Arthritis Advisory Committee Meeting Briefing Materials

AVACOPAN
INDICATION: Treatment of Adult Patients with Anti-Neutrophil Cytoplasmic Auto-Antibody (ANCA)-Associated Vasculitis

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TABLE OF CONTENTS

List of Tables

List of Figures

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANCA	anti-neutrophil cytoplasmic auto-antibody
AST	aspartate aminotransferase
AUC	area under concentration-time curve
BMI	body mass index
BVAS	Birmingham Vasculitis Activity Score
C5a	complement 5a
C5aR	complement 5a receptor, also called CD88
C5L2	a type of C5a receptor (also referred to as C5aR2 or GPR77)
C-ANCA	cytoplasmic anti-neutrophil cytoplasmic auto-antibody
CCR2	C-C chemokine receptor type 2
CCX168	avacopan (ChemoCentryx, Inc. designation for the compound)
CD11b	integrin alpha M
CD20	B-lymphocyte antigen
CI	confidence interval
C_{max}	maximum concentration
CPK	creatine phosphokinase
CYP	cytochrome P450
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EQ-5D-5L	EuroQuality of Life-5 domains-5 levels
FDA	Food and Drug Administration
GPA	granulomatosis with polyangiitis
GTI	Glucocorticoid Toxicity Index
GTI-AIS	Glucocorticoid Toxicity Index-Aggregate Improvement Score
GTI-CWS	Glucocorticoid Toxicity Index-Cumulative Worsening Score
HIV	human immunodeficiency virus
HRQoL	Health-related quality of life
hsCRP	high-sensitivity C-reactive Protein
iC3b	inactivated complement fragment 3b
IC_{50}	concentration associated with 50% inhibition
ICAM-3	intercellular adhesion molecule-3
IGRA	interferon γ release assay
IIF	indirect immunofluorescence
ITT	Intent-to-Treat
IV	intravenous(ly)
IVIg	intravenous immunoglobulin
LSM	least squares mean
M1	mono-hydroxylated CCX168-M1 (metabolite of avacopan) or Margin 1, related to non-inferiority margin determination
M2	Margin 2, related to non-inferiority margin determination
Mac-1	macrophage-1
MCID	minimum clinically important difference
MCP-1	monocyte chemoattractant protein-1
MDRD	Modification of Diet in Renal Disease
MCS	Mental Component Score
MPA	microscopic polyangiitis
MPO	myeloperoxidase
NDA	New Drug Application

OMERACT	Outcome Measurement in Rheumatology
P-ANCA	perinuclear anti-neutrophil cytoplasmic auto-antibody
PCP	Pneumocystis carinii pneumonia
PCS	Physical Component Score
PK	pharmacokinetic
PPD	purified protein derivative
PR3	proteinase 3
QoL	Quality of life
SAE	serious adverse event
SEM	standard error of mean
SF-36v2	Medical Outcomes Survey Short Form 36 version 2
SOC	system organ class
TB	tuberculosis
t_{max}	time of maximum concentration
TNF	tumor necrosis factor
TNFα	tumor necrosis factor-alpha
UACR	urinary albumin:creatinine ratio
ULN	upper limit of normal
WBC	white blood cell
QD	once a day
QoL	Quality of life
QT interval	Q wave to T wave interval
VDI	Vasculitis Damage Index

1 EXECUTIVE SUMMARY

1.1 Introduction

ChemoCentryx, Inc. is seeking approval of avacopan, an orally administered, highly potent, and selective inhibitor of the human complement 5a receptor (C5aR), indicated for the treatment of adult patients with anti-neutrophil cytoplasmic auto-antibody (ANCA)-associated vasculitis in the subtypes of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). ChemoCentryx has received orphan drug designation from the U.S. Food and Drug Administration (FDA) for avacopan.

This briefing document presents data from the avacopan New Drug Application (NDA) submission which support the efficacy and safety of avacopan in adult patients with ANCA-associated vasculitis. The primary substantial evidence of the positive benefit-risk profile of avacopan in adults comes from a completed Phase 3 clinical trial (Study CL010_168, also referred to as ADVOCATE), designed after consultation with regulatory agencies with a view towards its sufficiency to support a regulatory filing for approval of avacopan in this indication. A total of 331 patients were enrolled in the Phase 3 trial, which was supported by two Phase 2 studies in 109 patients with ANCA-associated vasculitis (Studies CL002_168 and CL003_168).

The clinical studies conducted with avacopan for the treatment of patients with ANCA-associated vasculitis provide a comprehensive evaluation of the efficacy and safety of this drug in the study population. The results from Study CL010_168 provide substantial evidence that avacopan is an efficacious treatment for patients with this rare disease and fulfills unmet medical needs for this patient population. The benefits of avacopan in the treatment of patients with ANCA-associated vasculitis outweigh the risks. Avacopan can provide a much-needed treatment option for patients with ANCA-associated vasculitis.

1.2 Background and Unmet Need

ANCA-associated vasculitis is a group of systemic autoimmune diseases. These diseases are characterized by necrotizing vasculitis, which predominantly affects the small to medium-sized blood vessels, with the two main clinical forms being GPA and MPA (Jennette et al., 2013). Patients typically have auto-antibodies against neutrophil enzymes, either proteinase 3 (PR3) or myeloperoxidase (MPO). Clinically, ANCA-associated vasculitis may present with a spectrum of disease severity and symptoms, ranging from skin manifestations to glomerulonephritis to life-threatening pulmonary hemorrhage. If untreated, 80% of patients with GPA or MPA die within 2 years of disease onset (Mukhtyar et al., 2008).

Current treatment of active ANCA-associated vasculitis generally includes high doses of glucocorticoids such as prednisone or an analog, typically with long term dosing over a period of months in combination with other immunosuppressive drugs, such as the alkylating agent cyclophosphamide or the B-cell depleting biologic treatment rituximab, to achieve control of inflammation that can threaten life or organ systems. This treatment is often followed by other drugs for maintenance of control, which may include additional glucocorticoids, azathioprine,

methotrexate, mycophenolate mofetil, or repeated administration of rituximab or cyclophosphamide.

These treatment regimens, while useful in many patients in controlling specific disease activity associated with active vasculitis, carry risks of serious side effects. These side effects comprise general immune suppression as well as metabolic and other toxicities often associated with glucocorticoids (Morgan et al., 2006). Among patients with ANCA-associated vasculitis treated with glucocorticoids, within the first year, 8.2% developed new-onset diabetes, 50% of which occurred within 1.7 months. Twenty-nine percent of patients gained more than 10 kg in weight, 2.6% developed peptic ulceration, 2.5% had fractures, 2% developed cataracts and 0.4% developed avascular necrosis (Little et al., 2010). The adverse effects of glucocorticoids are even more pronounced with increasing length of exposure. In a long-term follow-up (median 5 years) of 270 patients, 41% had hypertension, 38% osteoporosis, 28% diabetes mellitus, and 25% had developed cataracts (Robson et al., 2015). Glucocorticoids can also cause increases in blood lipids, cardiovascular disease, and psychiatric disorders.

Despite the above-mentioned therapies, there is a considerable unmet medical need in the treatment of patients with ANCA-associated vasculitis. Affected patients experience a 9-fold increased mortality risk in the first year of diagnosis compared to healthy controls, attributable to conditions that include infection, vasculitis and renal disease (Luqmani et al., 2011). Additionally, patients with ANCA-associated vasculitis often have severe impairment of quality of life, including fatigue and impaired physical and mental functioning (Basu et al., 2013, 2014a, 2014b).

The significant injury to vital organs from this disease as well as adverse events (AEs) associated with current therapies can have a highly significant impact on how individuals with ANCA-associated vasculitis feel, function and survive. Any effort to decrease the disease burden with new innovative treatment options and/or reduce the AE burden caused by current therapies is very important for physicians and their patients.

Additional details on unmet need are provided in Section 2.3.

1.3 Product Overview: Mechanism of Action, Pharmacodynamics, and Dose

Avacopan is a selective inhibitor of the human C5aR, acting through competitive inhibition of interaction between C5aR and the anaphylatoxin C5a, which is produced through activation of the complement cascade (Bekker et al., 2016). Avacopan does not inhibit the related receptor C5L2 (C5aR2), activation of which may have beneficial anti-inflammatory effects. Avacopan blocks the pro-inflammatory effects of C5a through the C5aR, which include neutrophil activation and migration, adherence to sites of small blood vessel inflammation, vascular endothelial cell retraction and increased blood vessel permeability (Camous L, 2011; Foreman et al., 1994; Hammerschmidt et al., 1981; Schraufstatter et al., 2002; Schreiber et al., 2009). Avacopan does not affect upstream activities of the complement system such as Bb, C3a, C3b, and properdin. Unlike C5 inhibitors such as eculizumab, avacopan does not block the production

of C5b and C5b-9 (membrane attack complex), which is necessary to defend against infections with encapsulated bacteria such as *Neisseria meningitidis*.

Avacopan blocks the C5a-induced upregulation of CD11b (integrin alpha M) on neutrophils taken from humans dosed with avacopan. CD11b facilitates neutrophil adherence to vascular endothelial surfaces, one of the steps in the vasculitic disease process. Avacopan was shown to rapidly normalize the elevated neutrophil count associated with ANCA-associated vasculitis.

The dosing regimen used in the Phase 3 study was 30 mg taken twice daily, preferably with food; 30 mg taken twice daily with food is the recommended dose for treatment of patients with ANCA-associated vasculitis. Data from Phase 1 studies confirmed that avacopan doses of up to 100 mg twice daily for 7 days (Study CL014_168) were well tolerated by healthy volunteers.

Additional information on the product and the mechanism of action is provided in Section 3, and additional details on clinical pharmacology are provided in Section 5.

1.4 Efficacy Findings

Additional details on clinical efficacy are provided in Section 6.

1.4.1 Efficacy Findings for Pivotal Phase 3 Study CL010_168

1.4.1.1 Study Design

Phase 3 clinical trial CL010_168 was a randomized, double-blind, double-dummy, active-controlled clinical study to assess the efficacy, safety, and tolerability of avacopan in patients with newly diagnosed or relapsing active ANCA-associated vasculitis, when administered with a standard background regimen of either cyclophosphamide or rituximab. The primary objective of the trial was to evaluate the efficacy of avacopan to achieve clinical remission and to sustain remission in patients with ANCA-associated vasculitis, without the need for daily oral prednisone therapy. The trial enrolled 331 patients at 143 centers in North America, Europe, Australia, New Zealand, and Japan. The study design is illustrated in Figure 1.

The Intent-to-Treat (ITT) and Safety Populations comprised 330 patients (one patient randomized to the prednisone group was not treated). The two treatment groups in study CL010_168 were as follows:

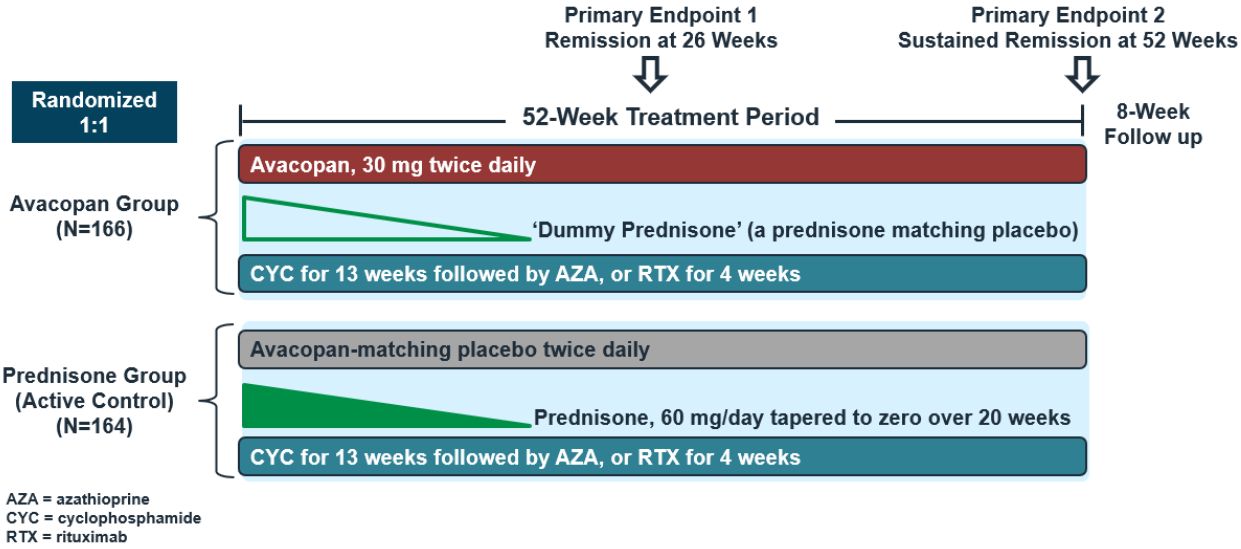
1. Avacopan group (N=166): Patients received 30 mg avacopan twice daily for 52 weeks plus prednisone-matching placebo for 20 weeks.
2. Prednisone group (N=164): Patients received avacopan-matching placebo twice daily for 52 weeks plus prednisone (tapered from 60 mg/day to 0 over 20 weeks).

Subsequent to the 52-week treatment period was an 8-week follow-up period. Eligible patients were stratified based on three factors:

1. Receiving intravenous (IV) rituximab, IV cyclophosphamide, or oral cyclophosphamide
2. Proteinase 3 (PR3) or myeloperoxidase (MPO) ANCA

3. Newly diagnosed or relapsing ANCA-associated vasculitis.

Figure 1: Pivotal Phase 3 Study CL010_168 Design



The aim of the trial was to determine if avacopan could provide an effective treatment for patients with ANCA-associated vasculitis, while also allowing for the elimination of daily glucocorticoid use without compromising safety or efficacy.

Efficacy was assessed using the Birmingham Vasculitis Activity Score (BVAS), a standard instrument (mainly used in clinical trial settings) for assessing the activity of vasculitis, with a range of 0 to 63 (Appendix 10.1; Mukhtyar et al., 2009). Higher scores indicate a greater disease activity. The two primary endpoints were (1) clinical remission at Week 26 and (2) sustained remission at Week 52. Clinical remission was defined as achieving a BVAS of 0 and not taking glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to Week 26. Sustained remission was defined as remission at Week 26 and remission at Week 52 (defined as for Week 26), without relapse between Week 26 and Week 52. The two primary endpoints were tested statistically for non-inferiority (with a margin of -20 percentage points) and for superiority of the avacopan group compared to the prednisone group. In order to preserve the Type I error, the endpoints were tested sequentially using a gatekeeping procedure as follows: non-inferiority at Week 26, non-inferiority at Week 52, superiority at Week 52, and lastly superiority at Week 26.

Detailed information on considerations for setting the non-inferiority margin is provided in Appendix 10.5.

The two treatment groups were well balanced with regard to demographics and baseline disease characteristics. The mean patient age was 60.9 years. Most patients were male (56.4%) and had newly diagnosed disease (69.4%). Patients had either GPA (54.8%) or MPA (45.2%). Patients were positive for either PR3 (43.0%) or MPO (57.0%). Regarding stratification factors for immunosuppressant treatment given during the study, approximately 65% of patients received

rituximab, 31% received IV cyclophosphamide, and 4% received oral cyclophosphamide. Mean baseline BVAS was 16.2, and 81.2% of patients had renal vasculitis at baseline.

1.4.1.2 Efficacy Results

Primary Endpoints

The study met both of its primary endpoints: remission at Week 26 and sustained remission at Week 52 (Table 1). The avacopan group was non-inferior to the prednisone group with respect to the rates of patients who achieved clinical remission at Week 26 and superior to the prednisone group with regard to those who achieved sustained remission at Week 52.

- At Week 26, 70.1% (115/164) in the prednisone group achieved remission compared to 72.3% (120/166) in the avacopan group.
- At Week 52, 54.9% (90/164) in the prednisone group achieved sustained remission compared to 65.7% (109/166) in the avacopan group.
- For each comparison, the non-inferiority tests were highly statistically significant (P< 0.0001).
- The superiority test comparing the sustained remission rates at Week 52 between the avacopan group and the prednisone group was also statistically significant (P=0.0066). The superiority test was not statistically significant for remission at Week 26 (P=0.2387).
- The efficacy observed was generally consistent across pertinent subgroups, i.e., those with newly diagnosed and relapsed disease, PR3 and MPO ANCA, GPA and MPA, those receiving cyclophosphamide, and those receiving rituximab.
- Pre-specified sensitivity analyses indicate that the primary endpoint results are robust (see Section 6.1.3.3 and Appendix 10.6).
- Missing data did not influence the outcome of the primary endpoints, as shown by tipping point analyses (see Section 6.1.3.5 and Appendix 10.7).

Table 1: Summary of Efficacy Results from Phase 3 Study CL010_168 (ITT Population)

	Avacopan (N=166)	Prednisone (N=164)	P-value for Difference Between Groups[a]
Primary Endpoints			
Remission[b] at Week 26, n (%)	120 (72.3)	115 (70.1)	< 0.0001 (non-inferiority) 0.2387 (superiority)
Estimate of common difference in percentages	3.4	--	
Two-sided 95% confidence interval for common difference	-6.0, 12.8	--	
Sustained remission[b] at Week 52, n (%)	109 (65.7)	90 (54.9)	< 0.0001 (non-inferiority) 0.0066 (superiority)
Estimate of common difference in percentages	12.5	--	
Two-sided 95% confidence interval for common difference	2.6, 22.3	--	

[a] One-sided P-values; the P-value is based the Summary score tests (Agresti, 2013).

[b] Summary score estimate of the common difference in remission rates by using inverse-variance stratum weights. The corresponding summary score estimates (and associated 95% CI) of the common difference in remission rates

between the avacopan and prednisone groups were calculated by using inverse-variance stratum weights and Miettinen-Nurminen (score) confidence limits.

Secondary Endpoints

Study CL010_168 met the majority of its secondary endpoints. Key secondary endpoints are discussed below. Additional information on secondary endpoint results for Study CL010_168 is provided in Section 6.1.4.

Risk of Relapse

The rate of relapse after remission had been achieved at Week 26 was 7.5% in the avacopan group and 12.2% in the prednisone group. The risk of relapses at any time during the study after BVAS=0 had been achieved was reduced significantly in the avacopan group compared to the prednisone group (P=0.0091) for the Log-rank test of the difference of time to relapse. The hazard ratio of the time to relapse between the two treatment groups was 0.46, 95% CI (0.25, 0.84). The estimated reduction in risk of relapse was 54% in the avacopan group compared to the prednisone group.

Glucocorticoid Toxicity Index

Regarding glucocorticoid toxicity, as measured by the Glucocorticoid Toxicity Index (McDowell et al., 2021; Miloslavsky et al., 2017), at both Week 13 and 26, the avacopan group had statistically significantly lower toxicity relative to the prednisone group for both Glucocorticoid Toxicity Indexes (GTIs), the Cumulative Worsening Score (GTI-CWS) and the Aggregate Improvement Score (GTI-AIS). The GTI quantifies changes in glucocorticoid toxicity including body mass index (BMI), blood pressure changes, glucose tolerance, lipid changes, myopathy, skin changes, neuropsychiatric changes, and infection. More information about the GTI is provided in Appendix 10.2.

