avacopan arm vs. 12.8% in the prednisone arm), and rash (11.4% in the avacopan arm vs. 7.9% in the prednisone arm).

Deaths

The overall number of deaths was low and similar between treatment arms with 4 patients who died in the prednisone arm (fungal sepsis, pleural empyema, acute ST elevation myocardial infarction with cardiogenic shock, and a death from unknown cause) and 2 patients in the avacopan arm (worsening GPA and *Aspergillus* pneumonia). The patients who died on avacopan are described in more detail below. Death from worsening GPA and infection is not unexpected in this patient population.

- A 70-year-old man with a diagnosis of newly diagnosed, PR3-positive GPA received rituximab for induction and died on Day 315 of the study from worsening GPA. The patient's last dose of avacopan was 61 days prior to the onset of the event that led to his death. On Day 297, he experienced epistaxis and was hospitalized for an acute exacerbation of his GPA. He received IV CYC and IV cortisone. He developed acute respiratory distress syndrome (ARDS) with tracheal secretions growing *Candida albicans* and a bronchial lavage growing *Enterococcus faecium* and *Candida albicans*. His condition continued to deteriorate until he died from "severe worsening of morbus Wegener."
- A 70-year-old woman with newly diagnosed, MPO-positive MPA received IV cyclophosphamide for induction and died on Day 160 from a bronchopneumonia. Her last dose of avacopan was on Day 50. The patient also received multiple doses of glucocorticoids throughout the study including IV methylprednisolone on Day -3 for AAV, IV hydrocortisone on Day 34 and IV methylprednisolone on Day 32 for drug allergic reaction, and oral prednisone from Day 50 to 141 for AAV. The patient was hospitalized for a bronchopneumonia with a bronchoalveolar lavage that grew *Aspergillus*. She developed ARDS that was attributed to infection, pulmonary hemorrhage, and her underlying vasculitis; however, her death was attributed to "*Aspergillus* superinfection."

Serious Adverse Events (SAEs)

The proportion of patients with SAEs was similar in both treatment arms, 45.1% in the prednisone arm and 42.2% in the avacopan arm. There were numerically more events in the prednisone arm (n=166) compared to the avacopan arm (n=116). Each SAE generally occurred in a small number of patients. Table 20 presents the SAEs that occurred in more than 1 patient in either treatment arm. The most common SAEs that occurred in more than 2 patients in the avacopan arm, by preferred terms (PTs), were ANCA-positive vasculitis (7.2% in the avacopan arm and 12.2% in the prednisone arm), pneumonia (4.8% in the avacopan arm and 3.7% in the prednisone arm), GPA (3.0% in the avacopan arm and 0.6% in the prednisone arm), acute kidney injury (1.2% in the avacopan arm and 0.6% in the prednisone arm), and urinary tract infection (1.8% in the avacopan arm and 1.2% in the prednisone arm).

Table 20. Serious Adverse Events (SAEs) by Preferred Term (≥ 2 Patients in Either Treatment Group) in Study CL010_168

	Prednisone N=164 n (%)	Avacopan N=166 n (%)
Any SAEs	74 (45.1)	70 (42.2)
ANCA antibody positive vasculitis	20 (12.2)	12 (7.2)
Pneumonia	6 (3.7)	8 (4.8)
Granulomatosis with polyangiitis	1 (0.6)	5 (3.0)
Acute kidney injury	1 (0.6)	3 (1.8)
Urinary tract infection	2 (1.2)	3 (1.8)
Angina pectoris	0	2 (1.2)
Cardiac failure	0	2 (1.2)
Device-related infection	0	2 (1.2)
Drug hypersensitivity	2 (1.2)	2 (1.2)
Hepatic enzyme increased	3 (1.8)	2 (1.2)
Hepatic function abnormal	0	2 (1.2)
Hyperglycemia	1 (0.6)	2 (1.2)
Influenza	1 (0.6)	2 (1.2)
Pyrexia	3 (1.8)	2 (1.2)
Acute myocardial infarction	2 (1.2)	1 (0.6)
Agranulocytosis	2 (1.2)	1 (0.6)
Blood creatinine increased	2 (1.2)	1 (0.6)
Lymphopenia	3 (1.8)	1 (0.6)
Pulmonary alveolar hemorrhage	2 (1.2)	1 (0.6)
Anemia	2 (1.2)	0
Dehydration	2 (1.2)	0
Diarrhea	3 (1.8)	0
Epistaxis	2 (1.2)	0
Glomerulonephritis	2 (1.2)	0
Herpes zoster	2 (1.2)	0
Infectious pleural effusion	2 (1.2)	0
Large intestine polyp	2 (1.2)	0
Microscopic polyangiitis	2 (1.2)	0
Mononeuropathy multiplex	2 (1.2)	0
Neutropenia	2 (1.2)	0
Pneumonia bacterial	2 (1.2)	0
Prostate cancer	2 (1.2)	0

Abbreviations: N=number of patients randomized who received at least one dose of drug; n=number of subjects with at least one event; SAE=serious adverse event.
Source: CL010_168 CSR, Table 25, pages 122-123.

The only SOC with an SAE ≥2% in the avacopan arm compared with the prednisone arm was Hepatobiliary disorders (3.6% in the avacopan arm and 0.6% in the prednisone arm). These patients are further discussed below under the discussion of AEs of Special Interest (Hepatotoxicity). SAEs that occurred in more than 1 subject with a >1% higher incidence in the avacopan group included pneumonia, GPA, acute kidney injury (AKI), angina pectoris, cardiac failure, device-related infection, and hepatic function abnormal. To explore these differences further, infection (which captures the PTs of

pneumonia and device-related infection), hepatotoxicity (including hepatic function abnormal), and vasculitis (including GPA) are discussed below under AESIs. Briefly, AKI and major cardiac adverse events (MACE) are discussed here.

- Acute Kidney Injury (AKI)
  Four patients in the avacopan arm and 3 patients in the prednisone arm experienced an SAE of acute kidney injury or blood creatinine increased. In the prednisone arm, none of the patients required study drug interruption, and all patients had resolution of their AKI. In the avacopan arm, one patient required study drug discontinuation from a hypersensitivity reaction (described below); the AKI required one session of dialysis. Two patients required study drug interruption, but avacopan was restarted without worsening in eGFR. One patient was able to continue avacopan.

- Major Cardiac Adverse Events (MACE)
  Although there were more SAEs of angina pectoris (n=2) and cardiac failure (n=2) in the avacopan arm compared to the prednisone arm (no patients with either AE), there were more MACE in the prednisone arm (3 patients in the prednisone arm and 1 patient in the avacopan arm). MACE was defined as nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death. The AEs included 2 non-fatal myocardial infarctions (MIs) and 1 fatal MI in the prednisone group and 1 non-fatal MI in the avacopan group.

  Based on the few observed events and the small safety database, it is difficult to draw conclusions regarding cardiac risk, but the number of patients with cardiac adverse events was generally balanced between the avacopan and prednisone arms.

Discontinuations due to AEs

The proportion of patients who discontinued study medication due to AEs was similar in both treatment arms (28 [17.1%] in the prednisone arm and 27 [16.3%] in the avacopan arm). In the avacopan arm, only the SOC of hepatobiliary disorders showed ≥ 2% greater incidence of discontinuation due to AE relative to the prednisone arm. Hepatotoxicity is further discussed below under the AESIs. In the prednisone arm, only the SOC of Blood and lymphatic disorders occurred in ≥ 2% greater incidence compared to the avacopan arm. This difference can be attributed to patients with PTs of anemia (n=1), leukopenia (n=1), lymphopenia (n=3), and thrombocytopenia (n=2) that occurred in the prednisone arm compared to patients with PTs of febrile neutropenia (n=1) and neutropenia (n=1) in the avacopan arm.

Adverse Events of Special Interest (AESIs)

The identified AESIs included infections, hepatotoxicity, neutropenia/lymphopenia, and hypersensitivity/angioedema.

<u>Infections</u>

Infections occurred in similar proportions of patients in both treatment arms, as displayed in Table 21. The difference in overall treatment-emergent infections was 7.5%, with a greater proportion of patients

in the prednisone arm with infections. An exposure-adjusted incidence rate was also generally similar across treatment arms but numerically greater in the prednisone arm, 155.7/100 patient-years in the prednisone arm and 133.3/100 patient-years in the avacopan arm. The proportion of patients with infections leading to study drug discontinuation, severe and life-threatening infections, and infections leading to death was similar across treatment arms. Serious infections are further discussed below.

Table 21. Overview of Infections in Study CL010_168 (52-week Treatment Period)

Number of patients with ≥ 1	Prednisone N=164	Avacopan N=166	Avacopan vs. Prednisone
	Subjects n (%)	Subjects n (%)	Diff (95% CI)
Any Treatment-Emergent Infections	124 (75.6)	113 (68.1)	-7.5% (17.2, 2.1)
Any Serious Treatment-Emergent Infections	25 (15.2)	22 (13.3)	-2.0% (-9.5, 5.6)
Any Severe Treatment-Emergent Infections	10 (6.1)	12 (7.2)	1.1% (-4.2, 6.5)
Any Treatment-Emergent Infection Leading to Study Drug Discontinuation	5 (3.0)	4 (2.4)	-0.6% (-4.2, 2.9)
Any Treatment-Emergent Life-threatening Infection	2 (1.2)	1 (0.6)	-0.6% (-2.7, 1.4)
Any Treatment-Emergent Infection Leading to Death	2 (1.2)	1 (0.6)	-0.6% (-2.7, 1.4)

Abbreviations: N=number of patients randomized who received at least one dose of drug; n=number of subjects with at least one event.
Source: CL010_168 CSR, Table 27, pages 127-128.

The most common infections were nasopharyngitis (15.1% in the avacopan arm and 18.3% in the prednisone arm), upper respiratory tract infection (14.5% in the avacopan arm and 14.6% in the prednisone arm), urinary tract infection (7.2% in the avacopan arm and 14.0% in the prednisone arm), pneumonia (6.6% in the avacopan arm and 6.7% in the prednisone arm), and sinusitis (6.0% in the avacopan arm and 7.3% in the prednisone arm). Of the common infections, only gastroenteritis (3.0% in the avacopan arm vs. 0.6% in the prednisone arm) and rhinitis (3.0% in the avacopan arm vs. 1.2% in the prednisone arm) occurred in a greater proportion in the avacopan arm compared to the prednisone arm. The other common treatment-emergent infections reported occurred in similar proportions or were higher in the prednisone arm.

The proportion of patients with serious infections was low and similar between treatment arms (n=22 [13.3%, 25 events] in the avacopan arm and n=25 [15.2%, 31 events]in the prednisone arm). An analysis of exposure-adjusted incidence rates of serious infections was also similar in both treatment arms, 15.7/100 patient-years in the avacopan arm and 14.1/100 patient-years in the prednisone arm. The most common serious infection by PT was pneumonia occurring in 4.8% (n=8) in the avacopan arm and 3.7% (n=6) in the prednisone arm. Only 4 serious infections occurred in more than 1 patient in the avacopan arm; these included pneumonia, urinary tract infection (n=3 [1.8%] in the avacopan arm and

n=2 [1.2%] in the prednisone arm), device-related infection (n=2 [1.2%] in the avacopan arm and none in the prednisone arm), and influenza (n=2 [1.2%] in the avacopan arm and n=1 [0.6%] in the prednisone arm).

More cases of serious opportunistic infections were reported in the prednisone arm (n=11, 6.7%) compared to the avacopan arm (n=6, 3.6%). The opportunistic infections in the avacopan arm included the following:

- *Chlamydia* pneumonia and sepsis
- 2 cases of *Aspergillus* pneumonia, one which led to death as already described above
- "infective COPD" with RSV on nasopharyngeal swab
- *Campylobacter* gastroenteritis
- HBV reactivation – this case was described as life-threatening but resolved. The event occurred 27 days after the last day of avacopan. Patient (b) (6) is described in more detail in Table 31 in the Appendix.

In general, these opportunistic infections were similar to the cases observed in the prednisone arm, which included 2 cases of Aspergillus, 2 cases of RSV, 2 cases of cryptococcus (one pneumonia, one meningitis), 2 cases of serious Herpes zoster, and the singles cases of Metapneumovirus respiratory infection and CMV pneumonia. In addition, non-serious herpes zoster was reported by 6 patients in the prednisone arm and 4 patients in the avacopan arm.

No cases of *Neisseria meningitides* or other infections by encapsulated organisms were reported in the avacopan treatment group.

In summary, infections, including treatment-emergent and serious infections, were generally similar between treatment groups. (b) (4) .
The types of serious opportunistic infections were generally similar between treatment groups.

SEE ATTACHED ERRATA

Hepatotoxicity

Hepatotoxicity was a specified adverse event of interest based on cases of liver enzyme elevation (specifically, AST and ALT) in the clinical development program. The Applicant evaluated any TEAEs associated with hepatic abnormalities, including PTs in the SOCs of Investigations (hepatic enzymes increased, alanine aminotransferase increased, blood bilirubin increased, liver function test increased, aspartate aminotransferase increased, transaminases increased, liver function test abnormal) and Hepatobiliary Disorders (hepatic function abnormal, drug-induced liver injury, hepatitis cholestatic, hepatocellular injury). Twenty-two patients (13.3%) in the avacopan arm and 19 patients (11.6%) in the prednisone arm had AEs associated with hepatic abnormalities. In the avacopan arm, this included 16 patients who had AEs in the Investigations SOC and 6 who had AEs in the Hepatobiliary Disorders SOC; in the prednisone arm, this included 18 patients who had AEs in the Investigations SOC and 1 who had AEs

in the Hepatobiliary Disorders SOC. AEs associated with hepatic abnormalities led to drug discontinuation in 7 patients in the avacopan arm and 2 patients in the prednisone arm.

The proportion of patients with SAEs within the hepatobiliary system organ class were also greater in the avacopan group (3.6 %) as compared to the prednisone group (0.6%). Nine patients (5.4%) in the avacopan arm and 6 patients (3.7%) in the prednisone arm experienced SAEs of increase in blood liver tests. These patients are summarized in Table 31 in the Appendix. The Investigators determined that 6 of these SAEs were possibly related to avacopan.

Leukopenia

The Applicant summarized the adverse events associated with low WBC count, absolute granulocytes, neutrophils, or low lymphocytes. These included the PTs of agranulocytosis, leukopenia, lymphopenia, neutropenia, febrile neutropenia, bone marrow failure, bone marrow toxicity, pancytopenia, white blood cell count decreased, lymphocyte count decreased, neutrophil count decreased, neutropenic sepsis, and similar. Overall, the AEs associated with a low WBC were similar across treatment arms, n=31 (18.7%) in the avacopan arm and n=39 (23.8%) in the prednisone arm. More SAEs of neutropenia or lymphopenia were reported in the prednisone arm (n=8 [4.9%]) compared to the avacopan arm (n=4 [2.4%]). Three of the 4 SAEs in the avacopan arm were associated with clinical infection, whereas 3 of the 8 SAEs in the prednisone arm were associated with clinical infection.

The Applicant also assessed decreased leukocytes, lymphocytes, and neutrophil count by CTCAE grade. Grade 3 and 4 decreased leukocyte and neutrophil counts occurred in a small number of patients, generally balanced by treatment group. Decreased lymphocyte counts were most frequently Grade 2 or 3, generally balanced by treatment arm. Grade 4 decreased lymphocyte count occurred more frequently in the prednisone arm (n=13 patients) than in the avacopan arm (n=4 patients).

Overall, cytopenias, including decreased WBC count, absolute granulocytes, neutrophils, and lymphocytes, occurred in both treatment arms and in small numbers, generally balanced by treatment group.

Hypersensitivity/angioedema

Hypersensitivity was assessed utilizing preferred terms from the Standardized MedDRA Query (SMQ) for hypersensitivity. Sixty-eight patients in the avacopan arm (41.0%) and 70 patients in the prednisone arm (42.7%) had an AE of hypersensitivity. Two patients had angioedema in the avacopan arm, one of which was an SAE, whereas no patients in the prednisone arm had angioedema. The patient with the SAE of avacopan was not rechallenged after avacopan was discontinued with resolution of the angioedema. An additional patient in avacopan arm developed rash and fevers in the setting of waxing-waning eosinophilia between study days 18 to 59 that resolved a day after avacopan was discontinued.

Hypersensitivity reactions were few in the study and occurred in both treatment arms. Two SAEs, as described above, could possibly be related to avacopan as determined by the Investigator.

Vasculitis

"Vasculitis" was reported as an adverse event in both treatment arms. However, in this study, a measure of vasculitis may also inform the efficacy. As shown in Table 20, AAV and GPA were amongst the most common SAEs reported by PT.

An Agency assessment of all PTs for TEAEs that could be attributed to active vasculitis is summarized in Table 22. This analysis shows that AEs consistent with active vasculitis occurred in low numbers; only AAV, GPA, and pulmonary hemorrhage were reported in more than 2 patients in either treatment arm. There were more patients with AEs of AAV in the prednisone arm, difference of 5.1%, while GPA was reported more frequently in the avacopan arm (difference of 2.4%). The confidence intervals for these differences did not exclude zero for either of these AEs. Pulmonary alveolar hemorrhage and pulmonary hemorrhage occurred in a similar number of patients in both treatment arms.