- GTI-CWS captures cumulative glucocorticoid toxicity over time, regardless of whether the toxicity has lasting effects or is transient. New toxicities that occur are added, but toxicities that resolve are not removed. The GTI-CWS can only increase or remain the same over time. If an investigational agent is effective at decreasing glucocorticoid toxicity over time, the CWS will be lower in the drug arm.
- GTI-AIS toxicities are removed if they improve and can be added if they are new or worsen. This score indicates whether a new therapy is effective at diminishing baseline glucocorticoid toxicity over time. If an investigational agent is effective at decreasing glucocorticoid toxicity over time, the GTI-AIS will be lower in the drug arm.

For the GTI-CWS, at Week 13, the least squares mean (LSM) was 25.7 in the avacopan group compared to 36.6 in the prednisone group (P=0.0140), and at Week 26, the GTI-CWS were 39.7 and 56.6, respectively (P=0.0002).

At Week 13, the LSM of the GTI-AIS was 9.9 in the avacopan group compared to 23.2 in the prednisone group (P=0.003), and at Week 26, the GTI-AIS were 11.2 and 23.4, respectively (P=0.008).

Kidney Function

Kidney function was measured using estimated glomerular filtration rate (eGFR) based on serum creatinine measurements (see Appendix 10.3 for more information about eGFR), and proteinuria measured by urinary albumin:creatinine ratio (UACR). Regarding kidney function:

- Avacopan demonstrated significant improvement in eGFR compared to prednisone at Week 26 and Week 52. At baseline, eGFR on average was 45.6 and 44.6 mL/min/1.73 m^2 in the prednisone and avacopan groups, respectively. At Week 26, the LSM increase in eGFR in the prednisone and avacopan groups was 2.9 and 5.8 mL/min/1.73 m^2 (P=0.046), respectively, and at Week 52, the LSM increase in the prednisone and avacopan groups was 4.1 and 7.3 mL/min/1.73 m^2, respectively (P=0.029).
- The treatment effect at Week 52 was most prominent in patients with Stage 4 kidney disease, defined as having an eGFR < 30 mL/min/1.73 m^2 at baseline. There was a continued pattern of improvement in eGFR between Week 26, when remission was achieved, and Week 52. The LSM increase in the avacopan group was 13.7 mL/min/1.73 m^2 at Week 52 compared to 8.2 mL/min/1.73 m^2 in the prednisone group; this difference was statistically significant (P=0.0050).
- For the analysis of urinary albumin to creatinine ratio (UACR), in patients with renal disease and albuminuria at baseline, at Week 4 the UACR decreased 40% on average in the avacopan group compared to no change in the prednisone group (P< 0.0001). This early improvement in albuminuria is important since proteinuria is a risk factor for progression of kidney disease (Kaplan-Pavlovcic et al., 2003; Stangou et al., 2005). The overall extent of improvement in UACR was similar between treatment groups at Week 52 (-74% in the avacopan group compared to -77% in the prednisone group; difference not statistically significant).

Health-Related Quality of Life

Detailed information on the assessments for health-related quality of life are provided in Section 6.1.1.2. Higher scores on these instruments represent better quality of life. Results from these assessments included the following:

- Patients in the avacopan group had a significantly greater improvement in the Physical Component Score of the Medical Outcomes Survey Short Form 36 version 2 (SF-36v2) compared to the prednisone group. At Week 26, the Physical Component Score improved on average 4.45 from a mean baseline of 39.24 in the avacopan group compared to 1.34 from a mean baseline of 40.14 in the prednisone group (P=0.002 for the difference between groups). At Week 52, the changes were 4.98 and 2.63, respectively (P=0.018). Within the Physical component, the Physical Functioning and Role Physical domains showed significantly greater improvement in the avacopan group compared to the

prednisone group. At Week 26, General Health Perception improved by 3.12 in the avacopan group and deteriorated -2.89 in the prednisone group (P=0.002), and at Week 52, the changes were 5.84 and -0.17, respectively (P=0.002).

- The Vitality and Role Emotional domains within the Mental Component Score of the SF-36v2 showed greater improvement in the avacopan group compared to the prednisone group at Week 26; There were no significant differences between the treatment groups in change in the Mental Component Score.
- At Week 52, the EuroQuality of Life-5 Domains-5 Levels (EQ-5D-5L) Visual Analogue Scale improved 13.0 points from a baseline of 65.8 in the avacopan group compared to 7.1 from a baseline of 63.4 in the prednisone group (P=0.002).

1.4.2 Efficacy Findings for Supportive Phase 2 Studies

1.4.2.1 Phase 2 Study CL002_168

Study CL002_168 in ANCA-associated vasculitis was a prospective, randomized, double-blind, double-dummy, placebo-controlled supportive Phase 2 clinical trial in 67 patients. The treatment period was 12 weeks. The study contained 3 treatment groups:

1. Full dose prednisone group: patients received avacopan-matching placebo twice a day plus cyclophosphamide or rituximab plus a full starting dose of prednisone (60 mg/day);
2. Avacopan plus reduced dose prednisone group: patients received avacopan 30 mg twice a day plus cyclophosphamide or rituximab plus a one-third starting dose of prednisone (20 mg/day);
3. Avacopan plus no prednisone group: patients received avacopan 30 mg twice daily plus cyclophosphamide or rituximab plus prednisone-matching placebo.

All patients, irrespective of treatment group, received cyclophosphamide 15 mg/kg (up to 1.2 g) IV every 2 to 4 weeks or rituximab 375 mg/m^2 IV once weekly for 4 weeks.

The study met its primary endpoint. Both of the avacopan treatment groups were statistically non-inferior to the prednisone group in terms of BVAS response (BVAS decrease from baseline to Week 12 by at least 50% and no worsening in any organ system). Additional details regarding the efficacy results for Phase 2 Study CL002_168 are provided in Section 6.2.3.

1.4.2.2 Phase 2 Study CL003_168

Study CL003_168 was primarily a safety study. This was a prospective, randomized, double-blind, double-dummy, placebo-controlled supportive Phase 2 clinical trial in 42 patients. The treatment period was 12 weeks.

Study CL003_168 contained three treatment groups:

1. Full dose prednisone group: patients received avacopan-matching placebo twice daily plus cyclophosphamide or rituximab plus a full starting dose of prednisone (60 mg/day);

2. Full dose prednisone plus low dose avacopan group: patients received avacopan 10 mg twice daily plus cyclophosphamide or rituximab plus a full starting dose of prednisone (60 mg/day);
3. Full dose prednisone plus high dose avacopan group: patients received avacopan 30 mg twice daily plus cyclophosphamide or rituximab plus a full starting dose of prednisone (60 mg/day).

All patients, irrespective of treatment group, received cyclophosphamide 15 mg/kg (up to 1.2 g) IV every 2 to 4 weeks or rituximab 375 mg/m^2 IV once weekly for 4 weeks.

Study CL003_168 was not powered statistically to evaluate efficacy. Descriptive results showed, as anticipated, that the response rate in the ITT Population, based on a BVAS decrease from baseline to Week 12 by at least 50% and no worsening in any organ system, was high across all three treatment groups. Additional details regarding the efficacy results for Phase 2 Study CL003_168 are provided in Section 6.3.3.

In summary, results from Study CL003_168 supported the results from Study CL002_168 that showed a rapid onset of action of avacopan and selection of a dose regimen of 30 mg avacopan twice daily as the preferred dose in treatment of patients with ANCA-associated vasculitis. Also, results from the two Phase 2 studies are consistent with those from the pivotal Phase 3 Study CL010_168.

1.5 Safety Findings

Additional details on safety findings are provided in Section 7.

1.5.1 Adverse Events Overview: Phase 3 Study

An overview of the adverse events (AEs) observed in the Phase 3 study is presented in Table 2. The number of AEs, serious AEs, life-threatening AEs, and deaths were higher in the prednisone group compared to the avacopan group. There were 4 deaths in the prednisone group (death of unknown cause, acute myocardial infarction, infectious pleural effusion, and generalized fungal infection) and 2 in the avacopan group (pneumonia and worsening of GPA). The percentage of patients who discontinued study medication due to an AE was similar between treatment arms.

Table 2: Study CL010_168: Adverse Event Overview

	Avacopan (N=166)	Prednisone (N=164)
Adverse event (AE) Number of patients (%) Number of events	 164 (98.8%) 1779 events	 161 (98.2%) 2139 events
Severe AE Number of patients (%) Number of events	 39 (23.5%) 71 events	 41 (25.0%) 94 events
Serious AE Number of patients (%) Number of events	 70 (42.2%) 116 events	 74 (45.1%) 166 events
Life-threatening Number of patients (%) Number of events	 8 (4.8%) 8 events	 14 (8.5%) 22 events
Death Number of patients (%)	 2 (1.2%)	 4 (2.4%)
AEs leading to study medication discontinuation Number of patients (%)	 27 (16.3%)	 28 (17.1%)

1.5.2 Common Adverse Events: Phase 3 Study

The AEs reported in at least 5% of patients in either treatment group are presented in Table 3. Overall, the number of AEs was 20% higher in the prednisone group, with 2139 events compared to 1779 in the avacopan group. Nausea, headache, and vomiting were reported more in the avacopan group. Nausea and vomiting were reported predominantly in patients in the cyclophosphamide stratum. All except one event of nausea were not serious. None of the AEs of vomiting were serious. Only 1 patient discontinued study medication due to nausea and vomiting.

Several AEs occurred more frequently in the prednisone group compared to the avacopan group. Many of these AEs are consistent with the known safety profile of glucocorticoids and are most likely related to their use.

Table 3: Study CL010_168: Most Commonly Reported AEs (≥ 5% of Patients in Either Treatment Group)

	Avacopan (N=166)		Prednisone (N=164)		Total (N=330)	
Preferred Term	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
Any Treatment-Emergent Adverse Event	164 (98.8)	1779	161 (98.2)	2139	325 (98.5)	3918
Nausea	39 (23.5)	54	34 (20.7)	46	73 (22.1)	100
Edema peripheral	35 (21.1)	39	40 (24.4)	56	75 (22.7)	95
Headache	34 (20.5)	43	23 (14.0)	30	57 (17.3)	73
Arthralgia	31 (18.7)	42	36 (22.0)	48	67 (20.3)	90
Hypertension	30 (18.1)	36	29 (17.7)	31	59 (17.9)	67
Anti-neutrophil cytoplasmic antibody positive vasculitis[a]	26 (15.7)	30	34 (20.7)	46	60 (18.2)	76
Cough	26 (15.7)	31	26 (15.9)	29	52 (15.8)	60

Preferred Term	Avacopan (N=166)		Prednisone (N=164)		Total (N=330)	
	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
Diarrhea	25 (15.1)	33	24 (14.6)	31	49 (14.8)	64
Nasopharyngitis	25 (15.1)	38	30 (18.3)	46	55 (16.7)	84
Vomiting	25 (15.1)	29	21 (12.8)	27	46 (13.9)	56
Upper respiratory tract infection	24 (14.5)	28	24 (14.6)	33	48 (14.5)	61
Rash	19 (11.4)	26	13 (7.9)	17	32 (9.7)	43
Muscle spasms	18 (10.8)	23	37 (22.6)	47	55 (16.7)	70
Fatigue	17 (10.2)	19	15 (9.1)	15	32 (9.7)	34
Back pain	16 (9.6)	16	22 (13.4)	22	38 (11.5)	38
Myalgia	16 (9.6)	17	22 (13.4)	25	38 (11.5)	42
Pyrexia	15 (9.0)	18	19 (11.6)	25	34 (10.3)	43
Epistaxis	14 (8.4)	21	21 (12.8)	30	35 (10.6)	51
Anemia	13 (7.8)	13	18 (11.0)	19	31 (9.4)	32
Insomnia	13 (7.8)	13	25 (15.2)	27	38 (11.5)	40
Pain in extremity	13 (7.8)	13	13 (7.9)	13	26 (7.9)	26
Hypercholesterolemia	12 (7.2)	13	20 (12.2)	21	32 (9.7)	34
Leukopenia	12 (7.2)	15	14 (8.5)	20	26 (7.9)	35
Urinary tract infection	12 (7.2)	19	23 (14.0)	33	35 (10.6)	52
Abdominal pain upper	11 (6.6)	12	10 (6.1)	13	21 (6.4)	25
Constipation	11 (6.6)	11	11 (6.7)	11	22 (6.7)	22
Dizziness	11 (6.6)	14	10 (6.1)	10	21 (6.4)	24
Pneumonia	11 (6.6)	12	11 (6.7)	11	22 (6.7)	23
Blood creatinine increased	10 (6.0)	10	8 (4.9)	10	18 (5.5)	20
Pruritus	10 (6.0)	15	10 (6.1)	11	20 (6.1)	26
Sinusitis	10 (6.0)	10	12 (7.3)	12	22 (6.7)	22
Paresthesia	9 (5.4)	10	7 (4.3)	8	16 (4.8)	18
Dyspnea	8 (4.8)	11	11 (6.7)	14	19 (5.8)	25
Alopecia	7 (4.2)	7	12 (7.3)	12	19 (5.8)	19
Increased tendency to bruise	7 (4.2)	7	10 (6.1)	11	17 (5.2)	18
Lymphopenia	6 (3.6)	7	18 (11.0)	27	24 (7.3)	34
Oropharyngeal pain	6 (3.6)	7	12 (7.3)	12	18 (5.5)	19
Bronchitis	5 (3.0)	7	10 (6.1)	11	15 (4.5)	18
Dyspepsia	5 (3.0)	6	10 (6.1)	12	15 (4.5)	18
Cushingoid	3 (1.8)	3	9 (5.5)	9	12 (3.6)	12
Tremor	2 (1.2)	2	10 (6.1)	11	12 (3.6)	13
Weight increased	1 (0.6)	1	17 (10.4)	19	18 (5.5)	20

N=number of patients randomized to treatment group in the Safety Population; n=number of patients in specified category.
Note: An adverse event was considered treatment-emergent if the start date/time of the event was on or after the date/time of first dose of study medication. Adverse events were coded using MedDRA (version 19.1).
[a] Worsening of vasculitis is reported as the Preferred Term of "anti-neutrophil cytoplasmic antibody-positive vasculitis."

1.5.3 Adverse Events of Interest: Phase 3 Study

Pre-specified adverse events of interest included infections, liver function test elevations, white blood cell (WBC) count abnormalities (neutropenia and lymphopenia), and hypersensitivity.

Infections: In the avacopan group, there was a lower proportion of patients with any AEs of infection (68.1% vs. 75.6% patients), serious AEs of infection (13.3% vs. 15.2%), serious opportunistic infections (3.6% vs. 6.7%), life-threatening AEs of infection (0.6% vs. 1.2%), and infections resulting in death (0.6% vs. 1.2%) compared with the prednisone group in the Phase 3 study. No *Neisseria meningitidis* infections occurred in any patients treated with avacopan.

Liver function tests: There was a higher incidence of AEs associated with liver function test increases in the avacopan group (13.3%) compared to the prednisone group (11.6%); SAEs occurred in 5.4% of patients in the avacopan group compared to 3.7% in the prednisone group. However, causality assessment was confounded by the presence of other known hepatotoxic drugs, such as co-trimoxazole (note: all patients in the protocol received prophylaxis for *Pneumocystis jerovecii*, mostly comprising co-trimoxazole), azathioprine, and alcohol, as well as potential viral etiologies.

WBC count: There was a lower incidence of AEs associated with WBC count decreases (neutropenia or lymphopenia) in the avacopan group (18.7%) compared to the prednisone group (23.8%). A total of 8 patients (4.9%) in the prednisone group had SAEs of neutropenia or lymphopenia compared to 4 patients (2.4%) in the avacopan group.

Hypersensitivity: The patient incidence of hypersensitivity reactions was similar in the avacopan group (41.0%) compared to the prednisone group (42.7%). Two patients receiving avacopan had events of angioedema that resolved without sequelae. In one of these patients, the event was an SAE and avacopan was withdrawn. In the other patient, who had a non-serious AE of angioedema, avacopan treatment was restarted and the event did not recur.

1.5.4 Safety Findings in the Phase 2 Studies

Results from the Phase 2 studies were generally consistent with results from the Phase 3 study.

1.6 Benefit-Risk Summary

Additional details on risk-benefit conclusions are provided in Section 8.

1.6.1 Benefits

The unmet medical needs in the treatment of ANCA-associated vasculitis were addressed as follows in the findings from the avacopan clinical program:

- Statistically significant and clinical meaningful superior efficacy in sustained remission at Week 52 and a lower relapse rate in the avacopan group compared to the prednisone group.
- Glucocorticoid toxicity was significantly reduced in the avacopan group compared to the prednisone group.

- Renal function was improved significantly more in the avacopan group compared to the prednisone group.
- Health-related quality of life, as measured by the SF-36v2 and EQ-5D-5L, improved more in patients in the avacopan group compared to those in the prednisone group.

1.6.2 Risks

Safety results showed that avacopan was generally well tolerated and had a favorable safety profile compared to prednisone. In the Phase 3 study, there was higher number of SAEs and a higher number of AEs in the prednisone group compared to the avacopan group.

The incidence of AEs such as infections, which are commonly observed in patients with ANCA-associated vasculitis who receive glucocorticoids plus cyclophosphamide or rituximab, was lower in the avacopan group compared to the prednisone group. Notably, there was a lower proportion of patients in the avacopan group compared to the prednisone group with any AEs of infection, SAEs of infection, serious opportunistic infections, life-threatening AEs of infection, and infections resulting in death.

The incidence of SAEs in the majority of system organ classes (SOCs) was higher in the prednisone group compared with the avacopan group. There was a higher incidence of SAEs associated with hepatic function test increases in the avacopan group compared with the prednisone group. Causality assessment for these events was confounded by several factors including other concomitant medications that could have caused the events such as co-trimoxazole, azathioprine, as well as alcohol and potential viral etiologies.

The patient incidence of hypersensitivity was similar between the two treatment groups. Two patients receiving avacopan had events of angioedema that resolved without sequelae.

There were more deaths in the prednisone group (4 patients) compared to the avacopan group (2 patients), and none of the 2 deaths in the avacopan group occurred while on avacopan treatment.

Avacopan does not block the production of C5b and C5b-9 (membrane attack complex) which is necessary to defend against infections with encapsulated bacteria such as *Neisseria meningitidis*. No *Neisseria meningitidis* infections occurred in any patients treated with avacopan.

1.6.3 Benefit-Risk Assessment

Avacopan was shown to be effective and safe for treatment of patients with active ANCA-associated vasculitis; it was also able to eliminate the need for daily glucocorticoid treatment. Based on clinical study results accumulated to date, the potential benefits of avacopan in patients with ANCA-associated vasculitis outweigh the potential risks.

2 BACKGROUND ON ANCA-ASSOCIATED VASCULITIS

Summary

- ANCA-associated vasculitis is an orphan disease that consists of a group of small vessel vasculitides, with the two main forms being granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).
- Cyclophosphamide plus glucocorticoids or rituximab plus glucocorticoids are currently considered the standard of care therapy for ANCA-associated vasculitis.
- Despite current standard of care treatment, patients with ANCA-associated vasculitis have a high mortality risk in the first year of disease compared to healthy controls.
- Current therapies limitations include:
    - Low sustained remission rate and high rate of relapse of ANCA-associated vasculitis after remission has been achieved
    - Limited efficacy on renal function
    - Detrimental effect of treatments such as glucocorticoids on health-related quality of life
    - High levels of toxicity with current therapies, including glucocorticoids

2.1 Overview of ANCA-Associated Vasculitis

ANCA-associated vasculitis is a heterogeneous group of systemic autoimmune diseases. These diseases are characterized by necrotizing vasculitis, which predominantly affects the small to medium-sized blood vessels (Jennette et al., 2013). The recurring inflammation of the vessels can ultimately accrue into irreversible organ damage and death.