Table 22. TEAEs Consistent with Active Vasculitis by Preferred Term (PT) in Study CL010_168

Preferred Terms	Prednisone (N=164)	Avacopan (N=166)	Difference	
	n (%)	n (%)	%	95% CI
ANCA vasculitis	34 (20.7%)	26 (15.7%)	-5.1%	(-13.4, 3.2)
GPA	3 (1.8%)	7 (4.2%)	2.4%	(-1.3, 6.1)
Scleritis	2 (1.2%)	3 (1.8%)	0.6%	(-2.0, 3.2)
Pulmonary alveolar hemorrhage	3 (1.8%)	2 (1.2%)	-0.6%	(-3.3, 2.0)
Episcleritis	2 (1.2%)	2 (1.2%)	-0.0%	(-2.4, 2.3)
MPA	2 (1.2%)	1 (0.6%)	-0.6%	(-2.7, 1.4)
Glomerulonephritis	2 (1.2%)	0	-1.2%	(-2.9, 0.5)
Mononeuropathy multiplex	2 (1.2%)	0	-1.2%	(-2.9, 0.5)
Uveitis	1 (0.6%)	0	-0.6%	(-1.8, 0.6)
Glomerulonephritis rapidly progressive	1 (0.6%)	0	-0.6%	(-1.8, 0.6)
Retinal vasculitis	1 (0.6%)	0	-0.6%	(-1.8, 0.6)
Nasal septum perforation	1 (0.6%)	0	-0.6%	(-1.8, 0.6)
Urticarial vasculitis	0	1 (0.6%)	0.6%	(-0.6, 1.8)
Vasculitis gastrointestinal	0	1 (0.6%)	0.6%	(-0.6, 1.8)
Cutaneous vasculitis	1 (0.6%)	0	-0.6%	(-1.8, 0.6)
Pulmonary vasculitis	0	1 (0.6%)	0.6%	(-0.6, 1.8)
Pulmonary hemorrhage	0	1 (0.6%)	0.6%	(-0.6, 1.8)

Abbreviations: N=number of patients randomized who received at least one dose of drug; n=number of subjects with at least one event; CI=confidence interval; GPA=granulomatosis with polyangiitis; MPA=microscopic polyangiitis

Source: Statistical Reviewer.

Phase 2 Studies

Table 23. Phase 2 Studies in ANCA-Associated Vasculitis

Study ID and Phase	Study Title	Study Population	Treatment Arms	Duration
CL002_168, phase 2 **CLEAR**	Randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of avacopan in patients with AAV on background CYC or RTX	67 patients with ANCA-associated vasculitis - 26 renal vasculitis - 41 systemic vasculitis	**Step 1**: total 12 patients with ANCA-associated renal vasculitis • Avacopan 30 mg BID + prednisone 20 mg (reduced dose) + CYC • PBO + prednisone 60 mg (full dose) + CYC **Step 2**: total 14 patients with ANCA-associated renal vasculitis • Avacopan 30mg BID + no prednisone + CYC • PBO + prednisone 60 mg + CYC **Step 3**: total 41 patients with AAV • Avacopan mg BID + prednisone 20 mg + CYC or RTX • Avacopan + no prednisone + CYC or RTX • PBO + prednisone 60 mg + CYC or RTX	12 weeks
CL003_168, phase 2 **CLASSIC**	Randomized, double-blind, placebo-controlled dose-ranging study to evaluate the safety and efficacy of avacopan in patients with AAV	42 patients with AAV	• PBO + prednisone 60 mg + CYC or RTX • Avacopan 10 mg BID (low dose) + prednisone 60 mg + CYC or RTX • Avacopan 30 mg BID (high dose) + prednisone 60 mg + CYC or RTX	12 weeks

Abbreviations: AAV=ANCA-associated vasculitis; CYC=cyclophosphamide; RTX=rituximab; PBO=placebo; BID=twice daily

Study CL002_168 (CLEAR)

Study CL002_168 was a randomized, double-blind, placebo-controlled, phase 2 study to assess safety, tolerability, and efficacy of avacopan. The study design for the phase 2 study CL002_168 is described in Table 23. The study was conducted in a stepwise manner. Steps 1 and 2 enrolled subjects with ANCA-associated glomerulonephritis and with active renal vasculitis as defined by renal biopsy or the presence of hematuria or proteinuria. Step 3 enrolled subjects with generalized AAV. All subjects in steps 1 and 2 received CYC 15 mg/kg IV on days 1, 15, 29, and 57 as background therapy. In step 3, background

therapy could be either CYC (same regimen as steps 1 and 2) or rituximab 375 mg/m^2 on days 1, 8, 15, and 22.

In step 1, 12 subjects were randomized in a 2:1 ratio to receive avacopan 30 mg BID orally plus low dose prednisone (20 mg daily) or placebo avacopan plus full dose prednisone (60 mg, also referred to as the "standard of care" arm). If step 1 was successful, step 2 would be initiated. In step 2, 14 subjects were randomized in a 2:1 ratio to receive avacopan 30 mg BID plus placebo prednisone or the standard of care arm. If step 2 was successful, then step 3 would proceed. In step 3, 41 subjects were randomized in a 1:1:1 ratio to three treatment arms: avacopan 30 mg BID plus low dose prednisone, avacopan 30 mg BID plus placebo prednisone, or standard of care. All subjects received a prednisone taper, but the taper varied based on the treatment arm. For the standard of care arm, prednisone was tapered from 60 mg to no prednisone by Week 20. For the avacopan/low dose prednisone arm, prednisone was tapered from 20 mg to no prednisone by Week 14. The avacopan/no prednisone group had a placebo prednisone taper.

The key efficacy endpoints were assessed at Week 12 followed by a 12-week follow-up period during which patients who received CYC were switched to azathioprine and patients who received RTX did not receive any additional treatment. For efficacy analyses, the sponsor pooled the data from all 3 steps, resulting in 3 groups:

(1) Standard of care group (Standard of Care group): Full starting dose prednisone (60 mg) plus placebo avacopan plus CYC/RTX
(2) Avacopan/Low dose prednisone group: Low starting dose prednisone (20 mg) plus avacopan 30 mg twice daily plus CYC/RTX
(3) Avacopan/No prednisone group: Placebo prednisone plus avacopan 30 mg twice daily plus CYC/RTX

The primary endpoint for Study CL002_168 was the proportion of subjects achieving disease response at Week 12 defined as BVAS percent reduction from baseline of at least 50% plus no worsening in any body system component. Table 24 presents the primary endpoint, BVAS 50% response, in Study CL002_168

Table 24. BVAS 50% Response and Other Efficacy Assessments at Week 12 in Study CL002_168

	PBO + CYC/RTX + High Dose Prednisone (Standard of Care)	Avacopan + CYC/RTX + Low Dose Prednisone	Avacopan + CYC/RTX + No Prednisone
Randomized, N	23	22	22
Intent-to-Treat (ITT) Population[1], N	20	22	21
Baseline Disease Characteristics of Randomized population			
Duration of ANCA disease in months, median (range)	0 (0-162)	0 (0-61)	1 (0-108)
Newly Diagnosed ANCA disease, n (%)	18 (78%)	15 (68%)	16(73%)
Relapsing ANCA disease, n (%)	5 (22%)	7 (32%)	6 (27%)
BVAS, mean ± SD	13.2 ± 5.8	14.3 ± 6.0	13.8 ± 6.4
Type of AAV, n (%)			
GPA, n (%)	10 (43.5)	11 (50.0)	12 (54.5)
MPA, n (%)	10 (43.5)	9 (40.9)	9 (40.9)
Renal-limited vasculitis, n (%)	2 (8.7)	2 (9.1)	1 (4.5)
Unknown	1 (4.3)	0	0
Background treatment of ITT population			
CYC, n (%)	17 (85%)	17 (77%)	16 (76%)
RTX, n (%)	3 (15%)	5 (23%)	5 (24%)
Efficacy Assessments in ITT Population			
BVAS 50% Response at Week 12, n (%)	14 (70.0%)	19 (86.4%)	17 (81.0%)
Difference in percentage vs. control	--	16.4%	11.0%
Two-sided 90% CI for difference, avacopan minus control	--	-4.3%, 37.1%	-11.0%, 32.9%
BVAS remission at Week 12, n/N (%)	7 (35.0%)	6 (27.3%)	4 (19.0%)
Difference in percentage vs. control	--	-7.7	-16.0
Two-sided 90% CI for difference, avacopan minus control	--	-31.2, 15.8	-38.5, 6.6
BVAS 0 at Week 12, n/N (%)	8 (40.0%)	10 (45.5%)	7 (33.3%)
Difference in percentage vs. control	--	5.5	-6.7
Two-sided 90% CI for difference, avacopan minus control	--	-19.6, 30.5	-31.4, 18.1

Intent-to-treat population is defined as the all patients randomized who received at least one dose of drug.

Abbreviations: BVAS=Birmingham Vasculitis Activity Score; CYC=cyclophosphamide; RTX=rituximab; CI=confidence interval

Source: CL002_168 CSR

The proportion of patients who achieved BVAS 50% response was greater in the treatment arms with avacopan and concomitant glucocorticoids. The highest response was noted in the avacopan plus low dose prednisone background therapy (86.4%) compared to 81.0% in the avacopan plus no prednisone arm and 70.0% in the standard-of-care arm. However, the Applicant's definition of disease response is not an acceptable surrogate endpoint. It is unknown if treatment effects at Week 12 in AAV are predictive of long-term clinical outcomes.