ANCA-associated vasculitis consists of a group of small vessel vasculitides, with the two main forms being granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). These conditions show distinct pathological profiles but have significant overlap of clinical characteristics and are often studied together. Patients with ANCA-associated vasculitis have auto-antibodies against the neutrophil-expressed antigens myeloperoxidase (MPO) and proteinase 3 (PR3), and complement activation with C5a production is an important part of the pathogenesis of the disease. Clinically, ANCA-associated vasculitis may present with a spectrum of disease severity and symptoms, ranging from skin manifestations to glomerulonephritis to life-threatening pulmonary hemorrhage. If left untreated, 80% of patients with GPA or MPA die within 2 years of disease onset (Mukhtyar et al., 2008).

2.2 Current Treatment Options

Managing ANCA-associated vasculitis starts with the goal of a rapid diagnosis and prompt treatment initiation. Once treatment is started, early remission is desired to prevent organ damage. Additionally, treatment-related toxicity needs to be limited while maintaining disease

remission and preventing relapse. Limiting toxicity has been challenging, since many patients have required chronic glucocorticoid treatment (Demiselle et al., 2017; Miller et al., 2010; Ntatsaki et al., 2014; Pearce et al., 2018).

Glucocorticoids combined with cyclophosphamide or glucocorticoids plus rituximab are currently considered the standard of care therapy for ANCA-associated vasculitis. Initial high doses of glucocorticoids are typically tapered over a period of 5 to 6 months to help manage toxicity associated with chronic use (Jayne, 2000; Jones et al., 2010; Stone et al., 2010). Current treatments are summarized in Table 4.

With the advent of high dose glucocorticoids plus cyclophosphamide or high dose glucocorticoids plus rituximab treatment, the mortality rate has decreased, but remains high overall. Despite current standard of care treatment, patients with GPA have a 9-fold increased mortality risk in the first year of disease compared to healthy controls, attributed primarily to infection, vasculitis, and renal disease (Luqmani et al., 2011). Approximately 11% of patients die within the first year after diagnosis (Flossmann et al, 2011; Little et al., 2010) and most deaths (59%) are attributable to the medications used (Little et al., 2010).

Table 4: Current Treatments for ANCA-Associated Vasculitis

Initial Treatment	**Glucocorticoid treatment:** • High dose IV (often methylprednisolone), followed by tapering regimen of oral glucocorticoids (prednisone or prednisolone)
	Immunosuppressants: • IV or oral cyclophosphamide • Rituximab
Maintenance Treatment	• Glucocorticoids • Azathioprine • Methotrexate • Mycophenolate mofetil • Repeated administration of rituximab or cyclophosphamide

2.3 Patient Medical Need

Patients with ANCA-associated vasculitis have significant unmet treatment needs, despite existing therapies. These needs include:

- Low sustained remission rate and high rate of relapse of ANCA-associated vasculitis after remission has been achieved: At 12 and 18 months in the RAVE study (Specks et al., 2013), less than half (48% and 39%, respectively), of the patients in the rituximab group had sustained remission, and in the cyclophosphamide/azathioprine comparison group only 39% and 33%, respectively. A high relapse rate remains a concern in patients with ANCA-associated vasculitis. The overall risk of relapse in a long term follow up study was 38% at 5 years (Walsh et al., 2012). Patients experiencing relapses are often treated with glucocorticoids (Yates et al., 2016) with associated toxicities. Relapses are also associated with increased chronic tissue and organ damage (Robson et al., 2015). A recent open label study (RITAZAREM) showed that repeat doses of rituximab in combination with glucocorticoids was more effective than daily oral azathioprine in preventing relapse

among ANCA-associated vasculitis patients with relapsing disease following induction of remission with rituximab (Smith et al., 2019). This study did not include newly-diagnosed patients and these patients were still treated with glucocorticoids.

- Need for more treatment options for patients who are refractory or relapse under the current standard of care. Not every patient can achieve remission under the current standard of care. Some patients who achieve remission under the current standard of care will relapse, as stated above, and they need treatment options after relapse.
- Limited efficacy on renal function: Renal involvement is common in patients with GPA or MPA, and patients with renal involvement have a worse prognosis than patients without renal involvement (Corral-Gudino et al., 2011); 23% of patients who require dialysis at time of diagnosis die within 6 months (de Joode et al., 2013). As early as 6 months after diagnosis, 8% of patients require long-term dialysis therapy for end-stage renal failure (Robson et al., 2015). A total of 42% of patients with renal involvement die or develop end-stage renal disease at 2 years (Jayne, 2000). Current therapies have limited efficacy on improving renal function (Geetha et al., 2015).
- Detrimental effect of vasculitis as well as treatments such as glucocorticoids on health-related quality of life: Patients with ANCA-associated vasculitis often have severe impairment of health-related quality of life, with fatigue, and impaired physical and mental functioning. Patient-reported adverse experiences in ANCA-associated vasculitis are often due to the impact of glucocorticoids. Glucocorticoids are associated with emotional, physical, and social effects, including depression, anxiety, irritation, weight gain and change in appearance, diabetes mellitus, and effects on family and work (Robson et al., 2018).
- High levels of toxicity with current therapies, including glucocorticoids: Chronic glucocorticoid use is associated with increased risk of infection, new onset/worsening of diabetes mellitus, hyperlipidemia, hypertension and cardiovascular disease, myopathy, osteoporosis, avascular necrosis of bone, glaucoma, cataracts, skin disorders, psychiatric disorders, and other debilitating side effects (Little et al., 2010; Robson et al., 2015).

Successful alternative therapies should focus on suppressing disease activity long-term, reducing relapse rates, improving renal function, improving health-related quality of life, and minimizing treatment-related toxicity. Reducing or even eliminating daily oral glucocorticoid treatment should be an important goal of new therapeutic approaches.

As described in this briefing document, statistically significant, as well as clinically meaningful efficacy, based on remission and relapse rates, was achieved in the avacopan group vs. the prednisone group in the Phase 3 pivotal study CL010_168. In addition to remission achievement and relapse prevention, avacopan therapy also exhibited a significant reduction in glucocorticoid-related toxicity, greater improvements in health-related quality of life metrics, improved kidney function, and more rapid improvement of albuminuria when compared to the prednisone group.

3 PRODUCT OVERVIEW

Summary

- The drug product contains the active substance avacopan, a C5aR inhibitor.
- Proposed indication: Avacopan is indicated for the treatment of adult patients with ANCA-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]).
- Recommended dosing regimen for avacopan (based on the Phase 3 study and supportive Phase 2 studies) is 30 mg twice daily with food.

3.1 Product Overview

The drug product contains the active substance avacopan, a C5aR inhibitor. Avacopan is a chiral molecule containing two stereocenters and has a chemical name of (2R,3S)-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide. It has a molecular formula of $C_{33}H_{35}F_4N_3O_2$ and a molecular weight of 582 g/mol.

The drug product is provided in 10 mg capsules. Therefore, 3 capsules are taken in the morning and 3 capsules in the evening for the proposed 30 mg twice daily dose.

3.2 Proposed Indication and Dosing

Avacopan is indicated for the treatment of adult patients with ANCA-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]).

The dosing regimen used in the Phase 3 study (CL010_168) was 30 mg twice daily, preferably with food; 30 mg twice daily with food is the recommended dose for treatment of patients with ANCA-associated vasculitis. Avacopan doses of up to 100 mg avacopan twice daily for 7 days were well tolerated in healthy volunteers (Study CL014_168).

3.3 Mechanism of Action

Avacopan is a selective inhibitor of the human C5aR (Figure 2). Avacopan, blocks the interaction of C5aR with the anaphylatoxin C5a, which is produced through activation of the complement cascade (Bekker et al., 2016). Avacopan does not inhibit the related receptor C5L2 (C5aR2), which may have beneficial anti-inflammatory effects. Avacopan reduces the pro-inflammatory effects of C5a, which include neutrophil activation and migration, adherence to sites of small blood vessel inflammation, vascular endothelial cell retraction and increased permeability (Camous L, 2011; Foreman et al., 1994; Hammerschmidt et al., 1981; Schraufstatter et al., 2002; Schreiber et al., 2009). Avacopan does not affect upstream activities of the complement system such as Bb, C3a, C3b, and properdin. Unlike C5 or C5 convertase inhibitors (such as eculizumab), avacopan as a selective C5aR inhibitor does not block the

production of C5b and the C5b-9 (membrane attack complex) which is necessary to defend against infections with encapsulated bacteria such as *Neisseria meningitidis*.

A central role for C5a and its receptor C5aR in the pathogenesis of ANCA-associated vasculitis is apparent (see Figure 3) (Furuta et al., 2013; Halbwachs et al., 2012; Kettritz, 2014). C5a primes neutrophils and enhances ANCA-induced neutrophil activation (Schreiber et al., 2009). Neutrophils activate the alternative complement pathway through endogenous properdin secretion; neutrophils also release C5a when stimulated by inflammatory cytokines such as tumor necrosis factor-alpha (TNFα) (Camous L, 2011). C5a, acting on C5aR, is a potent neutrophil chemoattractant and agonist which triggers homotypic neutrophil aggregation via interactions of the TNF-activated αMβ2 (Mac-1)-integrins with ICAM-3 or iC3b on bystander neutrophils (Hammerschmidt et al., 1981). Deformability is important for non-activated neutrophils for unperturbed movement through small blood vessels such as in the glomeruli. C5a decreases neutrophil deformability, particularly in the presence of ANCA (Tse et al., 2005). ANCA bound to endothelial-adherent neutrophils activates the classical complement pathway (Huugen et al., 2007). Lastly, C5a activates endothelial cells, promoting retraction and increased permeability (Foreman et al., 1994; Schraufstatter et al., 2002). Evidence supports that avacopan, as a selective C5aR inhibitor, blocks these potentially detrimental effects of C5a in patients with ANCA-associated vasculitis.

Figure 2: Avacopan Mechanism of Action: Highly Potent and Selective C5aR Inhibitor

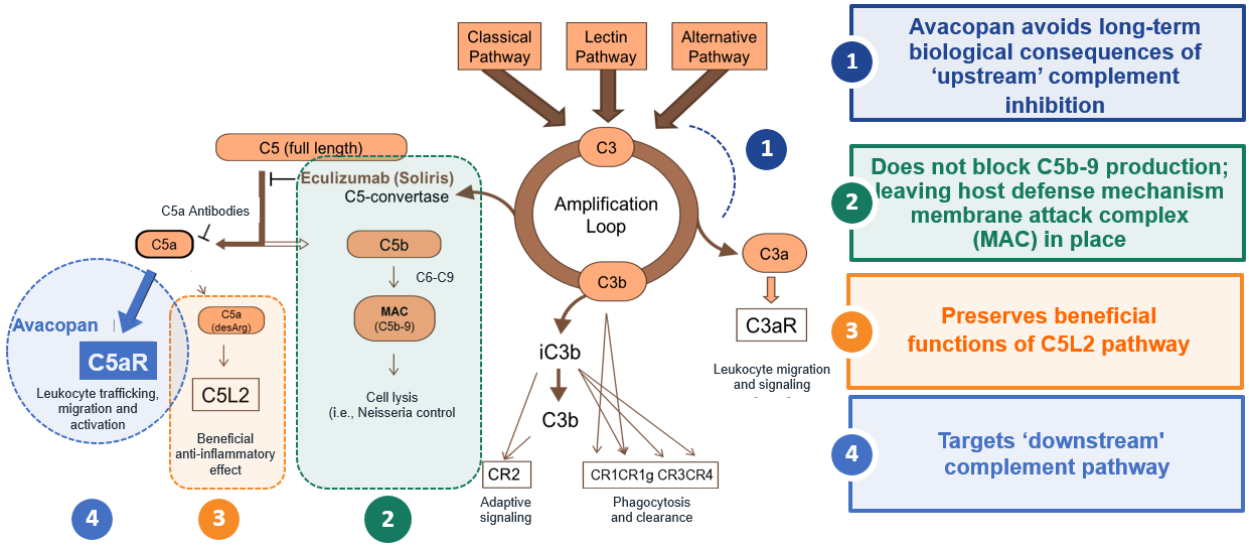
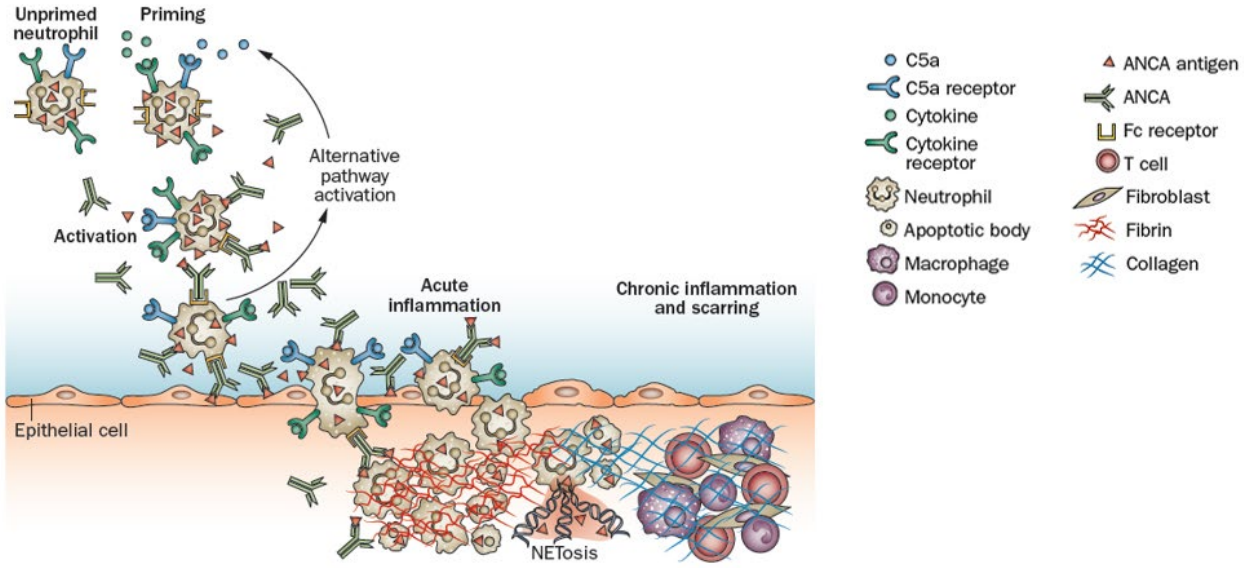


Figure 3: Central Role for C5a and C5aR in Pathogenesis of ANCA-Associated Vasculitis



Source: (Jennette et al., 2014)

Murine models have shown that alternative complement pathway activation is critical to development of MPO ANCA-induced glomerulonephritis. Anti-C5 treatment can prevent this glomerulonephritis (Huugen et al., 2007), as can depletion of complement using cobra venom factor (Xiao et al., 2007). Furthermore, complement factor B (an essential factor for alternative pathway activation) knockout mice are protected against development of ANCA-induced glomerulonephritis. Plasma C5a was significantly higher in patients with active ANCA-associated vasculitis compared with patients in remission (Gou et al., 2013). C5a was increased in the plasma and urine of patients with active ANCA-associated vasculitis in another study (Yuan et al., 2012). Importantly, blocking the C5aR with avacopan prevents the development of ANCA-induced glomerulonephritis in the anti-MPO murine model (Xiao et al., 2014).

4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- Avacopan has been granted orphan drug designation by the FDA for ANCA-associated vasculitis.
- One pivotal Phase 3 clinical trial, Study CL010 168, in 331 patients evaluated the efficacy and safety of avacopan in patients with ANCA-associated vasculitis, in the context of reducing or eliminating glucocorticoid treatment.
- Two Phase 2 clinical trials in 109 patients with ANCA-associated vasculitis (studies CL002_168 and CL003_168) provide supportive efficacy and safety data.
- Seven Phase 1 trials have been conducted, including a thorough QT/QTc study.

4.1 Key Regulatory Milestones

ChemoCentryx, Inc. is filing a 505(b)(1) application. Regulatory milestones for avacopan include the following:

- Orphan drug designation granted by FDA for ANCA-associated vasculitis: June 2014
- Original IND submission: June 2014
- NDA submission: July 2020

4.2 Clinical Development Program

The main indication for clinical development of avacopan is ANCA-associated vasculitis (GPA and MPA forms). All clinical trials to date with avacopan were conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonised Tripartite Guideline. The trials for ANCA-associated vasculitis are described below.

4.2.1 Pivotal Phase 3 Clinical Trial

The pivotal Phase 3 clinical trial, Study CL010_168 (also referred to as ADVOCATE), evaluated the efficacy and safety of avacopan in patients with ANCA-associated vasculitis, in the context of reducing or eliminating daily glucocorticoid treatment, which is currently part of standard of care in these patients. The study had a 52-week dosing period, with an 8-week follow-up period thereafter. A total of 331 patients were enrolled in North America, Europe, Australia, New Zealand, and Japan.

4.2.2 Phase 2 Clinical Trials

Two Phase 2 clinical trials (studies CL002_168 and CL003_168) included 109 patients.

Study CL002_168 was conducted in 11 countries in Europe, and 67 patients with active ANCA-associated vasculitis were enrolled. Clinical trial CL002_168 evaluated the efficacy and safety of

avacopan in patients with ANCA-associated vasculitis, in the context of reducing or eliminating oral glucocorticoid (prednisone) treatment.

Study CL003_168 was conducted in the USA and Canada, and 42 patients with active ANCA-associated vasculitis were enrolled. The main goal of clinical trial CL003_168 was to test the safety and efficacy of avacopan when given in addition to full-dose standard of care treatment, consisting of full-dose glucocorticoids plus cyclophosphamide or rituximab.

4.2.3 Phase 1 Clinical Trials

Avacopan has been tested in 7 Phase 1 clinical studies: CL001_168, CL004_168, CL007_168, CL008_168, CL013_168, CL014_168 and CCX1101. Descriptions of these studies are provided in Table 5.

Table 5: Description of Phase 1 Clinical Trials with Avacopan

Study ID (Country)	Study Title	Test Product, Dosing Regimen, and Route of Administration	Target Study Population
CL001_168 (Switzerland)	A Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of CCX168 in Healthy Male and Female Subjects	Avacopan or placebo; 1, 3, 10, 30, and 100 mg single dose; 1, 3, and 10 mg QD x 7 days; 30 and 50 mg twice daily x 7 days; all oral	48 healthy subjects; 35 received avacopan, 13 received placebo
CL004_168 (U.S.)	An Open-Label, Phase 1 Study in Healthy Volunteers to Evaluate the Mass Balance Recovery and Metabolic Disposition of a Single Oral Dose of [^{14}C]-CCX168	100 mg avacopan single dose containing 400 µCi of [^{14}C]-avacopan; oral	6 healthy male subjects; all received avacopan
CL007_168 (U.S.)	An Open-Label, Phase 1 Study in Healthy Volunteers to Evaluate the Pharmacokinetic Food Effect and Cardiac Safety of CCX168	PERIOD 1: 30 mg avacopan single dose, fed or fasted; PERIOD 2: 30 mg avacopan single dose, fed or fasted; PERIOD 3: 3 mg avacopan single dose, fasted; PERIOD 4: 100 mg avacopan single dose followed by 100 mg avacopan twice daily for 5 days, followed by 100 mg single dose for 1 day, fasted; all oral	16 healthy subjects; all received avacopan
CL008_168 (U.S.)	An Open-Label, Phase 1 Study in Healthy Volunteers to Evaluate the Drug-Drug Interaction Potential of CCX168 with Concomitant Medications	COHORT A: Day 1 and Day 13: single oral doses of 2 mg midazolam and 200 mg celecoxib; Day 3 to 18: avacopan 30 mg orally twice daily Day 16 to 19: once daily oral dose 200 mg itraconazole; Day 19: single morning oral dose avacopan 30 mg COHORT B: Day 1 and 14: avacopan 30 mg orally once daily Day 4 to 17: 600 mg rifampicin orally once daily	32 healthy subjects (16 in each cohort); all received avacopan

Study ID (Country)	Study Title	Test Product, Dosing Regimen, and Route of Administration	Target Study Population
CL013_168 (U.S.)	An Open-label, Phase 1 Study to Evaluate the Single-dose Pharmacokinetics of Avacopan (CCX168) in Male and Female Subjects with Mild or Moderate Hepatic Impairment	30 mg single dose; oral	24 subjects; 8 in each cohort (healthy subjects, subjects with mild hepatic impairment, or subjects with moderate hepatic impairment); all received avacopan
CL014_168 (U.S.)	A Multiple-Dose, Randomized, Double-Blind, Placebo-Controlled, Active-Comparator, Parallel Study to Investigate the Effect of Avacopan at Therapeutic and Supratherapeutic Doses on the QT/QTc Interval in Healthy Subjects	30 mg avacopan twice daily for 7 days, followed by 100 mg twice daily for another 7 day; or placebo	58 healthy subjects, 29 of whom received avacopan
CCX1101 (Japan)	A Phase 1 Clinical Study of CCX168 in Japanese and Caucasian Healthy Adult Males	Avacopan or placebo; 10, 30, or 100 single dose; 30 or 50 mg twice daily for 7 days; all oral	80 healthy Japanese and Caucasian subjects (10 in each cohort); 64 received avacopan

5 CLINICAL PHARMACOLOGY

Summary

- Orally administered avacopan is well-absorbed into the bloodstream with t_{max} at approximately 2.5 hours.
- Co-administration with a meal in a food-effect study increased the plasma exposure (AUC) by approximately 1.72-fold and delayed t_{max} by approximately 3 hours but did not affect C_{max}. Therefore, it is recommended that avacopan be taken with food to optimize its plasma exposure.
- Avacopan is metabolized by cytochrome P450 (CYP) 3A4 mediated oxidation; metabolites are primarily excreted into feces via bile. Direct excretion of avacopan through biliary or renal pathway is minimal.
- There is one major circulating metabolite, a mono-hydroxylated metabolite referred to as M1, which is present at approximately 12% of the total plasma drug-related exposure. This metabolite has about the same activity as avacopan on the C5aR. It was also present in animals dosed with avacopan in the toxicology studies.
- Consistent with avacopan being a substrate of the CYP3A4 enzyme, avacopan exposure is decreased by approximately 93% when administered concomitantly with rifampin, a strong inducer of CYP3A4. Therefore, concomitant use of strong CYP3A4 enzyme inducers should be avoided, while caution should be used when moderate CYP3A4 inducers are prescribed. When co-administered with a strong CYP3A4 inhibitor, such as itraconazole, the plasma exposure (AUC) of avacopan is approximately 2-fold of that without itraconazole. Even though avacopan has been tested up to 100 mg twice daily in humans (3.3 times higher than the therapeutic dose of 30 mg twice daily), it is recommended that concomitant strong CYP3A4 enzyme inhibitors should be used with caution.
- Avacopan is a weak inhibitor of CYP3A4 and CYP2C9 as indicated by an AUC ratio of 1.81 and 1.15 for the sensitive probe drugs midazolam and celecoxib, respectively, when given with avacopan.
- In Phase 3 study CL010 168 in which patients received 30 mg avacopan twice daily for 52 weeks, steady state plasma avacopan levels were reached by Week 13.
- Population pharmacokinetic analysis found that the exposures of avacopan and metabolite M1 were not significantly impacted by race, sex or age in patients with ANCA-associated vasculitis. No dose adjustment of avacopan is necessary for patients with mild to moderate hepatic impairment or renal function impairment.
- Regarding pharmacodynamics, avacopan functionally inhibits C5a-mediated chemotaxis in vitro, using a myeloid human cell line, with potency (IC_{50}) of 0.92 nM. The 30 mg twice daily dose of avacopan resulted in extended (> 12 hr) inhibition of C5aR in Study CL001 168, indicating that this dose regimen provides around-the-clock blockade of the C5a receptor.

5.1 Pharmacokinetics

5.1.1 Absorption

When dosed as an oral solution, avacopan is well absorbed. In such studies, the fraction of oral absorption is approximately 93% (Study CL004_168), and with peak plasma concentrations (C_{max}) occurring at a median time (t_{max}) of approximately 2.5 hours (Study CL004_168). Avacopan has also shown approximately dose-proportional exposures upon multiple dosing in the range of 10 mg to 100 mg. In a food-effect PK study, co-administration with a high-fat, high-calorie meal increased the plasma exposure (AUC) by approximately 1.72-fold and delayed t_{max} by approximately 3 hours but did not affect C_{max} (Study CL007_168). In order to obtain optimal avacopan plasma concentrations, the proposed labeling states that avacopan should be taken with food.

5.1.2 Metabolism and Elimination

Avacopan is metabolized by cytochrome P450 (CYP) 3A4 mediated oxidation; metabolites are primarily excreted into feces via bile. Avacopan is the most abundant circulating component following oral administration (Study CL004_168).

Direct excretion of unchanged avacopan is negligible, with < 0.1% and 7% of the administered parent compound recovered in urine and feces, respectively (Study CL004_168). There is one major circulating metabolite, mono-hydroxylated CCX168-M1 (abbreviated as M1), which is present at approximately 12% of the total plasma drug-related exposure. This metabolite has about the same activity as avacopan on the C5aR. It was also present in animals dosed in the toxicology studies.

Consistent with avacopan being a substrate of the CYP3A4 enzyme, avacopan exposure decreased approximately 93% when administered concomitantly with rifampin, a strong inducer of CYP3A4 (Study CL008_168). When co-administered with a strong CYP3A4 inhibitor, such as itraconazole, the plasma exposure (AUC) of avacopan increased approximately 2-fold of that without itraconazole.

Avacopan is a weak inhibitor of CYP3A4 and CYP2C9 as indicated by AUC ratios of 1.81 and 1.15 of the sensitive probe drugs midazolam and celecoxib, respectively, when dosed with avacopan (Study CL008_168). In vitro, avacopan is not an inhibitor of other CYP enzymes, neither is avacopan a strong inducer of CYP enzymes.

Hence, evidence indicates that avacopan, if co-administered with substrates of CYP enzymes, is unlikely to significantly affect the clearance and the exposure of substances that are metabolized by CYP enzymes.

5.1.3 Dose and Time-Dependencies

After single-dose oral administration of avacopan in healthy subjects in Study CL001_168, the C_{max} of avacopan increased approximately dose-proportionally from 1.84 to 197 ng/mL with doses of 1 mg to 100 mg avacopan, and the $AUC_{0\text{-}inf}$ values increased approximately dose-proportionally from 628 to 2,030 ng*hr/mL with doses of 30 and 100 mg (Study CL001_168).

The PK profiles for lower doses were insufficiently characterized due to inadequate assay sensitivity at the lower avacopan plasma concentrations.

After twice daily dosing in healthy human subjects (in Study CL001_168 and Study CL007_168), the plasma exposure of avacopan appeared to be dose-proportional in the range of 30 mg to 100 mg twice daily doses. Furthermore, the exposures of avacopan in Study CL003_168 have shown dose proportionality following administration of 10 mg and 30 mg b.i.d. for both Day 1 and at steady state. With 7 days of dosing in healthy subjects, the accumulation was 2.3-fold at the 30 mg twice daily dose.

In patients with ANCA-associated vasculitis receiving 30 mg avacopan twice daily for 84 days (Study CL002_168), the Day 1 $AUC_{0\text{-}6hr}$ was 580 ± 219 ng*hr/mL and 127 ± 43.8 ng*hr/mL for avacopan and metabolite M1, respectively, and steady state trough plasma concentrations of avacopan and metabolite M1 appeared to be reached by Day 43 or Day 57. The mean trough plasma concentrations for avacopan and metabolite M1 were 204 ± 82.6 ng/mL and 83.3 ± 30.8 ng/mL, respectively, on Days 57 - 85. In the Phase 3 study (CL010_168), in which patients also received 30 mg avacopan twice daily, but for a longer duration, i.e., 52 weeks, the steady state appeared to be reached by Week 13 and the mean steady state trough plasma concentrations of avacopan and M1 were 255 ± 120 ng/mL and 99.6 ± 37.7 ng/mL, respectively, from Week 13 through Week 52.

5.1.4 Special Populations

There were no apparent effects of race, sex or age on the clearance or volume of distribution of avacopan.

Based on all studies with patients within the Clinical Development Program, avacopan plasma exposure did not appear to change meaningfully in patients with renal impairment and no dose adjustment is needed based on the status of renal function. The PK results of Phase 1 Study CL013_168 show that mild to moderate hepatic impairment has no meaningful impact on avacopan exposure. As a result, no dose adjustment of avacopan is necessary for subjects with mild to moderate hepatic impairment. Additionally, no major impact on plasma exposure was observed with differing serum albumin levels, urine albumin:creatinine ratio (UACR), or ANCA-associated vasculitis disease severity.

5.1.5 Drug-Drug Interactions

5.1.5.1 Effects of Concomitant Medications on Avacopan

Avacopan is cleared primarily through metabolism by CYP3A4. Co-administration of the strong CYP3A4 inhibitor itraconazole increased exposure by approximately 2-fold, while co-administration of the strong CYP3A4 inducer rifampin reduced the exposure by 93%. Even though avacopan has been tested up to 100 mg twice daily in humans (3.3 times higher than the therapeutic dose of 30 mg twice daily), concomitant use of avacopan with strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, and grapefruit juice) should be done with caution.

Patients taking strong CYP3A4 inducers (e.g., phenytoin, rifampicin, carbamazepine, and St. John's Wort) have been excluded from the clinical trials since these drugs may substantially reduce the avacopan plasma levels. Moderate CYP3A4 inducers should be used with caution when co-administered with avacopan.

Proton-pump inhibitors such as omeprazole do not have a clinically significant effect on the pharmacokinetic profile of avacopan.

Medications used in patients with ANCA-associated vasculitis, such as prednisone, cyclophosphamide, and rituximab do not have any clinically significant effect on the avacopan pharmacokinetic profile. Medications such as azathioprine and mycophenolate are also not expected to interact with avacopan because these two medications do not share clearance pathways with avacopan.

5.1.5.2 Effects of Avacopan on Concomitant Medications

Avacopan is a weak inhibitor of CYP3A4 and CYP2C9 as indicated by a modest increase in the AUC of the sensitive probe drugs midazolam (1.81-fold) and celecoxib (1.15-fold), respectively. Avacopan does not inhibit or induce other CYP450 enzymes. Therefore, avacopan is not anticipated to pose a clinically significant risk on the plasma exposures of other drugs that are cleared through CYP450 enzymes.

Avacopan is not anticipated to significantly affect the plasma exposures of other medications used in patients with ANCA-associated vasculitis such as prednisone, cyclophosphamide, rituximab, azathioprine, mycophenolate, and angiotensin converting enzyme inhibitors or angiotensin II receptor blockers. In study CL003_168, administration of avacopan with prednisone did not appear to materially affect prednisone levels in vivo (or vice versa) (See Appendix 10.9).

Avacopan is not anticipated to have a clinically relevant interaction with important drug transporters.

5.2 Pharmacodynamics

As a potent inhibitor of the human C5aR, avacopan functionally inhibits C5a-mediated chemotaxis in vitro using a myeloid human cell line with potency (IC_{50}) of 0.92 nM. Additionally, avacopan displaces ^{125}I-C5a from human C5aR with an IC_{50} of 0.45 nM. When tested on freshly isolated human neutrophils, avacopan inhibits the C5a-mediated increase in cytoplasmic calcium levels with an IC_{50} of 0.2 nM.

In Phase 1 Study CL001_168, the effect of avacopan on neutrophil migration and C5a-induced CD11b upregulation was studied. To investigate the relationship between pharmacokinetic and pharmacodynamic profiles of avacopan in humans, two functional assays were developed and tested on blood samples collected from patients in Study CL001_168. In these assays, blood neutrophils from avacopan-treated, but not placebo-treated, patients were impaired in their ability to functionally respond to exogenously-added recombinant C5a, indicating that avacopan effectively blocked C5aR in the treated patients. The level of blockade correlated strongly with

avacopan plasma concentrations in each cohort in the single dose period (10, 30, and 100 mg avacopan) and the multi-dose period (30 mg avacopan twice daily). The 30 mg twice daily dose of avacopan resulted in extended (> 12 hr) inhibition of C5aR, indicating that this dose regimen provides around-the-clock coverage of the C5aR. Therefore, 30 mg avacopan twice daily was selected as the dose regimen to test in Phase 2 clinical trials CL002_168 and CL003_168, and in Phase 3 clinical trial CL010_168 in patients with ANCA-associated vasculitis.

6 CLINICAL EFFICACY

Summary

- Phase 3 Study CL010 168 met both of its primary endpoints, remission at Week 26 and sustained remission at Week 52:
  - At Week 26, 70.1% (115/164) in the prednisone group achieved remission compared to 72.3% (120/166) in the avacopan group.
  - At Week 52, 54.9% (90/164) in the prednisone group achieved sustained remission compared to 65.7% (109/166) in the avacopan group.
  - The avacopan group was statistically non-inferior to the prednisone group with respect to the incidence of patients who achieved clinical remission at Week 26 and statistically superior with regard to those who achieved sustained remission at Week 52.
  - Efficacy with avacopan was achieved without the need for daily oral glucocorticoid treatment.
  - Efficacy with avacopan to sustain remission, without the need for rituximab re-treatment after the first 4 weeks, was shown in the rituximab stratum.
  - The efficacy observed was generally consistent across pertinent subgroups, i.e., those with newly diagnosed and relapsed disease, PR3 and MPO ANCA, GPA and MPA, those receiving cyclophosphamide and those receiving rituximab.
- Key secondary endpoints for Study CL010_168 were also met, and included:
  - Relapse rate: The risk of relapses at any time during the study after BVAS=0 had been achieved, was reduced significantly in the avacopan group compared to the prednisone group (P=0.0091 for the Log-rank test of the difference of time to relapse). The hazard ratio of the time to relapse between the two treatment groups was 0.46, 95% CI (0.25, 0.84). Consequently, the estimated reduction in risk of relapse was 54% in the avacopan group compared to the prednisone group.
  - Glucocorticoid toxicity measurements: At both Week 13 and 26, the avacopan group had lower toxicity relative to the prednisone group for both the Glucocorticoid Toxicity Index Cumulative Worsening Score (GTI-CWS) and the Glucocorticoid Toxicity Index Aggregate Improvement Score (GTI-AIS).
  - The avacopan group demonstrated greater improvement in renal function, as measured by the change in eGFR, compared to the prednisone group at Week 26 and Week 52.
  - Urinary albumin: creatinine ratio (UACR) improved faster in the avacopan group compared to the prednisone group.
- Regarding health-related quality of life assessments in Study CL010_168:

- Patients in the avacopan group had greater improvement in the Physical Component Score of the SF-36v2 compared to the prednisone group.
- Improvement in general health status, as measured by the EQ-5D-5L Visual Analogue Scale and Index, improved more in the avacopan compared to the prednisone group.

- Results from Phase 2 Studies CL002_168 and CL003_168 also showed efficacy of avacopan.

6.1 Pivotal Phase 3 Study CL010_168

6.1.1 Investigational Plan

6.1.1.1 Overall Design

Phase 3 clinical trial CL010_168 was a randomized, double-blind, double-dummy, active-controlled clinical study to assess the efficacy, safety, and tolerability of avacopan in patients with newly diagnosed or relapsing active ANCA-associated vasculitis, when administered with a standard cyclophosphamide or rituximab regimen, but in the absence of daily oral prednisone therapy. The primary objective of the trial was to evaluate the efficacy of avacopan to achieve clinical remission and to sustain remission. The trial was conducted in 143 centers North America, Europe, Australia, New Zealand, and Japan.

A schema of the Phase 3 study design is provided in Figure 1 (within the Executive Summary, Section 1.4.1.1).

6.1.1.2 Primary Efficacy Endpoints – Clinical Remission at Week 26 and Sustained Remission at Week 52

The primary endpoints were based on the Birmingham Vasculitis Activity Score (BVAS). The BVAS is a validated instrument commonly used in clinical studies in patients with ANCA-associated vasculitis to evaluate disease activity (Mukhtyar et al., 2009). Refer to Appendix 10.1 for more information about the BVAS. Briefly, the BVAS is a composite score ranging between 0 and 63, with higher scores indicating more extensive ANCA-associated vasculitis disease activity. Disease activity in the BVAS is assessed across 9 organ systems. Individual items consist of major items (such as urinary RBC casts or glomerulonephritis, typically with a score of 6) and non-major items (such as arthralgia or myalgia, typically with a score of 1 or 2) related to the specific organ and includes signs and symptoms that are typical of each organ's involvement in systemic vasculitis. Each item is weighted; some items such as the major items contribute more to the total score than others, such as the minor items.

This instrument is designed to document new or worsening vasculitis. The clinician assesses the patient based on the presence or absence of each item and whether the causality is due to active vasculitis. The higher the score, the more active the disease.

A patient has achieved remission when the BVAS=0, indicating no new or worsening disease. In Study CL010_168, remission was defined as having a BVAS of 0 and not taking glucocorticoids

for vasculitis within 4 weeks prior to the visit of interest – either Week 26 or Week 52. Relapse was defined as having a return of disease activity based on having at least one major BVAS item, at least 3 non-major items, OR 1 or 2 non-major items for at least 2 consecutive study visits. To ensure accuracy and consistency across study centers, the Investigator-assessed scores were adjudicated by a blinded Adjudication Committee. This conforms to FDA guidance for clinical endpoint committees (Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006).

There were 2 primary efficacy endpoints in Study CL010_168:

1. The proportion of patients achieving clinical remission at Week 26.

   Clinical remission at Week 26 was defined as:

   - Achieving a BVAS of 0 as determined by the Adjudication Committee (AC);
   - No administration of glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to Week 26;
   - No BVAS > 0 during the 4 weeks prior to Week 26 (if collected for an unscheduled assessment).

2. The proportion of patients achieving sustained clinical remission at Week 52.

   Sustained remission at Week 52 was defined as:

   - Clinical remission at Week 26 as defined above;
   - Clinical remission at Week 52 defined as a BVAS of 0 as determined by the AC and no administration of glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to Week 52;
   - Also, no disease relapse between Week 26 and Week 52.