BVAS remission at Week 12 was a secondary endpoint. BVAS remission was defined as a BVAS score of zero or one plus no worsening in eGFR and urinary RBC count <10/hpf. Importantly, there are limitations

to the remission assessment in this study. Because of the protocol-specified prednisone tapering schedule, patients may be treated with concomitant prednisone (10 mg) at Week 12, depending on the treatment arm and patient weight. Thus, it is difficult to isolate the treatment effect of avacopan with that of the different concomitant glucocorticoid regimens used at the time of assessment. However, despite these limitations, more patients on standard of care (35.0%) achieved BVAS remission compared to patients on avacopan (27.3% in patients on low dose prednisone and 19.0% in patients on no prednisone).

Another secondary efficacy endpoint was the assessment of BVAS of 0 at Week 12. This is a similar the endpoint used in the pivotal trial, except at an earlier endpoint and with protocol-specified glucocorticoids still administered at the time of assessment. BVAS of 0 was achieved in the greatest proportion in the avacopan and low dose prednisone arm, and the lowest proportion of patients who achieved BVAS of 0 was the avacopan and no prednisone arm.

In Study CL002_168, BVAS 50% response and BVAS of 0 was higher in the group that received avacopan and low dose prednisone, while BVAS remission was highest in the standard of care arm. Responses were lower in the avacopan and no prednisone group compared to avacopan and low dose prednisone. The study design that included two interventions, treatment with avacopan vs. placebo and the use of different prednisone regimens in each arm, as well as the endpoint assessment at a timepoint when patients continued to receive protocol-specified prednisone, and the overall small study size, limits a determination of a treatment effect of avacopan.

The safety assessment is limited by the small database. An overview of safety in Study CL002_168 is presented in Table 25. The proportion of patients who experienced any AE were similar across treatment arms. SAEs were reported by a greater proportion of patients in the avacopan and no prednisone arm (36.4%), compared to the avacopan and low dose prednisone (13.6%), and standard of care (17.4%). T In addition, a greater number of patients in the avacopan and no steroids arm discontinued treatment due to AEs.

Table 25. Overview of Safety in Study CL002_168 (84-day treatment period)

	PBO + CYC/RTX + High Dose Prednisone (Standard of Care) N=23 n (%)	Avacopan + CYC/RTX + Low Dose Prednisone N=22 n (%)	Avacopan + CYC/RTX + No Prednisone N=22 n (%)
TEAEs	21 (91.3%)	19 (86.4%)	21 (95.5%)
Deaths	0	0	0
Serious TEAEs (SAEs)	4 (17.4%)	3 (13.6%)	8 (36.4%)
Severe-life-threatening TEAEs	2 (8.7%)	2 (9.1%)	2 (9.1%)
TEAEs Leading to Treatment Discontinuations	2 (8.7%)	1 (4.5%)	3 (13.6%)

Abbreviations: N=number of patients randomized who received at least one dose of drug; n=number of subjects with at least one event; TEAE=treatment-emergent adverse event; SAE=serious adverse event; PBO=placebo; CYC=cyclophosphamide; RTX=rituximab
Source: CL002_168 CSR, Table 18.

The most frequently reported AEs (i.e., ≥ 5% of patients) by Preferred Term in the combined avacopan arms included nausea (10 [22.7%]), vomiting (8 [18.2%]), and nasopharyngitis and hypertension (each with n=7 [15.9%]). The most frequently reported AEs in the placebo standard-of-care arm included nausea, muscle spasms, constipation, and peripheral edema.

Study CL003_168 (CLASSIC)

CL003_168 was a randomized, double-blind, placebo-controlled, dose assessment study to assess the safety, tolerability, and efficacy of avacopan in patients with new or relapsing AAV on background standard of care cyclophosphamide or rituximab treatment plus prednisone use. The study design for CL003_168 is described in Table 23. Patients were stratified based on (1) newly diagnosed or relapsing AAV, (2) MPO or PR3 ANCA positivity, and (3) cyclophosphamide or rituximab standard of care treatment. Patients were then randomized 1:1:1 to the following 3 treatment arms:

(1) Group A: Avacopan 10 mg twice daily plus CYC/RTX plus prednisone
(2) Group B: Avacopan 30 mg twice daily plus CYC/RTX plus prednisone
(3) Group C: Placebo twice daily plus CYC/RTX plus prednisone

All patients received standard of care background therapy to include prednisone 60 mg daily with a protocol-specified schedule and either (1) IV CYC and oral AZA (starting on Day 99) or (2) RTX. The double-blind, placebo-controlled period lasted for 84 days, after which patients were assessed in an 84-day follow-up period during which time they did not receive avacopan.

The primary efficacy endpoint was BVAS 50% response at Day 85. The definition of BVAS 50% response in Study CL003_168 was the same as the definition used in study CL002_168. Table 26 presents the results of the primary endpoint analysis. In this small study, the greatest response was seen in the avacopan 10 mg BID arm at 91.7% compared to 80.0% in the avacopan 30 mg BID arm and 84.6% in the placebo arm.

Table 26. BVAS 50% Response and Other Efficacy Assessments in Study CL003_168

	PBO + CYC/RTX + Prednisone (Standard of Care)	Avacopan 10 mg BID + CYC/RTX + Prednisone	Avacopan 30 mg BID + CYC/RTX + Prednisone
Randomized, N	13	13	16
Intent-to-Treat (ITT) Population[1], N	13	12	15
Baseline Disease Characteristics of Randomized Population			
Duration of ANCA disease in months, median (range)	1 (0-95)	1 (0-347)	2.5 (0-170)
Newly Diagnosed ANCA disease, n (%)	8 (61.5%)	10 (76.9%)	9 (56.3%)
Relapsing ANCA disease, n (%)	5 (38.5%)	3 (23.1%)	7 (43.8%)
BVAS, mean ± SD	15.0 (4.45)	15.8 (8.84)	15.1 (6.43)
Background treatment of randomized population			
CYC, n (%)	1 (7.7%)	0	2 (12.5%)
RTX, n (%)	12 (92.3%)	13 (100%)	14 (87.5%)
Efficacy Assessments in ITT Population			
BVAS 50% Response at Day 85, n (%)	11 (84.6%)	11 (91.7%)	12 (80.0%)
Difference in percentage vs. control	--	7.1%	-4.6%
Two-sided 90% CI for difference, avacopan minus control	--	-14.0%, 28.1%	-28.3%, 19.0%
BVAS 0 at Day 85, n (%)	7 (53.8%)	8 (66.7%)	7 (46.7%)
Difference in percentage vs. control	--	12.8%	-7.2%
Two-sided 90% CI for difference, avacopan minus control	--	-19.1, 44.7	-38.3, 23.9
BVAS 0 at Days 29 and 85, n (%)	2 (15.4%)	1 (8.3%)	3 (20.0%)
Difference in percentage vs. control	--	-7.1	4.6
Two-sided 90% CI for difference, avacopan minus control	--	-28.1, 14.0	-19.0, 28.3

Intent-to-treat population is defined as all patients randomized who received at least one dose of drug
Abbreviations: BVAS=Birmingham Vasculitis Activity Score; CYC=cyclophosphamide; RTX=rituximab; CI=confidence interval; BID=twice daily
Source: CL003_168 CSR, Tables 6, 8, 10, 11.

Secondary endpoints of interest include the proportion of patients who achieved "disease remission," defined as BVAS of 0 at Day 85, and "early disease remission," defined as BVAS of 0 at Days 29 and 85. As all patients were treated with prednisone, at Day 85, all patients were receiving at least 10 mg of prednisone in this assessment of remission. As with BVAS response, disease remission was greatest in the avacopan 10 mg BID arm (66.7%) and lowest in the avacopan 30 mg BID arm (46.7%). Early remission was highest in the avacopan 30 mg BID arm (20.0%) and lowest in the avacopan 10 mg BID arm (8.3%).

In Study CL003_168, a dose dependent treatment effect of avacopan was not demonstrated. The greatest BVAS 50% response was observed in the avacopan 10 mg BID arm, which is not the dose selected for the pivotal trial. Additionally, as already noted in the discussion of Study CL002_168, the clinical meaningfulness of BVAS 50% response is unknown. Whether remission at Week 12, and even

more so at Week 4, correlates with long-term remission is unknown. The small number of patients in this study further limits the conclusions of efficacy.

Table 27 presents an overview of safety in Study CL003_168. Overall, the proportion of patients who experienced AEs and SAEs was similar across treatment arms with differences due to small numbers of patients. However, the safety database is very small.

Table 27. Overview of Safety in Study CL003_168

	PBO + CYC/RTX + Prednisone N=13 n (%)	Avacopan 10 mg BID + CYC/RTX + Prednisone N=13 n (%)	Avacopan 30 mg BID + CYC/RTX + Prednisone N=16 n (%)
TEAEs	13 (100%)	11 (84.6%)	15 (93.8%)
Deaths	0	0	0
Serious TEAEs (SAEs)	2 (15.4%)	2 (15.4%)	3 (18.8%)
Severe-life-threatening TEAEs	2 (15.4%)	3 (23.1%)	3 (18.8%)
TEAEs Leading to Treatment Discontinuations	2 (15.4%)	1 (7.7%)	3 (18.8%)

Abbreviations: N=number of patients randomized who received at least one dose of drug; n=number of subjects with at least one event; TEAE=treatment-emergent adverse event; SAE=serious adverse event; BID=twice daily
Source: CL003_168 CSR, Tables 15.