6.1.1.3 Secondary Efficacy Endpoints

Secondary endpoints in the pivotal Phase 3 study included the following:

- Risk of Relapse
- Glucocorticoid Toxicity
    - Glucocorticoid Toxicity Index (GTI)
        - GTI-Cumulative Worsening Score (GTI-CWS)
        - GTI-Aggregate Improvement Score (GTI-AIS)
- Kidney Function
    - Estimated glomerular filtration rate (eGFR)
    - Urinary albumin:creatinine ratio (UACR)
    - Urinary monocyte chemoattractant protein-1 (MCP-1):creatinine ratio

- Health Related Quality of Life Assessments
    - Short Form 36 version 2 (SF-36v2)
    - EuroQuality of Life-5 Domains-5 Levels (EQ-5D-5L)
- BVAS=0 at Week 4
- Vasculitis Damage Index (VDI)

6.1.1.4 Selection of Study Population

Inclusion Criteria

Patients were eligible for participation in the study if they met the following:

1. Had a clinical diagnosis of GPA or MPA, consistent with Chapel-Hill Consensus Conference definitions (Jennette et al., 2013).
2. Aged at least 18 years, with newly-diagnosed or relapsed ANCA-associated vasculitis where treatment with cyclophosphamide or rituximab was needed; where approved, adolescents (12 to17 years old) may have been enrolled. (Additional requirements were specified for females of childbearing potential and males with partners of childbearing potential; these criteria are listed in Appendix 10.4.)
3. Tested positive for anti-PR3 or anti-MPO (current or historic) antibodies.
4. Had at least one major item, or at least three minor items, or at least the two renal items of proteinuria and hematuria in the BVAS.
5. Had an eGFR $\geq$ 15 mL/minute/1.73 m^2.

Exclusion Criteria

Patients were to be excluded from the study if they met the following:

1. Was pregnant or breast-feeding.
2. Had experienced alveolar hemorrhage requiring invasive pulmonary ventilation support anticipated to last beyond the screening period of the study.
3. Had any other known multi-system autoimmune disease.
4. Required dialysis or plasma exchange within 12 weeks prior to screening.
5. Had a kidney transplant.
6. Received cyclophosphamide within 12 weeks prior to screening; if on azathioprine, mycophenolate, or methotrexate at the time of screening, these drugs must have been withdrawn prior to receiving the cyclophosphamide or rituximab dose on Day 1.
7. Received IV glucocorticoids, > 3000 mg methylprednisolone equivalent, within 4 weeks prior to screening.

8. Had been taking an oral daily dose of a glucocorticoid of more than 10 mg prednisone-equivalent for more than 6 weeks continuously prior to the screening visit.
9. Received rituximab or other B-cell antibody within 52 weeks of screening or 26 weeks provided B cell reconstitution has occurred (i.e., CD19 count > $0.01x10^9$/L); received anti-tumor necrosis factor (TNF) treatment, abatacept, alemtuzumab, intravenous immunoglobulin (IVIg), belimumab, tocilizumab, or eculizumab within 12 weeks prior to screening.
10. Was taking a strong inducer of the cytochrome P450 (CYP) 3A4 enzyme, such as carbamazepine, phenobarbital, phenytoin, rifampin, or St. John's wort.
11. Had any of the following within 12 weeks prior to screening: symptomatic congestive heart failure requiring prescription medication, unstable angina (unless successfully treated with stent or bypass surgery), clinically significant cardiac arrhythmia, myocardial infarction, or stroke.
12. Had a history or presence of any form of cancer within the 5 years prior to screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or carcinoma in situ such as cervical or breast carcinoma in situ that has been excised or resected completely and is without evidence of local recurrence or metastasis.
13. Had evidence of tuberculosis (TB) based on interferon γ release assay (IGRA), tuberculin purified protein derivative (PPD) skin test, or chest radiography (X-rays or computed tomography [CT] scan) done at screening or within 6 weeks prior to screening.
14. Had a hepatitis B virus, hepatitis C virus or human immunodeficiency virus (HIV) screening test showing evidence of active or chronic viral infection done at screening or within 6 weeks prior to screening.
15. Received a live vaccine within 4 weeks prior to screening.
16. Had a white blood cell (WBC) count less than 3500/µL, or neutrophil count less than 1500/µL, or lymphocyte count less than 500/µL before start of dosing.
17. Had evidence of hepatic disease: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, or bilirubin > 3 times the upper limit of normal (ULN) before start of dosing.
18. Had a clinically significant abnormal ECG during screening, e.g., QT interval corrected by Fredericia greater than 450 msec.
19. Had a known hypersensitivity to avacopan or inactive ingredients of the avacopan capsules (including gelatin, polyethylene glycol, or Cremophor), cyclophosphamide or its metabolites (for patients scheduled to receive cyclophosphamide), or known Type I hypersensitivity or anaphylactic reactions to murine proteins, Chinese Hamster Ovary cell proteins, or to any component of rituximab (for patients scheduled to receive rituximab), or any contraindications or hypersensitivity to the use of azathioprine, cyclophosphamide, mycophenolate, or prednisone, or excipients, where applicable, as per

the local prescribing information; for patients who received azathioprine, concomitant use with allopurinol was contraindicated.

20. For patients scheduled to receive cyclophosphamide treatment, urinary outflow obstruction, had an active infection (especially varicella zoster infection), or platelet count < 50,000/μL before start of dosing.
21. Had participated in any clinical study of an investigational product within 30 days prior to screening or within 5 half-lives after taking the last dose.
22. Had participated previously in an avacopan study.
23. Had a history or presence of any medical condition or disease which, in the opinion of the Investigator, may have placed the patient at unacceptable risk for study participation.

6.1.1.5 Treatments

6.1.1.5.1 Stratification and Study Treatment Groups

The treatment period of the study was 52 weeks with an 8-week follow-up period. Eligible patients were randomized according to three stratification factors:

- Background immunosuppressive therapy: Receiving IV rituximab, IV cyclophosphamide, or oral cyclophosphamide.
- ANCA type: PR3 or MPO ANCA.
- Newly diagnosed or relapsed ANCA-associated vasculitis.

Patients were randomized in a 1:1 ratio into two treatment groups:

- Prednisone Group: Avacopan-matching placebo plus cyclophosphamide/azathioprine or rituximab plus full starting dose of prednisone.
- Avacopan Group: Avacopan 30 mg twice daily plus cyclophosphamide/azathioprine or rituximab plus prednisone-matching placebo.

The prednisone starting dose for adults in the prednisone group was 60 mg/day (if ≥ 55 kg) or 45 mg/day (if < 55 kg), and for adolescents 45 mg/day (if > 37 kg) and 30 mg/day (if ≤ 37 kg). The prednisone dose was tapered to 0 mg by the end of 20 weeks (Day 140). The prednisone tapering schedule is provided in Table 6.

Table 6: Study CL010_168: Prednisone/Matching Placebo Schedule

Study Day	Avacopan	Prednisone			
		Daily Prednisone Dose			
	All	Adults		Adolescents	
		≥ 55 kg	< 55 kg	> 37 kg	≤ 37 kg
Day 1 to 7	0	60 mg	45 mg	45 mg	30 mg
Day 8 to 14	0	45 mg	45 mg	45 mg	30 mg
Day 15 to 21	0	30 mg	30 mg	30 mg	30 mg
Day 22 to 42	0	25 mg	25 mg	25 mg	25 mg
Day 43 to 56	0	20 mg	20 mg	20 mg	20 mg
Day 57 to 70	0	15 mg	15 mg	15 mg	15 mg
Day 71 to 98	0	10 mg	10 mg	10 mg	10 mg
Day 99 to 140	0	5 mg	5 mg	5 mg	5 mg
≥ Day 141	0	0	0	0	0

6.1.1.5.2 Avacopan Dose Selection

The following results are pertinent to dose selection:

- Results from nonclinical studies in human C5aR transgenic knock-in mice, in which avacopan had a similar potency on the C5aR as in humans, showed that an avacopan average plasma trough concentration of 188 ng/mL was most effective in improving renal histology, proteinuria, leukocyturia, and hematuria, when compared to lower trough concentrations.
- Results from a Phase 1 study in healthy human volunteers (CL001_168) showed that an avacopan average plasma concentration of 150.9 ng/mL produced ~95% inhibition of C5a-induced upregulation in CD11b on leukocytes.
- Results from Phase 2 study CL002_168 in ANCA-associated vasculitis showed that a 30 mg avacopan twice daily dosing regimen provided an avacopan average trough plasma concentration of 204 ng/mL, and was associated with efficacy based on BVAS and other efficacy measurements.
- Results from Phase 2 study CL003_168 in ANCA-associated vasculitis showed that a 30 mg avacopan twice daily dosing regimen provided an avacopan average trough plasma concentration of 223 ng/mL, similar to study CL002_168.
- In Phase 2 study CL003_168, 30 mg twice daily avacopan had a more favorable efficacy profile compared to 10 mg twice daily.

In summary, an avacopan dosing regimen of 30 mg twice daily provided avacopan plasma levels of ~200 ng/mL, a level that is associated with efficacy in nonclinical studies, an optimal pharmacodynamic effect in healthy volunteers in Phase 1, and an early onset of improvement in disease activity in patients with ANCA-associated vasculitis in the two Phase 2 studies. Therefore, 30 mg avacopan given twice daily was considered the preferred dosing regimen to produce a therapeutic effect in ANCA-associated vasculitis, and was therefore selected as the dosing regimen for Phase 3.

6.1.1.5.3 Immunosuppressant Treatment

All patients in both treatment groups received either rituximab or cyclophosphamide at the discretion of the Investigator, as follows:

- The rituximab dose was 375 mg/m^2 IV once weekly given for the first 4 weeks of the dosing period. No azathioprine or mycophenolate was administered to patients in the rituximab stratum.
- The IV cyclophosphamide dose was 15 mg/kg up to 1.2 g maximum at baseline, Week 2, 4, 7, 10, and 13. Patients receiving cyclophosphamide were switched to oral azathioprine up to 2 mg/kg/day, mycophenolate mofetil up to 2 g/day, or mycophenolate sodium up to 1440 mg/day from Week 15 through the end of the study.
- The oral cyclophosphamide dose was 2 mg/kg/day orally for 14 weeks. Patients receiving cyclophosphamide were switched to oral azathioprine up to 2 mg/kg/day, mycophenolate mofetil up to 2 g/day, or mycophenolate sodium up to 1440 mg/day from Week 15 through end of the study.

As mentioned above, all patients were stratified prior to start of dosing based on the immunosuppressant they were to receive and randomized between the two treatment groups to ensure balance across treatment groups.

6.1.1.5.4 Glucocorticoid Treatment Other Than Prednisone Study Medication

Glucocorticoid use up to 3 g methylprednisolone equivalent IV within the 4-week period prior to screening, or oral use of not more than 10 mg prednisone-equivalent per day for not more than 6 weeks continuously prior to screening, was allowed per protocol.

During the screening period, IV glucocorticoids were allowed as long as the cumulative dose did not exceed 3 g methylprednisolone equivalent during the screening period plus the pre-screening period. If a patient received oral glucocorticoids during the screening period, the dose needed to be tapered to a dose that did not exceed 20 mg prednisone equivalent on Day 1 of the study.

Patients in both treatment groups, who were on ≤ 20 mg prednisone equivalent on Day 1, needed to be tapered to zero by the end of Week 4. Patients who experienced a relapse during the study could be treated with IV glucocorticoids (typically 0.5 to 1 g methylprednisolone per day for 3 days) and/or oral glucocorticoids, tapered according to the patient's condition. Glucocorticoid pre-medication for rituximab infusions, typically 100 mg methylprednisolone equivalent IV, was allowed. Patients who experienced worsening of disease during the study that involved a major item in the BVAS could be treated with IV glucocorticoids (typically 0.5 to 1 g methylprednisolone per day for 3 days) and/or oral glucocorticoids, tapered according to the patient's condition. Worsening of disease not involving a major item in the BVAS could be treated with a short burst (i.e., not more than 2 weeks) of oral glucocorticoids, at a maximum dose of 20 mg prednisone equivalent. Any glucocorticoid use was recorded meticulously in the case report form.

In order to maintain the study blind, a double-dummy design was utilized. Patients in the prednisone group took avacopan-matching placebo capsules. Patients in the avacopan group took prednisone-matching placebo capsules. The study-supplied prednisone was over-encapsulated in order to provide matching placebo capsules.

Patients in the two strata, cyclophosphamide and rituximab, were randomly assigned to each of the two treatment groups, the avacopan group and the prednisone group, and baseline results showed that balance was achieved between the two treatment groups.

6.1.1.6 Statistical and Analytic Plans

Study Populations

The Intent-to-Treat (ITT) population and the Safety population included all patients who were randomized and received at least one dose of study medication (avacopan/placebo).

Endpoint Calculations

For the first primary endpoint, the number of patients adjudicated as having achieved remission at Week 26 was divided by the total number of patients in the ITT population in the respective treatment group. For the second primary endpoint, the proportion of patients was calculated as the number who achieved sustained remission at Week 52 divided by the total number of patients in the ITT population in the respective treatment group.

- Patients who discontinued the study prior to Week 26 or Week 52, as applicable, were assessed as not in remission for assessment of the endpoint for the ITT analysis.
- Patients who permanently discontinued treatment with blinded study drug prior to Week 26 or Week 52, as applicable, for any reason, but who remained in the study were assessed as being in remission or not in remission based on adjudication for the ITT analysis.
- Patients with missing data at Week 26 or Week 52, as applicable, were assessed as not achieving remission for the ITT analysis.

The primary analysis compared the remission rates for the two primary efficacy endpoints for the ITT population based on summary score tests (Agresti, 2013). The stratification variables in the Summary score tests were the same factors used in the randomization stratification: standard of care immunosuppressant regimen, ANCA type, and ANCA-associated vasculitis status. The primary endpoint measurement were based on the adjudicated remission at Week 26 and adjudicated sustained remission at Week 52 results. The corresponding Summary score estimate (and associated 95% CI) of the common difference in remission rates between the avacopan and prednisone groups by using inverse-variance stratum weights and Miettinen-Nurminen (score) confidence limits at Weeks 26 and 52 were to be provided.

Handling of Missing Data

For the primary endpoints, missing data at Week 26 and Week 52 were imputed as not achieving remission (Week 26) or sustained remission (Week 52), respectively, for the ITT population analyses.

Statistical Hypothesis Testing and Procedures

For both primary endpoints, the avacopan group was evaluated for non-inferiority and superiority compared to the prednisone group. The two primary endpoints were tested sequentially using a gatekeeping procedure to preserve the overall Type I error rate at the 5% level, according to the following sequence: (1) non-inferiority at Week 26, (2) non-inferiority at Week 52, (3) superiority at Week 52, and (4) superiority at Week 26.

For the two primary efficacy endpoints, the proportion of patients achieving clinical remission at Week 26 and sustained clinical remission at Week 52, and the two-sided 95% confidence intervals (CIs) for the difference in proportions (avacopan minus prednisone) was estimated for the comparison between the avacopan group and the prednisone group. For both the non-inferiority and superiority tests, the one-sided P-values are presented. Statistical significance was claimed based on the one-sided Type I error of 0.025.

For the non-inferiority test of the first primary efficacy endpoint, if the lower bound of the two-sided 95% CI was greater than -0.20 (the non-inferiority margin) and the prednisone group clinical remission rate was at least 40% at Week 26, the avacopan group was considered not inferior to the prednisone group. For the superiority test, if the lower bound of the two-sided 95% CI was greater than 0.0, the avacopan group was considered superior to the prednisone group in achieving clinical remission at Week 26.

In deriving the non-inferiority margin, the historical clinical remission rate at Week 26 in the control group was based on a meta-analysis of 20 published studies in patients treated with rituximab plus glucocorticoids or cyclophosphamide plus glucocorticoids. The lower bound of the 95% CI for the remission rate across these studies was approximately 60%.

Detailed information on considerations for setting the non-inferiority margin is provided in Appendix 10.5.

For the second primary endpoint, the proportion of patients in sustained remission at Week 52 and the two-sided 95% CI for the difference in proportion (avacopan minus prednisone) was estimated for the comparison between the avacopan group and the prednisone group. For the non-inferiority test of the second primary endpoint, if the lower bound of the 95% CI was greater than -0.20 and the prednisone group clinical remission rate was at least 40% at Week 26, the avacopan group was considered not inferior to the control group. For the superiority test, if the lower bound of the 95% CI was greater than 0.0, the avacopan group was considered superior to the prednisone group in achieving sustained remission at Week 52.

A successful study was to be declared if (at minimum) non-inferiority was achieved for the avacopan group versus the prednisone group for remission at Week 26.

Determination of Sample Size

The proportion of patients in the prednisone group achieving clinical remission at Week 26 was estimated to be ~60%, a blended proportion of 64% and 53% observed in the rituximab and cyclophosphamide/azathioprine groups, respectively, in the largest prior registration study in ANCA-associated vasculitis (Stone et al., 2010).

A non-inferiority margin of -20 percentage points was derived for the difference between the avacopan and prednisone groups, and a one-sided alpha level of 0.025. This non-inferiority margin was based on a thorough review and meta-analysis of all previous clinical studies conducted in patients with ANCA-associated vasculitis, as well as precedent (Stone et al., 2010).

A sample size of 150 patients per group (300 in total) was estimated to provide more than 90% power for the non-inferiority test. This sample size provided 90% power to detect approximately 18% superiority in the proportion of patients achieving clinical remission at Week 26 if the control group remission rate was 60%.

The proportion of patients in the prednisone group with sustained remission at Week 52 was estimated to be ~45%, a blended proportion observed in a prior study comparing rituximab and cyclophosphamide/azathioprine in ANCA-associated vasculitis (Specks et al., 2013). A sample size of 150 patients per group (300 in total) was estimated to provide 85% power to detect approximately 18% superiority if the control group sustained remission rate at Week 52 was 45%.

6.1.2 Study Patients

6.1.2.1 Disposition

A consort diagram of patient flow through the study is shown in Figure 4 and disposition of patients enrolled in Study CL010_168 is shown in Table 7.

A total of 331 patients were randomized, 165 to the prednisone group and 166 to the avacopan group. One patient in the prednisone arm did not receive any study medication (the patient was withdrawn from the study by the Investigator since, upon re-review, the renal biopsy did not clearly indicate the presence of vasculitis); therefore, the Safety and ITT populations contained 164 patients in the prednisone group and 166 in the avacopan group. A total of 152 patients (92.1%) in the prednisone group and 151 patients (91.0%) in the avacopan group completed the 52-week treatment period.

Study medication was discontinued early in 35 patients (21.2%) in the prednisone group and 37 patients (22.3%) in the avacopan group. The most common reason for early discontinuation of treatment was AE (17.6% in the prednisone group and 15.7% in the avacopan group) (Table 7).

Early withdrawal from the study occurred in 9.1% of patients in the prednisone group and 9.0% or patients in the avacopan group. The most common reasons for early withdrawal from the study were AE (3.6% of patients in the prednisone group and 1.8% of patients in the avacopan

group) and patient withdrawal (1.8% of patients in the prednisone group and 3.6% of patients in the avacopan group) (Table 7).