Limitations in Phase 2 studies

The Applicant submitted two phase 2 studies that provide limited supportive efficacy data. Both studies were a shorter duration (12 weeks) and evaluated a different primary endpoint than the phase 3 study. One of the difficulties with drawing conclusions from the data is the early timepoint of the efficacy assessment. The primary endpoints of both studies were assessed at Week 12. Whether a clinical response at Week 12 translates to long-term remission is unknown. Along with timing of endpoint assessment, the ability to interpret the clinical meaningfulness of the efficacy assessments in the phase 2 studies is limited. The primary endpoint in the studies was BVAS 50% response, defined as BVAS percent reduction from baseline of at least 50% plus no worsening in any body system component. The clinical meaningfulness of BVAS 50% response is unknown, whereas the BVAS remission or BVAS of 0, assessed as secondary endpoints, is more clinically interpretable. However, BVAS remission and BVAS of 0 in these studies were assessed while patients may have been receiving protocol-specified prednisone, which makes disentangling the treatment effect of avacopan from an effect of prednisone more complex.

Further, the results of the phase 2 studies do not confirm a treatment benefit of avacopan 30 mg BID in AAV. In CL002_168, BVAS 50% response was higher in the group that received avacopan plus low dose prednisone, compared to the avacopan plus no prednisone group or the standard-of-care group. Response based on BVAS remission (defined as BVAS of 0 and urinary RBCs < 10/hpf) was highest in the control standard-of-care arm that did not receive avacopan. The efficacy based on BVAS 50% response, BVAS remission, and BVAS of 0, was greater in the group that received avacopan with low dose steroids than the avacopan without prednisone group. In CL003_168, the phase 2 dose-ranging study, no dose-

response was observed for avacopan; the greatest BVAS response was reported in the avacopan 10 mg BID arm (91.7%), while lower response rates were reported in the avacopan 30 mg BID arm (80.0%) and control standard-of-care arm (84.6%). Similarly, BVAS of 0 at Week 12 was also lowest in the avacopan 30 mg BID plus standard-of-care group. Overall, the phase 2 data do not provide support for the efficacy of avacopan over standard of care nor support for avacopan as a steroid-sparing agent.

Summary of the Avacopan Program for AAV

ChemoCentryx submitted the data from a single randomized, double-blinded, active-controlled study to support avacopan for the treatment of adult patients with AAV (GPA and MPA).Patients with AAV were randomized to two treatment arms, either avacopan 30 mg BID for the duration of the study or a protocol-specified prednisone taper for 20 weeks. All patients received background induction therapy with cyclophosphamide (CYC, oral or IV) or rituximab (RTX). Patients who received CYC for induction received azathioprine for maintenance treatment. Patients who received RTX for induction did not receive maintenance therapy. Both treatment arms could receive non-study supplied glucocorticoids at the Investigator's discretion.

Efficacy

Study CL010_168 met its primary endpoints by demonstrating non-inferiority of avacopan to prednisone in disease remission at Week 26 (72.3% in the avacopan arm vs. 70.1% in the prednisone arm) and sustained remission at Week 52 (65.7% in the avacopan arm vs. 54.9% in the prednisone arm) based on the Applicant's specified margin. Sustained remission at Week 52 also showed superiority of avacopan over prednisone. Superiority was not demonstrated in disease remission at Week 26.

- Considerations on the clinical meaningfulness and interpretation of a non-inferiority comparison of avacopan to prednisone for remission at Week 26 and sustained remission at Week 52
    - First, there is a lack of relevant historical data for justification of an appropriate non-inferiority margin. The Applicant has not provided adequate data or information that would isolate the effect of prednisone to inform the margin of the non-inferiority comparison in this study.
    - As the Agency reiterated in pre-submission communications, a non-inferiority comparison is not sufficient to show that avacopan can replace glucocorticoids, as it would be difficult to determine whether the background CYC or RTX was driving the efficacy results in both treatment arms.
    - Both treatment arms received non-study supplied glucocorticoids at the Investigator's discretion, including 145 patients in the avacopan arm (87.3%) and 149 patients in the prednisone arm (90.9%).
    - The mean cumulative total glucocorticoid use, including both protocol-specified prednisone and non-study supplied glucocorticoids, over 52 weeks was greater in the prednisone arm, as expected (3654.5 mg in the prednisone arm and 1348.9 mg in the avacopan arm). However, comparing the mean cumulative non-study

supplied glucocorticoid dose was much more similar, 1265.3 mg in the prednisone arm and 1348.9 mg in the avacopan arm. The clinical relevance of the differences in the nominal glucocorticoid doses between the prednisone and avacopan arms is uncertain, as it may be an artifact of the study design rather than a reflection of avacopan's control of disease activity.

- The clinical pharmacology program has identified avacopan as a CYP3A4 inhibitor that has the potential to increase exposures to systemic glucocorticoids which are CYP3A4 substrates, raising further uncertainties about the true difference in glucocorticoid exposures and its impact on the non-inferiority comparisons between the two groups at Week 26, and respectively the proposed role of avacopan as a steroid-sparing agent, as glucocorticoid exposures were not assessed in Study CL010_168.

Thus, the non-inferiority comparison was not a comparison of avacopan versus steroid, but is more accurately described as avacopan plus potentially lower doses of glucocorticoids compared to higher doses of glucocorticoids, in addition to background induction therapy (CYC or RTX) and maintenance therapy (only in the CYC arm). The clinical meaningfulness of this non-inferiority comparison is very difficult to interpret to support a treatment benefit of avacopan.

- Considerations on the superiority assessment of sustained remission at Week 52.
  - There were discrepancies between the Investigator and Adjudication Committee assessments of BVAS. While superiority was met at Week 52 using the adjudicated BVAS score, superiority was not met using the Investigator assessed score. Differences between Adjudication Committee and Investigators were driven by assessment of persistent active disease, which was not scored in the modified version of the BVAS used in this study. While the pre-specified analysis used the Adjudicator assessments, the assessment based on the Investigators, experienced in management of vasculitis, may better reflect real-world use.
  - Subgroup analyses showed a greater treatment difference in sustained remission in the RTX subgroup (71.0% in the avacopan arm vs. 56.1% in the prednisone arm) who did not receive standard of care maintenance therapy, while no treatment difference was observed in the CYC subgroup (55.9% in the avacopan arm vs. 52.6% in the prednisone arm). The result of the subgroup analysis suggests the possibility that avacopan was efficacious only in the population who did not receive standard-of-care maintenance immunosuppression therapy and may be considered undertreated, raising questions about the adequacy of the comparisons and clinical meaningfulness of the avacopan effect at Week 52.

Avacopan has been proposed as a steroid-sparing agent in AAV. Considerations on the use of avacopan as a replacement for glucocorticoids:

- As previously discussed, patients in both treatment arms received non-study supplied glucocorticoids, including for management of vasculitis.
- Use of glucocorticoids was similar between treatment groups after completion of the specified prednisone taper at Week 20.
- Based on the literature, the ideal regimen for glucocorticoids in the induction and maintenance treatment of AAV is evolving. It has been proposed that a reduced dose regimen or a rapid taper of steroids may be appropriate. Thus, since the prednisone taper was pre-specified in the prednisone arm, it is unknown whether a lower dose regimen may have also been effective for the comparator arm. Based on the study design, it cannot be determined whether the differences in use of glucocorticoids from Weeks 0 to 26 was due to a treatment effect of the avacopan or was due to the specified prednisone taper administered to the prednisone arm.

There is limited support of a treatment benefit of avacopan from the secondary endpoints. In addition, the secondary endpoints were not adjusted for multiplicity, and therefore nominal significance achieved by a secondary endpoint should be interpreted with caution.

- More relapses were observed in the prednisone arm compared to the avacopan arm through the study duration (20.1% in the prednisone arm compared to 9.6% in the avacopan arm). However, the study was not designed to assess time to relapse or proportion of relapses. The Applicant's analyses based on the subset of patients who achieved remission condition on post-randomization variables, i.e., having first achieved remission and the timing of achieving remission. As a result, the subset of patients included in this analysis and the time those patients are at risk for relapse can no longer be assumed to be similar across treatment arms. The advantages of randomization are eliminated because the treatment arms are no longer balanced with respect to possible confounders, leading to biased comparisons between treatment arms and limiting the interpretability of these results.
- The Glucocorticoid Toxicity Index (GTI), intended to quantitatively capture glucocorticoid toxicity and the glucocorticoid-sparing ability of therapies, showed a greater improvement from baseline in the avacopan arm on GTI-CWS and GTI-AIS at Weeks 13 and 26. Differences in GTI between the treatment groups may reflect the study design which specified the prednisone doses to be used in the control group. GTI was not assessed at later time points to assess the effects of glucocorticoids after completion of the pre-specified prednisone taper. In the case of Study CL010_168, where differences in glucocorticoid use were pre-specified in the protocol, the GTI does not provide information beyond that of the cumulative glucocorticoid doses to further inform the effect of avacopan.
- Multiple renal endpoints were assessed as secondary endpoints. Mean improvement in eGFR from baseline to Week 52 for patients meeting BVAS criteria for renal disease at baseline was greater in the avacopan group compared to the prednisone group, however difference between groups was small 3.3 mL/min/1.73 m^2 (95% CI: [-0.4, 6.9]), and was not sustained by 8 weeks post-treatment. Percent change in UACR at Week 52 was similar in the avacopan and prednisone arms, and need for dialysis was also similar between groups.

- Similar mean increase in Vasculitis Damage Index, an instrument intended to assess cumulative organ damage as a result of ANCA-associated vasculitis, was observed between treatment groups from baseline to Week 52.
- Favorable trends towards improvement were observed in quality of life, based on the SF-36 and EQ-5D-5L, in the avacopan group compared to the prednisone group, however there was large variability around the point estimates, and these measures are not specific to vasculitis.

To support the pivotal trial, the Applicant also submitted two phase 2 studies, both randomized, double-blind, controlled studies. These studies included different treatment arms (with different doses avacopan and varying concomitant prednisone tapers), shorter treatment duration, small patient populations, and different efficacy assessments. The results also did not show that avacopan 30 mg BID without concomitant prednisone (i.e., the Applicant's proposed dose) had the greatest treatment response in multiple efficacy measures over standard of care. Thus, the phase 2 studies do not provide confirmatory evidence of efficacy and the pivotal trial provides the sole support for the Applicant's proposed dose of avacopan 30 mg BID in the proposed indication.

Safety

The safety database in Study CL010_168 was small with 166 patients exposed to at least 1 dose of avacopan and 134 patients who received study drug for > 6 months. The proportions of patients with treatment-emergent adverse events (TEAEs) were similar across treatment arms or nominally lower in the avacopan arm, including deaths, serious adverse events, and AEs leading to discontinuation. AEs of special interest (AESIs) included infections, AEs due to hepatic abnormalities, neutropenia, and hypersensitivity/angioedema. The proportion of patients with serious infections was low and similar across treatment arms (13.3% in the avacopan arm and 15.2% in the prednisone arm). More cases of opportunistic infections occurred in the prednisone arm (6.7%) compared to the avacopan arm (3.6%). No cases of *Neisseria meningitides* occurred in the avacopan arm.

More patients in the avacopan arm experienced AEs related to hepatic abnormalities and hypersensitivity events. The proportion of patients with hepatobiliary AEs and SAEs were greater in the avacopan group (6.0% and 3.6 %, respectively) as compared to the prednisone group (1.8% and 0.6%, respectively). Hepatobiliary SAEs included one patient with a liver biopsy consistent with drug induced liver injury and one patient with increased liver enzymes upon positive rechallenge with avacopan, suggesting potential hepatotoxicity. AEs associated with hepatic abnormalities led to drug discontinuation in 7 patients in the avacopan arm and 2 patients in the prednisone arm. As for hypersensitivity, 2 patients in the avacopan arm experienced angioedema, and no patients in the prednisone arm experienced angioedema. There was an additional case of rash and fever in the avacopan arm that resolved after discontinuation of avacopan. Although the database is small, there is a greater incidence of hepatotoxicity and hypersensitivity with avacopan.

Appendix 1: Alternative Trial Design Considerations

As detailed in the section on Pertinent Regulatory History (Table 2), during the clinical development of avacopan for AAV, including the stage of designing the phase 3 study, the Agency communicated many concerns with Study CL010_168. To help address these concerns, the Agency proposed several alternative trial designs that could more directly and reliably assess the efficacy of avacopan for the proposed indication and mitigate many of the uncertainties discussed in this document, as outlined in the Pertinent Regulatory History Table 2.

Provided below is a more detailed discussion of different treatment arms and comparisons for consideration that may address the uncertainties identified in the avacopan clinical program. In these proposals, all treatment arms should receive background standard of care, including adequate maintenance throughout the controlled period, and matching placebo should be used to maintain blinding.

A. Treatment Arm A: Placebo plus 20-week prednisone taper (i.e., the pre-specified prednisone taper arm in Study CL010_168)
B. Treatment Arm B: Avacopan plus 20-week prednisone taper
C. Treatment Arm C: Avacopan plus no/low dose prednisone

For the proposed objectives of the avacopan development program, one possible trial design includes 3 treatment arms (A, B, C). The primary analysis would be a comparison of treatment arms A and B to provide an assessment of the treatment effect of avacopan compared to placebo, with background use of prednisone (i.e., 20-week prednisone taper). Arm C could also be included to provide information on the use of avacopan with no or low-dose glucocorticoids and to be compared with treatment arm A. Together, these comparisons would inform the benefit of avacopan and the necessity of the 20-week prednisone taper.

Additional study designs could be considered for assessment of maintenance of remission or to reliably assess a clinically meaningful steroid sparing effect.

Assessment of glucocorticoid pharmacokinetics in any of the alternative study designs could also address the potential for clinically meaningful drug-drug interactions between avacopan and glucocorticoids where co-administration can result in increased systemic exposure to glucocorticoids, as detailed in the section on Clinical Pharmacology.

These alternative study designs serve only as ideas for potential future trial(s) to address any residual uncertainties and provide additional evidence of effectiveness of avacopan in the treatment of AAV.

Appendix 2: Additional Tables and Figures

Table 28. Protocol-Specified Prednisone Taper in Standard of Care Arm in Study CL010_168

Study Day	Adults		Adolescents	
	≥ 55 kg	< 55 kg	> 37 kg	≤ 37 kg
Day 1 to 7	60 mg	45 mg	45 mg	30 mg
Day 8 to 14	45 mg	45 mg	45 mg	30 mg
Day 15 to 21	30 mg	30 mg	30 mg	30 mg
Day 22 to 42	25 mg	25 mg	25 mg	25 mg
Day 42 to 56	20 mg	20 mg	20 mg	20 mg
Day 57 to 70	15 mg	15 mg	15 mg	15 mg
Day 71 to 98	10 mg	10 mg	10 mg	10 mg
Day 99 to 140	5 mg	5 mg	5 mg	5 mg
≥ Day 141	0	0	0	0

Source: CL010_168 CSR, Table 6, page 122.

Table 29. Protocol-Specified Prednisone Tapers in AAV Studies

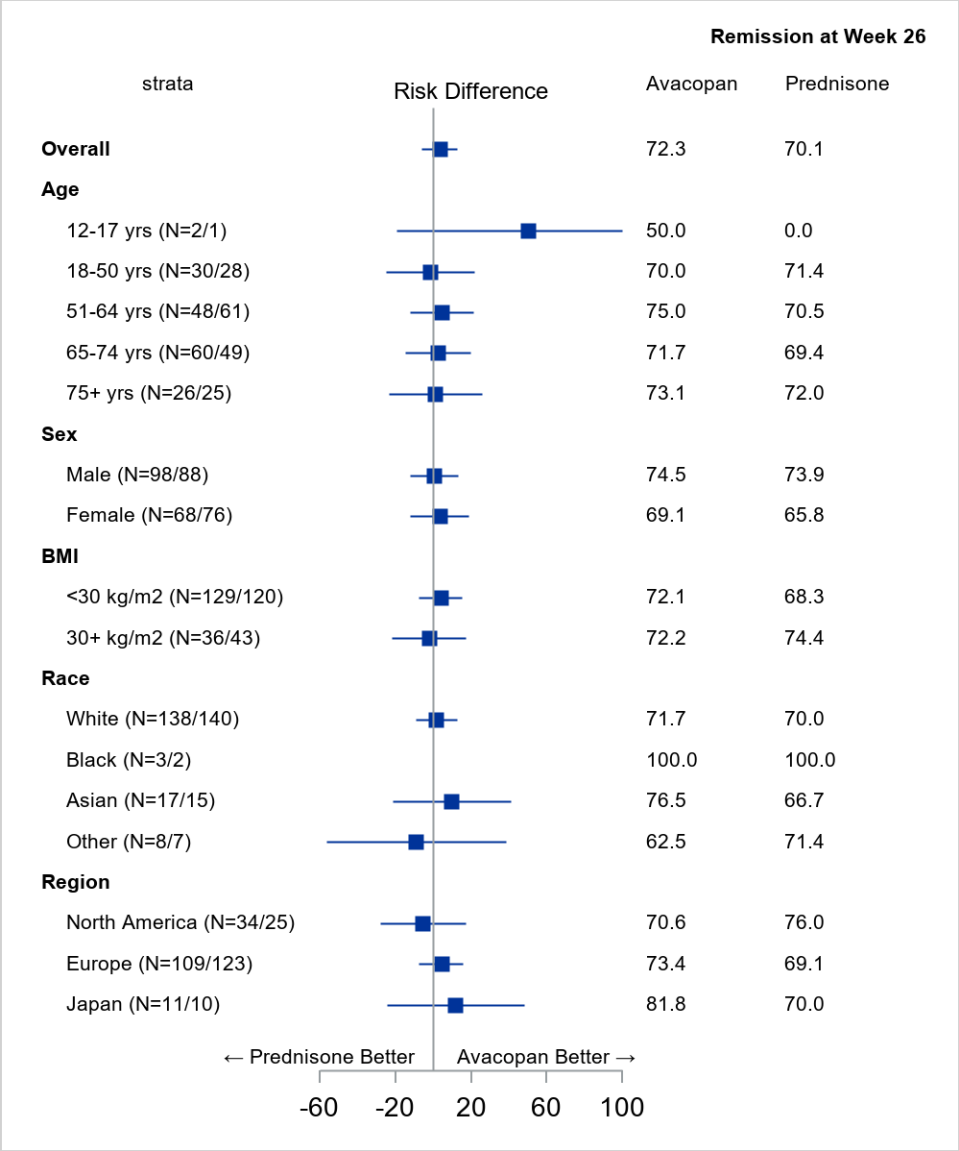
Weeks	PEXIVAS		RAVE	CLEAR
	Lower-Dose	Higher-Dose		
1	60 mg	60 mg	70 mg	60 mg
2	30 mg	60 mg	40-70 mg	45 mg
3-4	25 mg	50 mg	40-70 mg	30 → 25 mg[a]
5-6	20 mg	40 mg	30-40 mg	25 mg
7-8	15 mg	30 mg	20-30 mg	20 mg
9-10	12.5 mg	25 mg	15-20 mg	15 mg
11-12	10 mg	20 mg	10-15 mg	10 mg
13-14	7.5 mg	15 mg	7.5-10 mg	10 mg
15-16	5 mg	10 mg	5-7.5 mg	5 mg
17-18	5 mg	10 mg	2.5-5 mg	5 mg
19-20	5 mg	7.5 mg	0-2.5 mg	5 mg
21-22	5 mg	7.5 mg	0	0
23-52	5 mg	5 mg	0	0