Figure 4: Consort Diagram of Patient Flow Through Study CL010_168

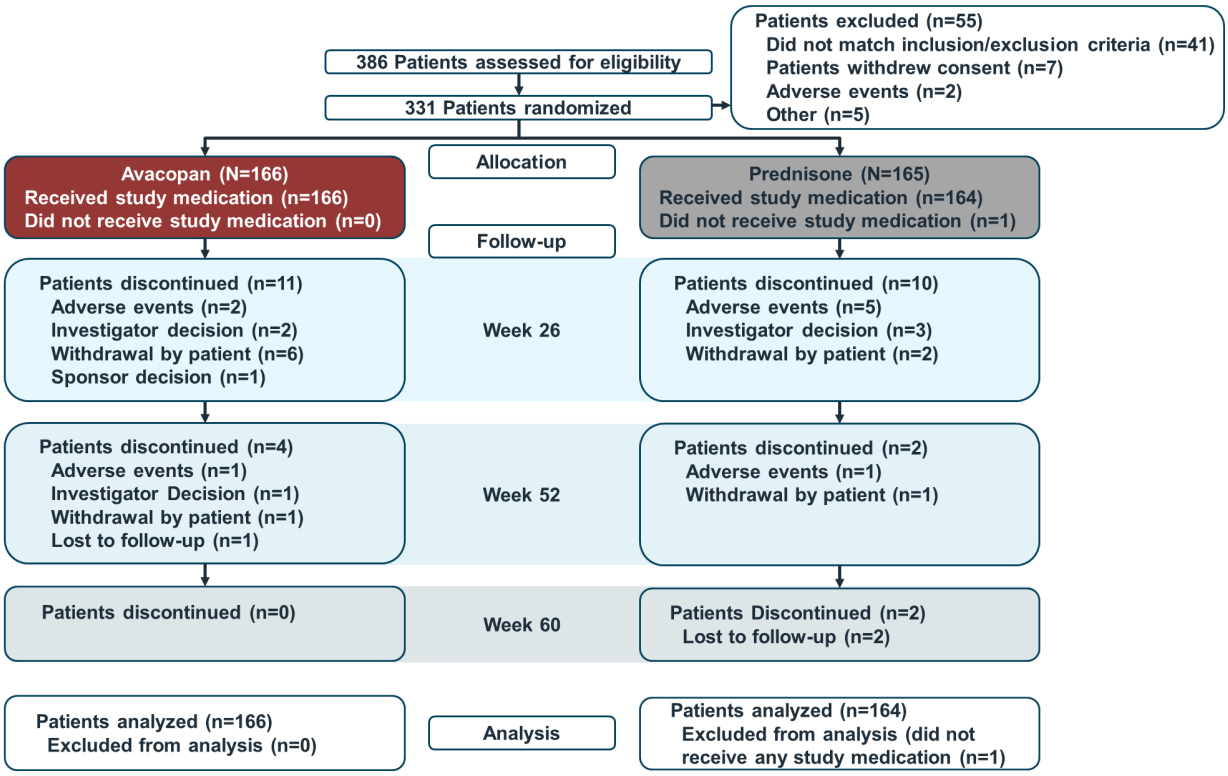


Table 7: Patient Disposition in Study CL010_168

Category	Avacopan n (%)	Prednisone n (%)	Total n (%)
Randomized	166 (100)	165 (100)	331 (100)
Safety Population	166 (100)	164 (99.4)	330 (99.7)
Intent-to-Treat Population	166 (100)	164 (99.4)	330 (99.7)
Per Protocol Population	162 (97.6)	161 (97.6)	323 (97.6)
Completed Week 26	155 (93.4)	154 (93.3)	309 (93.4)
Completed Week 52	151 (91.0)	152 (92.1)	303 (91.5)
Completed Week 60	151 (91.0)	150 (90.9)	301 (90.9)
Early discontinuation of study treatment (avacopan/placebo)	37 (22.3)	35 (21.2)	72 (21.8)
Sponsor decision	2 (1.2)	0	2 (0.6)
Withdrawal by parent/guardian	0	0	0
Withdrawal by patient	3 (1.8)	1 (0.6)	4 (1.2)
Lost to follow-up	1 (0.6)	0	1 (0.3)
Adverse event	26 (15.7)	29 (17.6)	55 (16.6)
Investigator decision	4 (2.4)	4 (2.4)	8 (2.4)
Other	1 (0.6)	1 (0.6)	2 (0.6)
Early withdrawal from study	15 (9.0)	15 (9.1)	30 (9.1)
Sponsor decision	0	0	0
Withdrawal by parent/guardian	1 (0.6)	0	1 (0.3)
Withdrawal by patient	6 (3.6)	3 (1.8)	9 (2.7)
Lost to follow-up	1 (0.6)	2 (1.2)	3 (0.9)
Adverse event	3 (1.8)	6 (3.6)	9 (2.7)
Investigator decision	3 (1.8)	4 (2.4)	7 (2.1)
Other	1 (0.6)	0	1 (0.3)
Death	2 (1.2)	4 (2.4)	6 (1.8)

Note: Percentages of Safety Population, ITT Population, Per Protocol Population and patients completed and early withdrawals were based on the number of patients randomized. The ITT and Safety Populations include all patients who were randomized and received at least one dose of study drug.

6.1.2.2 Baseline Characteristics

In Study CL010_168, most patients were White and approximately 10% were Asian; there were more men than women, approximately 70% had newly diagnosed disease, 57% were MPO-positive, and 55% were diagnosed with GPA (Table 8 and Table 9). Approximately 65% of patients received rituximab background treatment.

The baseline BVAS was similar across the two treatment groups. The mean BVAS at baseline was approximately 16. This indicates that, on average, several BVAS disease activity items were present at baseline and many patients had multi-organ involvement (Appendix 10.1). More than 80% of patients had renal vasculitis at baseline. The extent of renal involvement at baseline is shown in Table 10. Proteinuria was the most common renal disease manifestation (in ~two-thirds of patients). On average, patients had 3 BVAS renal items at baseline, and ~21% of patients had 4 or more renal items at baseline.

Prior immunosuppressant use was similar for the two treatment groups. The incidence of prior glucocorticoid use was higher in the prednisone group compared to avacopan (82.3% vs. 75.3%).

Table 8: Key Demographics in Study CL010_168 (ITT Population)

Category	Avacopan (N=166)	Prednisone (N=164)
Age (years) at Screening, mean ± SD	61.2 ± 14.56	60.5 ± 14.50
Sex, n (%)		
Male	98 (59.0)	88 (53.7)
Female	68 (41.0)	76 (46.3)
BMI (kg/m^2), mean ± SD	26.72 ± 5.997	26.78 ± 5.212
Race, n (%)		
White	138 (83.1)	140 (85.4)
Asian	17 (10.2)	15 (9.1)
Other	8 (4.8)	6 (3.7)
Black or African American	3 (1.8)	2 (1.2)
Multiple	0	1 (0.6)

Table 9: Key Baseline Characteristics in Study CL010_168 (ITT Population)

Category	Avacopan (N=166)	Prednisone (N=164)
ANCA-Associated Vasculitis Status, n (%)		
Newly diagnosed	115 (69.3)	114 (69.5)
Relapsed	51 (30.7)	50 (30.5)
ANCA Type, n (%)		
Proteinase 3 positive	72 (43.4)	70 (42.7)
Myeloperoxidase positive	94 (56.6)	94 (57.3)
Standard of Care Treatment, n (%)		
Rituximab	107 (64.5)	107 (65.2)
Cyclophosphamide IV	51 (30.7)	51 (31.1)
Cyclophosphamide Oral	8 (4.8)	6 (3.7)
Cyclophosphamide IV/Oral	59 (35.5)	57 (34.8)
ANCA Disease Type, n (%)		
Granulomatosis with polyangiitis	91 (54.8)	90 (54.9)
Microscopic polyangiitis	75 (45.2)	74 (45.1)
BVAS, mean ± SD Median (range)	16.3 ± 5.87 15.0 (5, 37)	16.2 ± 5.69 15.5 (5, 33)
BVAS Components*, n (%)		
General	111 (66.9)	114 (69.5)
Cutaneous	24 (14.5)	23 (14.0)
Mucous Membranes/Eyes	26 (15.7)	40 (24.4)
Ear Nose and Throat	75 (45.2)	69 (42.1)
Chest	71 (42.8)	71 (43.3)
Cardiovascular	6 (3.6)	3 (1.8)
Abdominal	4 (2.4)	1 (0.6)
Renal	134 (80.7)	134 (81.7)
Nervous System	38 (22.9)	31 (18.9)
Estimated Glomerular Filtration Rate (mL/min/1.73 m^2), mean ± SD	50.7 ± 30.96	52.9 ± 32.67

Category	Avacopan (N=166)	Prednisone (N=164)

*Patients may have more than one component
ANCA=anti-neutrophil cytoplasmic autoantibody; BMI=body mass index; BVAS=Birmingham Vasculitis Activity Score; IV=intravenous; SD=standard deviation

Table 10: Extent of Renal Disease Involvement at Baseline Based on BVAS

	Avacopan (N=166) n (%)	Prednisone (N=164) n (%)
Renal disease at baseline based on BVAS	134 (80.7)	134 (81.7)
Hypertension	21 (12.7)	23 (14.0)
Proteinuria	110 (66.3)	107 (65.2)
Hematuria	77 (46.4)	68 (41.5)
Serum creatinine increase	87 (52.4)	81 (49.4)
Rise in serum creatinine >30% or fall in creatinine clearance >25%	17 (10.2)	20 (12.2)
RBC casts and/or glomerulonephritis	60 (36.1)	59 (36.0)
Number of BVAS renal criteria met at baseline		
Mean	2.8	2.7
Median	3.0	3.0
Met 1 renal criterion	21 (12.7)	21 (12.8)
Met 2 renal criteria	25 (15.1)	41 (25.0)
Met 3 renal criteria	53 (31.9)	38 (23.2)
Met 4 or more renal criteria	35 (21.1)	34 (20.7)

6.1.3 Primary Efficacy Endpoints

6.1.3.1 Clinical Remission at Week 26

The primary endpoint of clinical remission at Week 26 was met. A total of 120 of 166 patients (72.3%) in the avacopan group achieved remission at Week 26 compared to 115 of 164 patients (70.1%) in the prednisone group (Table 11 and Figure 5). The avacopan group was non-inferior to the prednisone group for Week 26 remission (P< 0.0001). This effect in the avacopan group was achieved without the need for daily oral glucocorticoid use.

Table 11: Primary Endpoint: Stratified Analyses of the Proportion of Patients with Clinical Remission at Week 26 (ITT Population)

Treatment	N	n	(%)	95% CI[a]	Difference in %	Estimate of Common Difference in %[b]	Two-sided 95% CI for Difference in %[c]	Non-inferior p-value	Superior p-value
Avacopan	166	120	72.3	64.8, 78.9	2.2	3.4	-6.0, 12.8	< 0.0001	0.2387
Prednisone	164	115	70.1	62.5, 77.0					

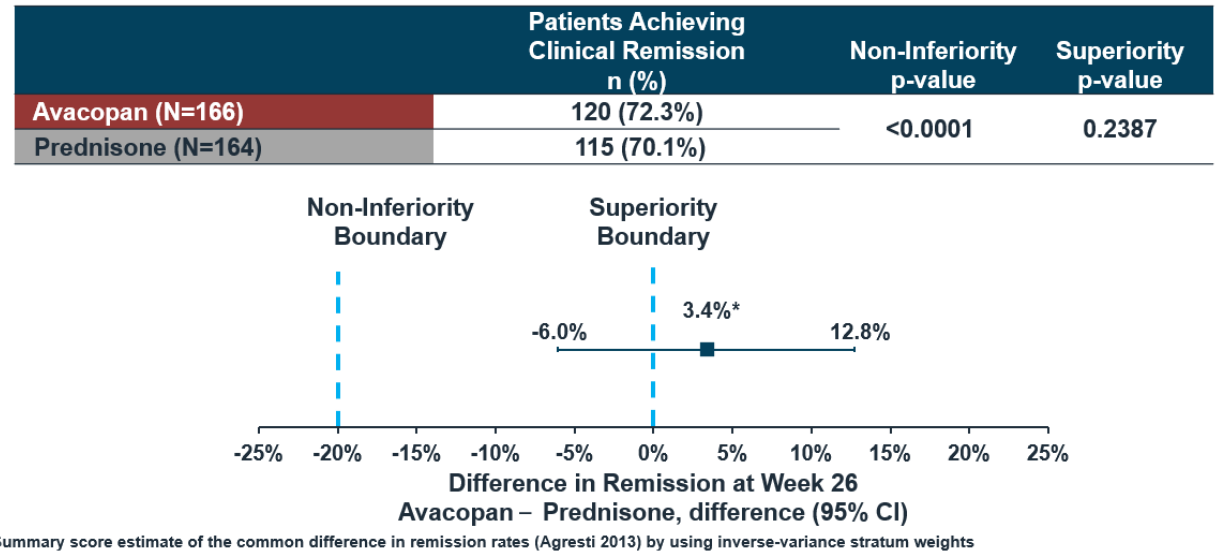
CI=confidence interval; ITT=intent to treat; N=number of patients in the analysis population for the specified treatment group; n=number of patients with clinical remission; %=100*n/N

[a] Clopper and Pearson exact CI

[b] Summary score estimate of the common difference in remission rates (Agresti, 2013) by using inverse-variance stratum weights

[c] Miettinen-Nurminen (score) confidence limits for the common difference in remission rates

Figure 5: Clinical Remission at Week 26



6.1.3.2 Primary Endpoint: Sustained Remission at Week 52

The primary endpoint of sustained remission at Week 52 was also met. A total of 109 of 166 patients (65.7%) in the avacopan group achieved sustained clinical remission at Week 52 compared to 90 of 164 patients (54.9%) in the prednisone group (Table 12). The avacopan group was statistically superior to the prednisone group in sustained remission at Week 52 (P=0.0066). As illustrated in Figure 6, the 12.5% treatment difference and 95% confidence interval are to the right of both non-inferiority and superiority boundaries, demonstrating superior efficacy of the avacopan group compared to the prednisone group at Week 52.

Table 12: Primary Endpoint: Stratified Analyses of the Proportion of Patients with Sustained Clinical Remission at Week 52 (ITT Population)

Treatment	N	n	(%)	95% CI[a]	Difference in %	Estimate of Common Difference in %[b]	Two-sided 95% CI for Difference in %[c]	Non-inferior P-value	Superior P-value
Avacopan	166	109	65.7	57.9, 72.8	10.8	12.5	2.6, 22.3	< 0.0001	0.0066
Prednisone	164	90	54.9	46.9, 62.6					

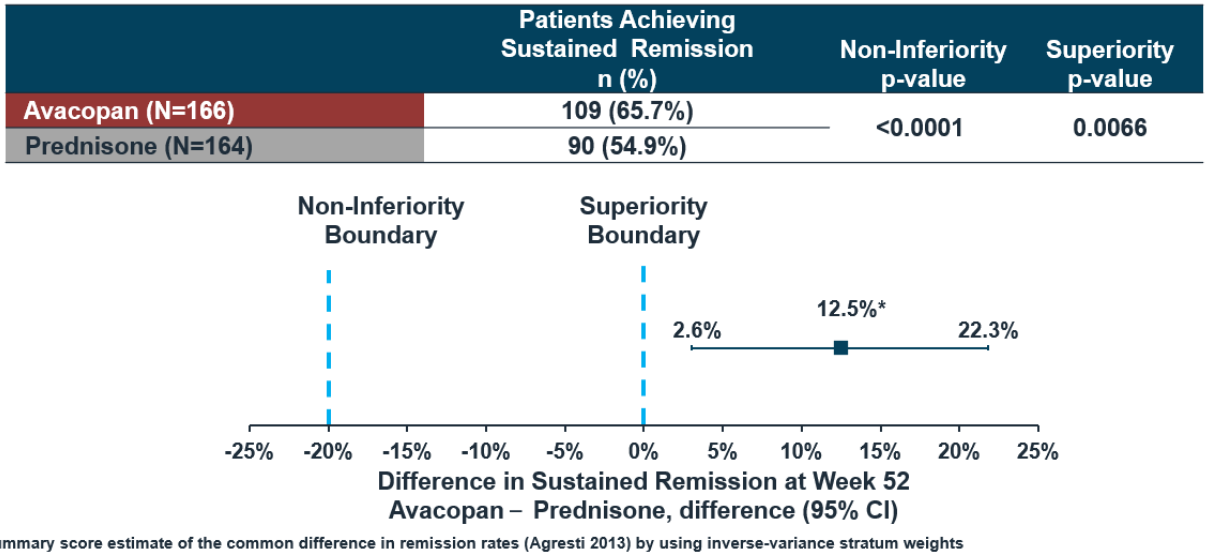
CI=confidence interval; ITT=intent to treat; N=number of patients in the analysis population for the specified treatment group; n=number of patients with sustained remission; %=100*n/N

[a] Clopper and Pearson exact CI

[b] Summary score estimate of the common difference in remission rates (Agresti, 2013) by using inverse-variance stratum weights

[c] Miettinen-Nurminen (score) confidence limits for the common difference in remission rates

Figure 6: Sustained Remission at Week 52



* Summary score estimate of the common difference in remission rates (Agresti 2013) by using inverse-variance stratum weights

Results for the two primary endpoints were evaluated in a number of subgroups. Avacopan was effective across subgroups, including patients with newly diagnosed or relapsed disease, patients with PR3+ or MPO+ ANCA-associated vasculitis, patients receiving rituximab or cyclophosphamide, and patients with GPA or MPA (Table 13 presents clinical remission at Week 26 by subgroup and Table 14 shows sustained remission at Week 52 by subgroup).

In the rituximab stratum, where patients did not receive immunosuppressive treatment during the last 26 weeks, 71.0% of the avacopan group achieved sustained remission at Week 52 compared to 56.1% of the prednisone group. These results demonstrate avacopan's efficacy as a single agent in maintaining remission.

Table 13: Remission at Week 26 by Subgroup (ITT Population)

	Avacopan (N=166)	Prednisone (N=164)
All Patients*	120 / 166 (72.3%)	115 / 164 (70.1%)
Disease Status		
Newly diagnosed patients	76 / 115 (66.1%)	76 / 114 (66.7%)
Relapsing disease	44 / 51 (86.3%)	39 / 50 (78.0%)
ANCA Type		
Anti-proteinase 3 positive	51 / 72 (70.8%)	50 / 70 (71.4%)
Anti-myeloperoxidase positive	69 / 94 (73.4%)	65 / 94 (69.1%)
Background Immunosuppressant Treatment		
Cyclophosphamide	37 / 59 (62.7%)	34 / 57 (59.6%)
Rituximab	83 / 107 (77.6%)	81 / 107 (75.7%)
Type of ANCA-Associated Vasculitis		
Granulomatosis with polyangiitis	65 / 91 (71.4%)	65 / 90 (72.2%)
Microscopic polyangiitis	55 / 75 (73.3%)	50 / 74 (67.6%)

* Results are shown for n / N (%), where n=the number of remitters and N=the number of patients in each stratum.

Table 14: Sustained Remission at Week 52 for Each Subgroup (ITT Population)

	Avacopan (N=166)	Prednisone (N=164)
All Patients*	109 / 166 (65.7%)	90 / 164 (54.9%)
Disease Status		
Newly diagnosed patients	70 / 115 (60.9%)	66 / 114 (57.9%)
Relapsing disease	39 / 51 (76.5%)	24 / 50 (48.0%)
ANCA Type		
Anti-proteinase 3 positive	43 / 72 (59.7%)	40 / 70 (57.1%)
Anti-myeloperoxidase positive	66 / 94 (70.2%)	50 / 94 (53.2%)
Background Immunosuppressant Treatment		
Cyclophosphamide	33 / 59 (55.9%)	30 / 57 (52.6%)
Rituximab	76 / 107 (71.0%)	60 / 107 (56.1%)
Type of ANCA-Associated Vasculitis		
Granulomatosis with polyangiitis	56 / 91 (61.5%)	52 / 90 (57.8%)
Microscopic polyangiitis	53 / 75 (70.7%)	38 / 74 (51.4%)

* Results are shown for n / N (%), where n=the number of remitters and N=the number of patients in each stratum.

6.1.3.3 Sensitivity Analysis: Primary Efficacy Endpoints in Per Protocol Population

In addition to the primary analyses in the ITT population, other pre-specified sensitivity analyses were conducted to evaluate the robustness of the study outcome. These sensitivity analyses included the primary endpoints in the Per Protocol population.