CLEAR = CL002_168

a= prednisone was tapered to 25 mg at Week 4

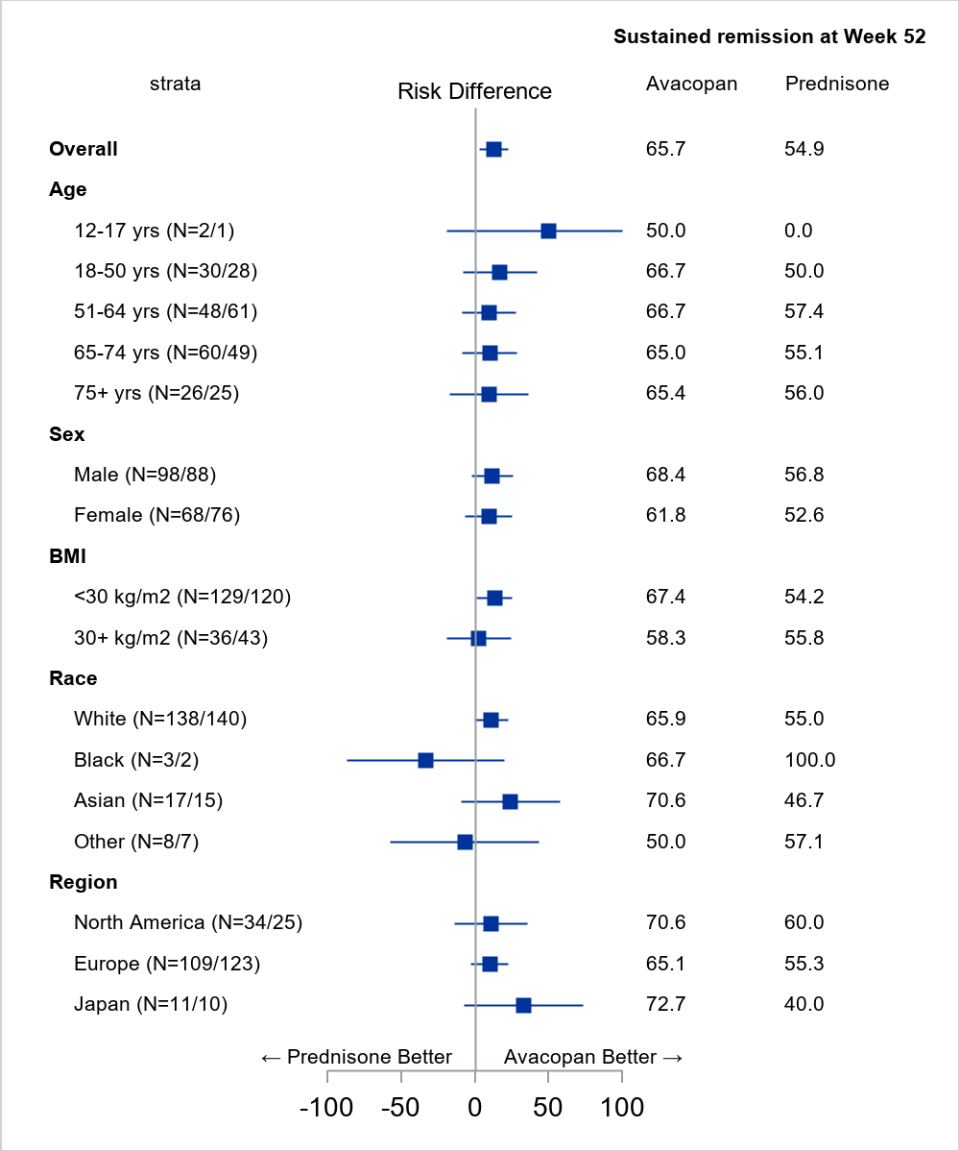
Source: Cortazar FB and Niles JL. The fate of plasma exchange and glucocorticoid dosing in ANCA-associated vasculitis after PEXIVAS. *AJKD*. 2020; 76: 595-597.

Figure 12. Remission at Week 26 by Demographic Subgroup



The notation N=XXX/YYY indicates the number of patients randomized who received at least one dose of drug in avacopan and prednisone arm, respectively.
Source: Statistical Reviewer.

Figure 13. Sustained Remission at Week 52 by Demographic Subgroup



The notation N=XXX/YYY indicates the number of patients randomized who received at least one dose of drug in avacopan and prednisone arm, respectively.
Source: Statistical Reviewer.

Table 30. Examples of Case Summaries of Patients who Required Non-Study Supplied Glucocorticoids

Prednisone	Patient (b) (6) received glucocorticoids on a few occasions for vasculitis and non-vasculitis-related reasons. • IV dexamethasone 10 mg twice daily on Day 109-110 and then prednisone 20 mg on Day 110, tapered to 5 mg through Day 119 for vasculitis • Prednisone 10 mg on Day 228-283 for nasal congestion (deemed vasculitis related) • Prednisone 30 mg from Day 266-271 for epistaxis (deemed not vasculitis related) • IV methylprednisolone on Days 273 and 284 for infusion prophylaxis This patient was in remission at Weeks 26 and 52. As no glucocorticoids were given within 4 weeks prior to Weeks 26 and 52, this patient was considered a responder at both timepoints.
	Patient (b) (6) received glucocorticoids for vasculitis and non-vasculitis-related reasons. • Prednisone 25 mg from Day-1 to Day 2 for vasculitis • Prednisone 30 mg on Day 6, tapered to 10 mg through Day 35 for vasculitis • Prednisone 20 mg as needed from Day 2 to Day 420 for asthma BVAS was 0 at Weeks 26 and 52. Additionally, the patient did not receive glucocorticoids within 4 weeks prior to Weeks 26 and 52. This patient was considered a responder at both timepoints.
Avacopan	Patient (b) (6) received prednisone several times for vasculitis. • Prednisone 10 mg on Day 50, tapered to 2.5 mg through Day 60 • Prednisone 20 mg on Day 107, tapered to 5 mg through Day 123 • Prednisone 10 mg on Day 149-157 • Prednisone 20 mg on Day 196, tapered to 2.5 mg through Day 222 • Prednisone 20 mg on Day 223, tapered to 5 mg This patient did not receive glucocorticoids within 4 weeks prior to Week 26 or Week 52 and achieved BVAS 0 at Weeks 26 and 52. Thus, this patient was considered a responder at both timepoints.
	Patient (b) (6) required dexamethasone PO 20 mg daily from Day -6 to Day 7 for a lung mass. Then, on Days 6 through 8, the subject was pulsed with methylprednisolone 1g for pulmonary hemorrhage. On Day 12, the subject was treated with prednisone 60 mg for pulmonary hemorrhage; prednisone was tapered to 5 mg through Day 61. As the patient had a BVAS of 0 at Weeks 26 and 52 and did not receive glucocorticoids within 4 weeks prior to Weeks 26 and 52, this patient was deemed a responder at both time points.
	Patient (b) (6) received glucocorticoids for vasculitis or vasculitis-related clinical findings. • Patients received IV methylprednisolone 1 g on Day 112 and then prednisone 25 mg on Day 115, tapered to 12.5 mg through Day 132 for worsening lung nodules. • Patient received IV methylprednisolone 250 mg on Day 332, 333, 335, and 407 to 409 for vasculitis. The patient had a BVAS of 0 at Weeks 26 and 52 and did not receive glucocorticoids within 4 weeks prior to Weeks 26 and 52. Therefore, this patient was also considered a responder at both time points.

Table 31. Case Summaries of SAEs of Elevated Liver Tests

	Reported Term	AE Start Day	Summary of Adverse Event
(b) (6)	Elevated liver function tests	50	65-year-oldfemale with MPA received IV CYC for induction on study day 1 (q2w through study day 93) and then started oral AZA for maintenance on study day 106-423. The patient started with normal "liver function tests" which were then noted to be elevated on study day 50 with ALT of 336 U/L, AST 163 U/L, and ALP 314 U/L. Total bilirubin was normal. Per report, this was the first and highest elevation documented. The patient received Keflex for a UTI on study day 45-49, just before these LFT elevations. The last dose of avacopan was received on study day 52 when the LFTs were already decreasing. The patient was not re-challenged, and avacopan was discontinued. Laboratory testing showed normal LFTs by study day 65. Investigators attributed the event to possibly related to study drug or IV CYC.
(b) (6)	Hepatic function disorder	114	62-year-old female with newly-diagnosed GPA received RTX for induction starting on study day 1. The patient was noted to have a gradual increase in LFTs on study day 113 with the highest values on study day 161 with ALT 1933 U/L, AST 1708 U/L, and ALP 189 U/L. The highest bilirubin was 13.56 mg/dL on study day 169. Albumin increased over the course of the study, and INR remained normal. LFTs returned to normal on study day 225. Other significant labwork was central agranulocytosis on study day 155, which resolved without intervention. Avacopan was discontinued on study day 147. Diagnostic work-up for LFTS was conducted by GI from study day 164 to 171 – including abdominal ultrasound, abdominal CT, and liver biopsy. Viral serologies (HAV, EBV, CMV) were notable for IgG positivity. Liver biopsy was suggestive of a resolving inflammatory process, and the diagnosis was chronic and active portal and lobular hepatitis suggestive of toxic or drug-induced etiology. Investigators did not determine an etiology for either the elevated LFTs or the agranulocytosis but that the "hepatic function disorder" was possibly related to study drug.
(b) (6)	Hepatic cytolysis	37	80-year-old female with newly-diagnosed MPA with pauci-immune GN received RTX for induction on study day 1. She was noted to have elevated in LFTs (ALT 300 U/L, AST 150 U/L) on study day 37. Avacopan and Bactrim were discontinued. LFTs subsequently decreased. The patient was re-challenged with avacopan on study day 43 when the ALT, ALP, GGT levels were not at baseline (ALT 137 U/L, ALP 22 IU/L, GGT 582 IU/L). The patient was also switched from Bactrim to pentamidine for PCJ prophylaxis. On study day 51, the LFTs further increased (ALT 355 IU/L, AST 158 IU/L, TB

			normal, GGT elevated, ALP elevated). Avacopan was then permanently discontinued on study day 51. Pentamidine was continued. LFTs (AST, ALT, ALP) returned to normal on study day 85. Other AEs that were reported when the patient actively had elevated LFTs included diarrhea, cholestasis, and pancreatic failure. The Investigator determined the "asymptomatic hepatitis" to be possibly related to study drug, as it recurred with drug re-challenge.
(b) (6)	Cytolytic hepatitis, Cholestatic hepatitis	93, 93	54-year-old female with newly-diagnosed MPA received IV CYC starting on study day 1 and then transitioned to oral AZA on study day 107. The patient was enrolled in the trial while hospitalized for symptoms of fatigue, GN, sinus involvement, and minimal pulmonary hemorrhage. Her hospitalization was prolonged due to nausea attributed to CYC. LFTs were normal at baseline. On study day 70, the patient was first noted to have elevated LFTs (ALT 64 U/L, AST 55 U/L). These LFTs further increased with the highest reported values at ALT 380 U/L and AST 229 U/L on study day 93. No significant increase in ALP or TB were noted. Avacopan was discontinued on study day 97. LFTs were already starting to decrease and were normal by study day 113. The Investigator attributed the severe (Grade 3) "cytolytic hepatitis" and "cholestatic hepatitis" as possibly related to study drug or IV CYC.
(b) (6)	Azathioprine-induced liver toxicity	131	81-year-old female with GPA received IV CYC for induction on study day 1 and was transitioned to oral AZA on study day 114. The patient had mildly elevated LFTs during the screening period (study day -7), but these normalized by her baseline visit. On study day 131, the patient's LFTs were elevated (ALT, AST, ALP, GGT). AZA and Bactrim were discontinued, and pantoprazole was reduced. AST was decreased on study day 134, and ALT and AST normalized by study day 140. Avacopan was continued throughout the event. The Investigator attributed the severe (Grade 3) liver toxicity as probably not related to study drug, rather related to azathioprine.
(b) (6)	Elevated AST values >5x ULN	50	68-year-old male with newly-diagnosed GPA received IV CYC for induction on study day 1 and started mycophenolate mofetil (MMF) on study day 166. The patient's medical history is significant for a cholecystectomy. The patient had normal LFTs at baseline. On study day 50, the patient had elevated AST >5x ULN at 222 U/L, ALT 192 U/L, ALP 165 U/L, and normal total bilirubin. The patient underwent multiple diagnostic testing including abdominal ultrasound, abdominal

			nuclear magnetic resonance (NMR), and EGD, and MRCP. The patient was diagnosed with biliary sludge biliary duct dilatation. He was treated with ursodeoxycholic acid therapy on study day 113 with improvement. AST was significantly reduced by study day 120 and normal by study day 141. Avacopan was continued throughout this event, and the patient completed the study. The Investigator attributed the elevation in LFTs (AST) to cholestasis and probably not related to study drug.
(b) (6)	Elevated liver enzymes	103	79-year-old female with newly-diagnosed MPA received IV CYC for induction on study day 1 and received a total of 6 doses. At baseline, the patient had elevated LFTs (ALT 88 U/L, AST 35 U/L, normal ALP and TB) but subsequently normalized. However, from study day 49 to 74, the patient had elevated LFTs (highest on day 49 with ALT 336 U/L, AST 224 U/L, ALP 190 U/L). Avacopan and Bactrim were discontinued for this non-serious AE. LFTs normalized on study day 74. Both avacopan and Bactrim were re-started (avacopan on study day 70), and LFTs remained normal. Because of worsening AAV, the patient was treated with IV RTX on study day 96. LFTs increased on study day 103. Both avacopan and Bactrim were again discontinued and not restarted. The second elevation in LFTs was considered serious and resolved by study day 131. The Investigator considered the elevation in LFTs to be a "moderate" (Grade 2) AE and possibly related to study drug.
(b) (6)	Alcoholic hepatic enzyme elevation	23	68-year-old female with relapsed GPA was induced with IV RTX starting on study day 1. Baseline labs revealed normal LFTs. LFTs were elevated on study day 23 (AST 56 U/L, ALT 124 U/L, ALP 1035 U/L, GGT 248 U/L). Prior to this SAE, the patient admitted to vacationing (b) (6) (study days 15 to 22) and to drinking alcohol at least twice daily. Subsequent labwork showed decreased LFTs, and LFTs were considered resolved by study day 71. Avacopan was continued throughout this event, and the patient continued in the study. The Investigator considered this a mild (Grade 1) event of "alcoholic hepatic enzyme elevation," probably not related to study medication.
(b) (6)	Liver dysfunction	43	81-year-old female with newly-diagnosed MPA received IV CYC for induction on study day 1 (total 3 doses). She was then switched to RTX on study day 71. She had normal LFTs at baseline. On study day 43, she had elevated LFTs (ALT 207 U/L and AST 117 U/L). The highest ALP recorded was on study day 44 at 1503 U/L. The first

			elevation in TB (<2x ULN) was also noted on study day 44. Hepatitis B DNA was positive on study day 50 (serologies not provided) and normalized by study day 356 after treatment with entecavir hydrate. Avacopan was discontinued on study day 43 and not restarted. LFTs began decreasing by study day 44. ALT/AST normalized by study day 92, and GGT normalized by study day 113. The Investigator considered this AE to be "severe" (Grade 3) and possibly related to study drug or IV CYC.
SAE of HBV reactivation (associated with Grade 3/4 elevation in AST and ALT)			
(b) (6)	HBV reactivation	391	79-year-old male with newly-diagnosed MPA received RTX on study day 1. On study day 50, the patient had mild hepatic enzyme elevation (ALT 90 U/L, AST 51 U/L, GGT 208 U/L). He continued study medication, and labwork was resolved by study day 70. On study day 391, he experienced life-threatening HBV with elevated ALT and AST. Although the patient had a negative HBsAg at baseline, he did test positive for HBcAb in the past (2 years prior to study). The patient was hospitalized and received entecavir hydrate, ursodeoxycholic acid, and prednisolone. The patient completed the study on study day 432 at which time he was still hospitalized. He was discharged the following day but was re-hospitalized about 2 weeks later when another deterioration in LFTs was observed. The event of HBV was reported as resolved almost 3 months later. The Investigator and Gastroenterologist reported that HBV levels could have increased during exposure to study drug, thus, possibly related to study drug. The Applicant, on the other hand, attributed the event to RTX induction.

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