Results of the Per Protocol population sensitivity analyses for the Week 26 remission endpoint (Table 15) and the Week 52 sustained remission endpoint (Table 16) were consistent with the ITT analyses.

Results from other pre-specified sensitivity analyses are shown in Appendix 10.6.

Table 15: Sensitivity Analysis of Primary Endpoint: Stratified Analyses of the Proportion of Patients with Clinical Remission at Week 26 (Per Protocol Population)

Treatment	N	n	(%)	95% CI[a]	Difference in %	Estimate of Common Difference in %[b]	Two-sided 95% CI for Difference in %[c]	Non-inferior P-value	Superior P-value
Avacopan	162	110	67.9	60.1, 75.0	0.2	2.0	-7.6, 11.6	<0.0001	0.3419
Prednisone	161	109	67.7	59.9, 74.8					

CI=confidence interval; N=number of patients in the analysis population for the specified treatment group; n=number of patients with disease remission; %=100*n/N

[a] Clopper and Pearson exact CI

[b] Summary score estimate of the common difference in remission rates (Agresti, 2013) by using inverse-variance stratum weights

[c] Miettinen-Nurminen (score) confidence limits for the common difference in remission rates

Table 16: Sensitivity Analysis of Primary Endpoint: Stratified Analyses of the Proportion of Patients with Sustained Clinical Remission at Week 52 (Per Protocol Population)

Treatment	N	n	(%)	95% CI[a]	Difference in %	Estimate of Common Difference in %[b]	Two-sided 95% CI for Difference in %[c]	Non-inferior P-value	Superior P-value
Avacopan	162	95	58.6	50.6, 66.3	8.3	11.0	1.0, 21.1	<0.0001	0.0159
Prednisone	161	81	50.3	42.3, 58.3					

CI=confidence interval; N=number of patients in the analysis population for the specified treatment group; n=number of patients with sustained remission; %=100*n/N

[a] Clopper and Pearson exact CI.

[b] Summary score estimate of the common difference in remission rates (Agresti, 2013) by using inverse-variance stratum weights

[c] Miettinen-Nurminen (score) confidence limits for the common difference in remission rates

6.1.3.4 Rituximab Stratum Results

The aim of rituximab therapy in ANCA-associated vasculitis is to diminish B cells and their production of immunoglobulin, including ANCA. The consequences of this depletion for Ig-dependent responses (including vaccination) are recognized limitations of rituximab therapy.

Patients in the rituximab stratum in study CL010_168 did not receive re-treatment with rituximab after the first 4 weeks of the study. This was consistent with medical practice and rituximab prescribing information at the time of study design (2016), and the study design was developed in discussion with the FDA (at the time of the End-of-Phase 2 meeting) and Global Health Authorities.

Such a design also now allows an evaluation of the efficacy of avacopan in the rituximab stratum where rituximab re-treatment was not given during the last 26 weeks of the 52-week treatment period (and where avacopan could be compared directly to matching placebo). Results for sustained remission at Week 52 are shown in Table 17.

Results from this analysis indicate that avacopan, without any additional rituximab treatment, was able to sustain remission in 71% of patients.

Table 17: Stratified Analyses of the Proportion of Subjects with Sustained Disease Remission at Week 52 in Subjects in the Rituximab Stratum (ITT Population)

Treatment	N	n	(%)	95% CI[a]	Difference in %	Estimate of Common Difference in %[b]	Two-sided 95% CI for Difference in %[c]	Non-inferior P-value	Superior P-value
Prednisone	107	60	56.1	46.1, 65.7	15.0	16.5	4.3, 28.6	<0.0001	0.0040
Avacopan	107	76	71.0	61.5, 79.4					

CI=confidence interval; ITT=intent-to-treat; N=number of subjects in the analysis population for the specified treatment group; n=number of subjects with sustained disease remission; %=100*n/N

[a] Clopper and Pearson exact CI

[b] Summary score estimate of the common difference in remission rates (Agresti 2013) by using inverse-variance stratum weights

[c] Miettinen-Nurminen (score) confidence limits for the common difference in remission rates

6.1.3.5 Potential Influence of Missing Data on Primary Endpoint Results

ANCA-associated vasculitis is a serious, often life-threatening disease. Therefore, when designing Phase 3 trial CL010_168, it was envisioned that a major cause for missing data could be withdrawal from the trial for clinical reasons. Therefore, early withdrawal from the study was considered part of the patient response and early withdrawal was defined as treatment failure.

This is consistent with the discussion on estimand by Kenward (2015): "…the missing value may itself be regarded as part of the patient response. A good example of this is dropout being defined as treatment failure. In such cases the missing data have been defined away, and essentially this is no longer a missing data problem."

The imputation of missing data for the Phase 3 study was consistent with this approach:

- Patients who discontinued the study before Week 26 were imputed as non-remitters at Week 26 and non-sustained remitters at Week 52.
- Patients who discontinued the study before Week 52 were imputed as non-sustained remitters at Week 52.

Under this realistic and conservative imputation of missing data analysis, the avacopan group was non-inferior to the prednisone group in achieving remission at Week 26 and superior to the prednisone group in achieving sustained remission at Week 52.

The missing data rates in the Phase 3 study are low and balanced between the 2 treatment groups:

- 10 of 164 (6.1%) and 10 of 166 (6.0%) patients at Week 26 in the prednisone and avacopan groups, respectively.
- 12 of 164 (7.3%) and 15 of 166 (9.0%) patients at Week 52 in the prednisone and avacopan groups, respectively.

Early withdrawal from the study constituted the major reason for missing data in the ITT population (see Table 18).

Table 18: Summary of Remission at Week 26 and Sustained Remission at Week 52 Status (ITT Population)

Visit Category	Avacopan (N=166)	Prednisone (N=164)
Week 26		
Remitters	120 (72.3)	115 (70.1)
Non-remitters	46 (27.7)	49 (29.9)
Observed non-remitters	36 (21.7)	39 (23.8)
Non-remitters due to study discontinuation	10 (6.0)	7 (4.3)
Non-remitters due to missing data	0 (0.0)	3 (1.8)
Week 52		
Sustained remitters	109 (65.7)	90 (54.9)
Non-sustained remitters	57 (34.3)	74 (45.1)
Observed non-remitters	42 (25.3)	62 (37.8)
Non-sustained remitters due to study discontinuation	15 (9.0)	12 (7.3)
Non-sustained remitters due to missing data	0 (0.0)	0 (0.0)

N=number of patients in the Intent-to-Treat population, n=number of patients in the specific category, %=percentage of patients in the treatment arm in the specific category.

Most of the patients who withdrew early from the study were not doing well clinically and withdrew due to AEs or consent withdrawal (see Table 7). If these patients were to continue the study assessments, non-remission would be a more likely outcome than remission as could be envisioned in some of the tipping point analysis outcomes. Hence, the pre-specified strategy of imputing non-remission for these patients appeared to be sound.

To further substantiate our contention that missing data did not have a significant effect of the primary endpoint results, tipping point analyses were conducted for the two primary endpoints. The methodology and results are shown in Appendix 10.7. In summary, results showed that:

1. The lower limit of the 95% confidence interval of the difference between avacopan and prednisone groups was above -20 percentage points for all cases in the Week 26 remission tipping point analysis. Therefore, the outcome of the Week 26 remission analysis was not influenced by missing data.
2. The lower limit of the 95% confidence interval of the difference between avacopan and prednisone groups was above -20 percentage points for all cases in the Week 52 sustained remission tipping point analysis, and
3. The lower limit of 95% CI of difference between avacopan and prednisone groups was above 0 for 81% of all cases in the tipping point analysis. More than 5 of 12 patients in the prednisone group and none of the 15 patients in the avacopan group needed to flip from non-remission to remission before the tipping point would be reached. Therefore, the outcome of the Week 52 sustained remission analysis was not materially influenced by missing data.

6.1.4 Secondary Efficacy Endpoints

6.1.4.1 Risk of Relapse

The rate of relapse after remission had been achieved at Week 26 was 7.5% in the avacopan group and 12.2% in the prednisone group (Table 19). The time to relapse analysis is summarized in Table 20. The risk of relapses at any time during the study after BVAS=0 had been achieved was reduced significantly in the avacopan group compared to the prednisone group (P=0.0091 for the Log-rank test of the difference of time to relapse) (Figure 7). The hazard ratio of the time to relapse between the two treatment groups was 0.46, 95% CI (0.25, 0.84). The estimated reduction in risk of relapse was 54% in the avacopan group compared to the prednisone group.

Table 19: Proportion of Patients Experiencing a Relapse After Previously Achieving Disease Remission at Week 26 as Assessed by the Adjudication Committee (ITT Population)

Treatment	N	n	(%)	95% CI[a]	Difference in %	Estimate of Common Difference in %[b]	Two-sided 95% CI for Difference in %[c]	Superiority P-value
Avacopan	120	9	7.5	3.5, 13.8	-4.7	-6.0	-14.4, 2.4	0.0810
Prednisone	115	14	12.2	6.8, 19.6				

CI=confidence interval; ITT=intent-to-treat; N=number of patients in the analysis population for the specified treatment group; n=number of patients with relapse; %=100*n/N.

[a] Clopper and Pearson exact CI.

[b] Summary score estimate of the common difference in remission rates (Agresti, 2013) by using inverse-variance stratum weights.

[c] Miettinen-Nurminen (score) confidence limits for the common difference in remission rates.

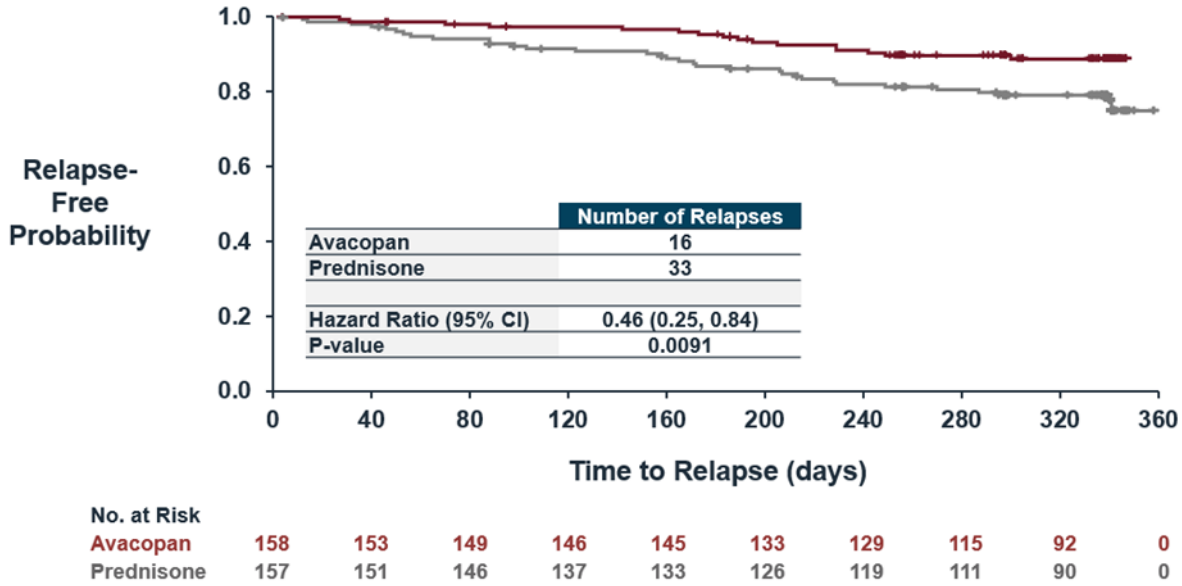
Table 20: Time to Relapse for Avacopan Compared to Prednisone (ITT Population)

Statistic	Avacopan (N=166)	Prednisone (N=164)
Number of patients who achieved BVAS=0	N'=158	N'=157
Number of patients experiencing relapse after BVAS=0 was achieved, n (%)	16 (10.1)	33 (21.0)
Number of patients censored, n (%)	142 (89.9)	124 (79.0)
Treatment comparison (versus prednisone)		
Hazard Ratio	0.461	NA
95% CI for Hazard Ratio	0.254, 0.838	NA
P-value	0.0091	NA

BVAS=Birmingham Vasculitis Activity Score; CI=confidence interval; ITT=intent-to-treat, N=Number of patients in the ITT Population. N'=number of patients who achieved BVAS=0 during the 52-week treatment period which is used as the denominator for percentage calculations; n (%)=number of patients in the specified category

Note: The median time to relapse was not estimable because less than 50% of patients relapsed. Therefore, the Kaplan-Meier estimates were not calculated. The P-values are from the log-rank test to compare the treatment groups.

Figure 7: Risk of Relapse with Avacopan Compared to Prednisone



Time to relapse defined as time from when BVAS = 0 first achieved up to time when relapse occurred

6.1.4.2 Glucocorticoid and Immunosuppressant Use

During the 14-day screening period, 125 patients in the avacopan group (75.3%) and 135 in the prednisone group (82.3%) used glucocorticoids. This was not surprising given the serious and life-threatening nature of ANCA-associated vasculitis. The average prednisone-equivalent dose during the screening period in patients who received glucocorticoids was 868.5 mg in the avacopan group compared to 884.2 mg in the prednisone group.

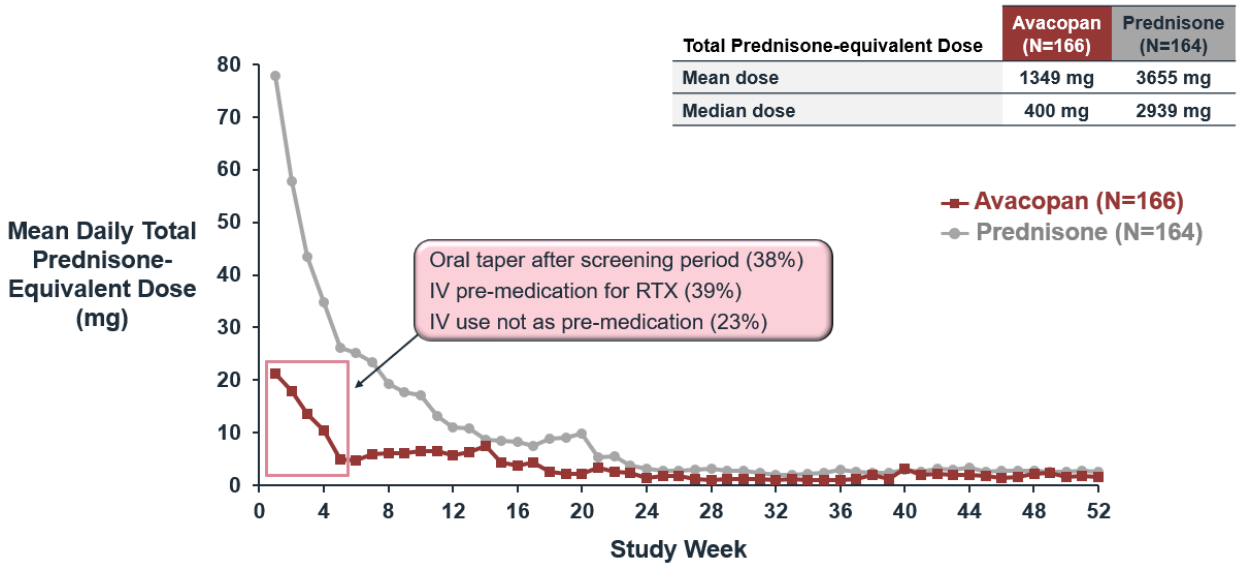
The patient incidence of concomitant glucocorticoid use (other than prednisone study medication) during the 52-week treatment period was 90.9% in the prednisone group and 87.3% in the avacopan group. Immunosuppressant drug use (other than protocol allowed use) was 22.0% in the prednisone group versus 17.5% in the avacopan group. Therefore, any potential bias was in favor of the prednisone group.

Overall, the mean total cumulative prednisone-equivalent dose (including prednisone study medication and other glucocorticoids) from Day 1 to End of Treatment was approximately 2.7-fold higher in the prednisone compared to avacopan group (3654.5 mg vs. 1348.9 mg, respectively) and the median dose was more than 7-fold higher in the prednisone compared to the avacopan group (2939.4 mg vs. 400.0 mg). When the prednisone study medication is subtracted, the mean total cumulative glucocorticoid dose was similar between the two treatment groups (1265.3 mg in the prednisone group vs. 1348.9 mg in the avacopan group).

One-third (446.5 mg) of this glucocorticoid dose in the avacopan group was during the first 4 weeks of the study; 38% of this dose of 446.5 mg was for the oral taper after glucocorticoid use during the screening period, while 39% was IV use as pre-medication for rituximab, and 23%

was IV use not as pre-medication (Figure 8). All of this glucocorticoid use was allowed per protocol.

Figure 8: Mean Daily Total Oral or IV Prednisone-Equivalent Glucocorticoid Dose (in mg) by Study Week by Treatment Group



6.1.4.3 Glucocorticoid-Induced Toxicity

6.1.4.3.1 Glucocorticoid-Induced Toxicity Assessment Results

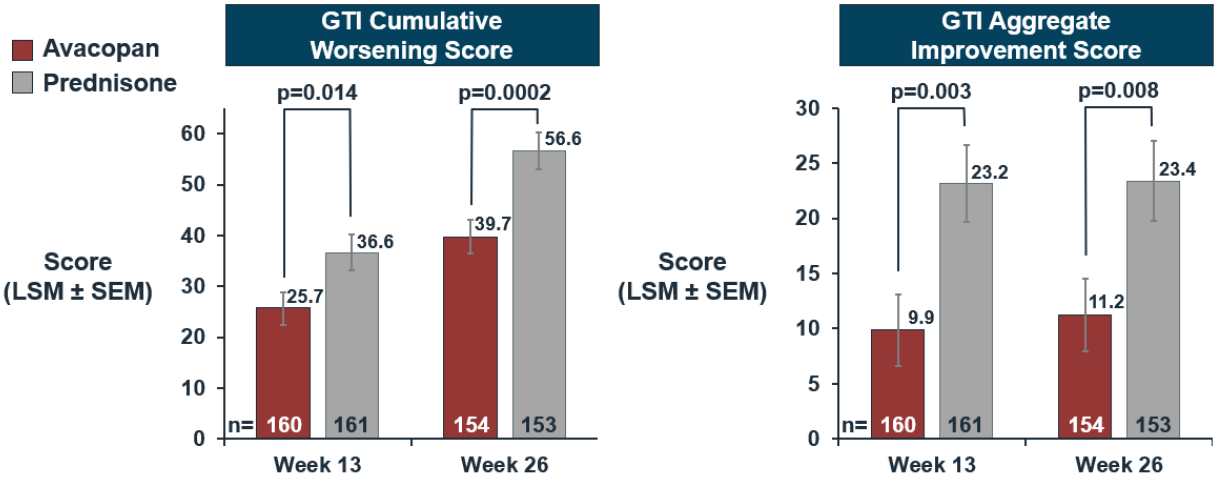
The Glucocorticoid Toxicity Index (GTI) quantifies changes in glucocorticoid toxicity and is calculated based on an assessment of changes in body mass index (BMI), blood pressure, glucose tolerance, lipids, myopathy, skin changes, neuropsychiatric changes, and infection (Miloslavsky et al., 2017). Version 2 of the GTI includes two scores that are calculated from the raw data: 1) the GTI-Cumulative Worsening Score (GTI-CWS) and 2) the GTI Aggregate Improvement Score (GTI-AIS) (McDowell et al., 2021). Refer to Appendix 10.2 for more information about the GTI.

- GTI- CWS captures cumulative glucocorticoid toxicity over time, regardless of whether the toxicity has lasting effects or is transient. New toxicities that occur are added, but toxicities that resolve are not removed. The GTI-CWS can only increase or remain the same over time. If an investigational agent is effective at decreasing glucocorticoid toxicity over time, the GTI-CWS will be lower in the drug arm.
- GTI-AIS captures improvement and worsening in toxicities. Improvement is indicated by a negative score and worsening by a positive score. This score indicates whether a new therapy is effective at diminishing baseline glucocorticoid toxicity over time. If an investigational agent is effective at decreasing glucocorticoid toxicity over time, the GTI-AIS will be lower in the drug arm.

For the GTI-CWS, at Week 13, the least squares mean (LSM) of the GTI-CWS was 25.7 in the avacopan group compared to 36.6 in the prednisone group (P=0.0140), and at Week 26, the GTI-CWS were 39.7 and 56.6, respectively (P=0.0002; Figure 9). The LSM difference between the avacopan and prednisone group for the GTI-CWS exceeded the published minimum clinically important difference (MCID) of at least 10 points (McDowell et al., 2021) at both Week 13 (11.0 points) and Week 26 (16.8 points). The beneficial effect in the avacopan group was evident across all components of the GTI, except for blood pressure changes (which, in ANCA-associated vasculitis, may be multi-factorial and not necessarily related to glucocorticoid use) and neuropsychiatric changes. The GTI-CWS components by treatment group are shown in Figure 10.

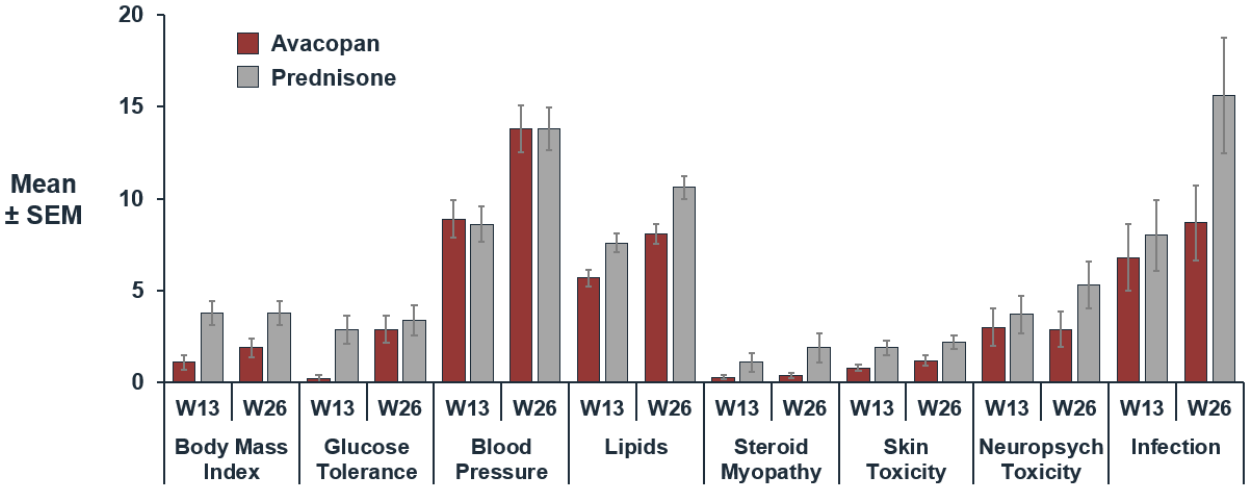
At Week 13, the LSM of the GTI-AIS was 9.9 in the avacopan group compared to 23.2 in the prednisone group (P=0.003), and at Week 26, the GTI-AIS were 11.2 and 23.4, respectively (P=0.008; Figure 9). The LSM difference between the avacopan and prednisone group for the GTI-AIS exceeded the MCID of at least 10 points at both Week 13 (13.3 points) and Week 26 (12.1 points). The GTI-AIS components by treatment group are shown in Figure 11.

Figure 9: Glucocorticoid-Related Toxicity (Cumulative Worsening Score and Aggregate Improvement Score) for Avacopan Compared to Prednisone (ITT Population)



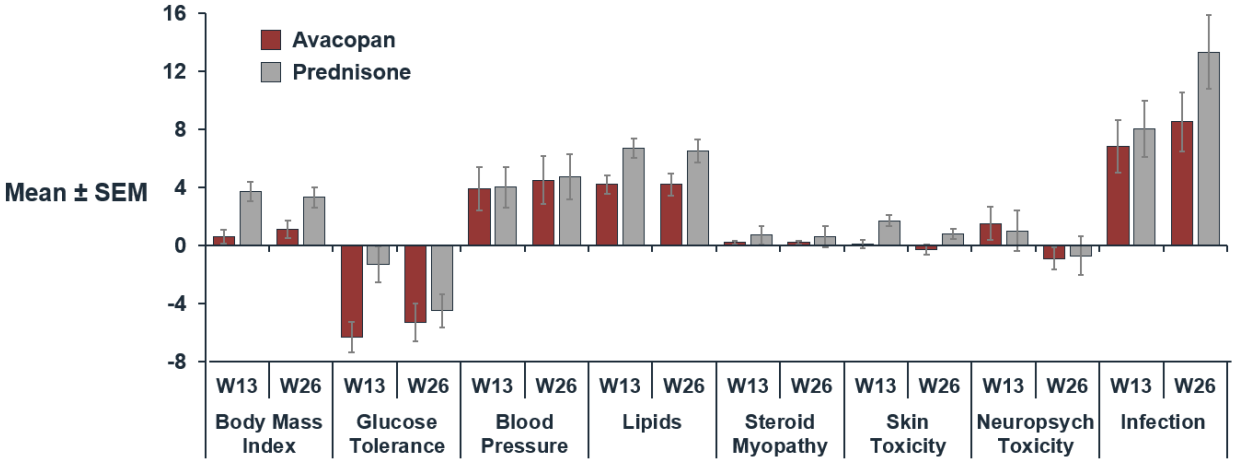
- Higher score indicates greater toxicity
- Minimum clinically important difference = 10 points (McDowell et al., 2020)

Figure 10: Glucocorticoid Toxicity Index Cumulative Worsening Score Components by Treatment Group (ITT Population)



ITT=intent-to-treat; SEM=standard error of mean; W=Week

Figure 11: Glucocorticoid Toxicity Index Aggregate Improvement Score Components by Treatment Group (ITT Population)



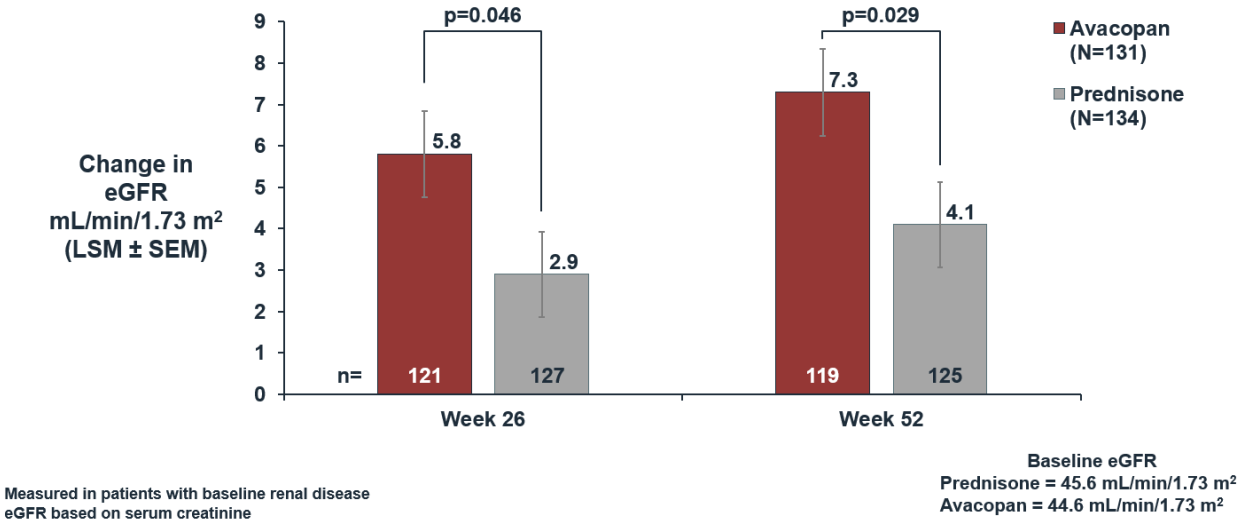
ITT=intent-to-treat; SEM=standard error of Mean; W=Week

6.1.4.4 Estimated Glomerular Filtration Rate (eGFR)

ANCA-associated vasculitis commonly affects the kidneys. In this study, 81% of patients had evidence of kidney disease at baseline based on the BVAS. The eGFR was used to assess changes in kidney function. Refer to Appendix 10.3 for more information about eGFR. In these patients, at baseline, eGFR on average was 45.6 and 44.6 mL/min/1.73 m^2 in the prednisone and avacopan groups, respectively, indicating that patients on average had Stage 3 kidney disease (eGFR 30 to 59 mL/min/1.73 m^2). The avacopan group demonstrated significant improvement in eGFR compared to the prednisone group over the course of the 52-week treatment period. At Week 26, the LSM increase in eGFR in the prednisone and avacopan groups was 2.9 and 5.8

mL/min/1.73 m^2 (P=0.046), respectively, and at Week 52, the LSM increase in the prednisone and avacopan groups was 4.1 and 7.3 mL/min/1.73 m^2 (P=0.029), respectively (Figure 12).

Figure 12: Change in eGFR in Patients with Renal Disease at Baseline for Avacopan Compared to Prednisone (ITT Population)

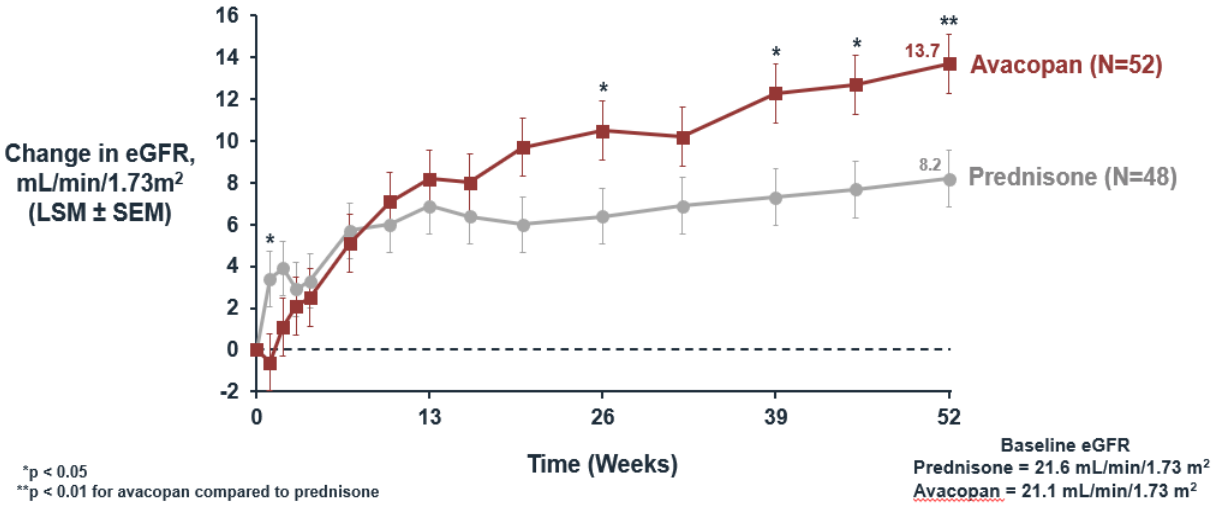


6.1.4.5 Renal Function in Patients with eGFR < 30 mL/min/1.73 m^2 at Baseline

A total of 100 of the 330 patients in the study (30.3%) had an eGFR < 30 mL/min/1.73 m^2 at baseline, indicating Stage 4 kidney disease. In these patients, eGFR on average was 21.6 and 21.1 mL/min/1.73 m^2 at baseline in the prednisone and avacopan groups, respectively. The treatment effect in the avacopan group was most prominent in these patients with Stage 4 kidney disease, who are most at risk of developing end-stage renal disease (requiring dialysis or kidney transplant). There was a continued pattern of improvement in eGFR between Week 26, when remission was achieved, and Week 52 (Figure 13). The LSM increase in the avacopan group was 13.7 mL/min/1.73 m^2 at Week 52 compared to 8.2 mL/min/1.73 m^2 in the prednisone group (P=0.0050).

Changes from baseline in eGFR in patients with a baseline eGFR between 30 and 59 mL/min/1.73 m^2, and those with baseline eGFR ≥ 60 mL/min/1.73 m^2 were higher in the avacopan compared to the prednisone group, but differences between groups did not reach statistical significance.

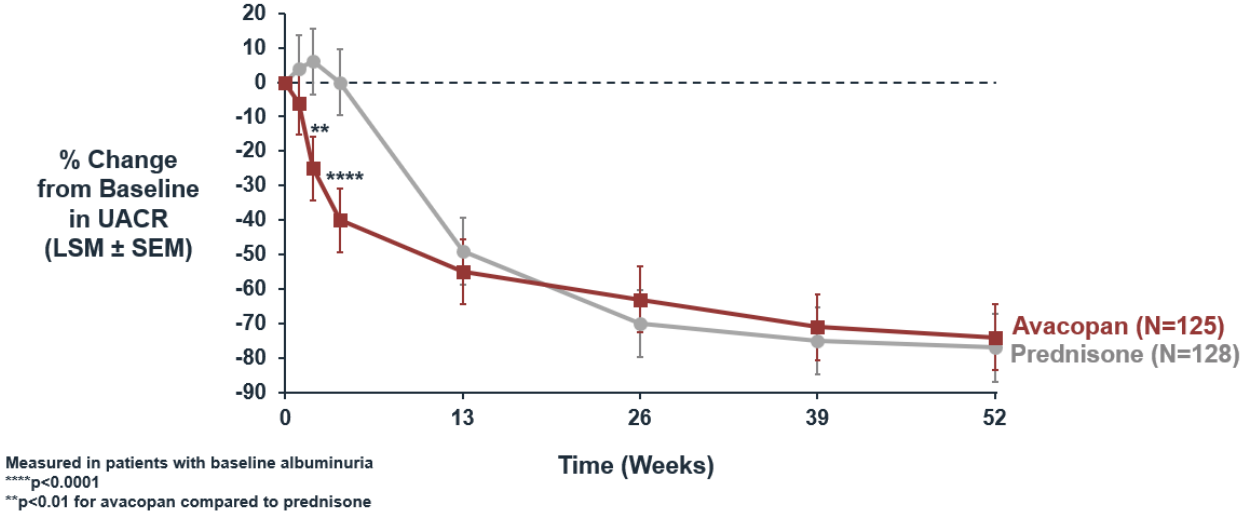
Figure 13: Change from Baseline in eGFR in Patients with eGFR < 30 mL/min/1.73 m^2 at Baseline Over 52 Weeks (ITT Population)



6.1.4.6 Urinary Albumin:Creatinine Ratio (UACR) Change over 52 Weeks

Proteinuria is a common manifestation of renal disease and is also a risk factor for progression of disease in patients with vasculitis (Kaplan-Pavlovcic et al., 2003; Stangou et al., 2005). Albuminuria, measured by urinary albumin to creatinine ratio (UACR), was assessed in patients with renal disease and albuminuria at baseline in this study. At baseline, the geometric mean (and range) UACR was 312 (11 to 5367) mg/g creatinine in the prednisone group and 433 (20 to 6461) mg/g in the avacopan group. At Week 4, the UACR improved (decreased) 40% on average in the avacopan group compared to no change in the prednisone group (P< 0.0001; Figure 14). This more rapid improvement in albuminuria in the avacopan group is important since proteinuria is a risk factor for progression of kidney disease. The extent of decrease in UACR was similar between treatment groups at Week 52 (-74% in the avacopan group compared to -77% in the prednisone group, not statistically different).

Figure 14: Urinary Albumin:Creatinine Ratio Change over 52 Weeks (ITT Population)



6.1.4.7 Urinary Monocyte Chemoattractant Protein-1:Creatinine Ratio

Monocyte chemoattractant protein-1 (MCP-1) is one of the chemokine ligands for C-C chemokine receptor type 2 (CCR2) and is one of the key chemoattractants for monocyte/macrophage infiltration to sites of inflammation. Urinary MCP-1, corrected for urinary creatinine, is a marker of renal inflammation and high levels generally correlate with poor renal outcome in patients with active renal vasculitis and other renal diseases (Jonsson et al., 2018; Tam et al., 2004; Tesch, 2008; Wolkow et al., 2008).

The baseline geometric mean levels of urinary MCP-1:creatinine ratio were 947.76 and 983.84 pg/mg creatinine in the prednisone and avacopan groups, respectively. These levels are ~4-fold higher than 263 pg/mg creatinine, the upper limit of the reference range for healthy subjects (Zheng et al., 2003), indicating a substantial degree of renal inflammation in patients with renal vasculitis in our study.

Urinary MCP-1 to creatinine ratios decreased more in the avacopan compared to the prednisone group at Week 13 (-59% vs. -52%, respectively; P=0.0339). At Week 52, both treatment groups showed a similar LSM percent decrease from baseline in urinary MCP-1 excretion (-71% in the prednisone group and -73% in the avacopan group; not statistically different).

6.1.4.8 Health-Related Quality of Life - SF-36v2 and EQ-5D-5L

The SF-36 is a widely used measure of health-related QoL, one aspect of quality of life that is affected by health status (Jenkinson et al., 1999; McHorney et al., 1992, 1994; Ware et al., 1992). The SF-36 consists of two overall scores, the Physical Component Score (PCS) and the Mental Component Score (MCS), and 8 domains, including 4 physical domains (Physical Function, Role Physical, Bodily Pain, and General Health) and 4 mental domains (Social Functioning, Role Emotional, Mental Health, and Vitality).

The Outcome Measurement in Rheumatology (OMERACT) initiative is an international collaboration of patients, researchers, clinicians, and methodologists to define core sets of

outcome measurements for use in randomized controlled trials. Stakeholder groups include treating clinicians, the Food and Drug Administration, and pharmaceutical companies. OMERACT has endorsed a core set of domains and outcome measures for use in clinical trials in ANCA-associated vasculitis (Merkel et al., 2011). Within the 2010 OMERACT core set for ANCA-associated vasculitis, the OMERACT Vasculitis Group included the generic SF-36 as the outcome measure to capture health-related quality of life (QoL) (Merkel et al., 2011).

Inclusion of the SF-36 has become standard practice for almost all clinical trials and observational studies for most rheumatic diseases, including vasculitis (Seo et al., 2005; Suppiah et al., 2011). SF-36 was found to have face and content validity as measures of health-related QoL, it showed construct validity as outcome measure in ANCA-associated vasculitis, it is discriminative of active ANCA-associated vasculitis vs sustained remission, it is feasible for use in clinical trials, and is sensitive to change based on results from clinical trials.

Patients in the Phase 3 study had impaired quality of life at baseline. Scores from the SF-36v2 assessment were consistently low across the mental and physical component scores and the individual domains (Figure 15). The baseline scores were evenly balanced between treatment groups.

The LSM change from baseline for the Physical Component Score and all physical domains in the avacopan group was consistently higher in the avacopan group compared to the prednisone group at Weeks 26 and 52 (Figure 16).

The avacopan group changes were statistically significantly higher in a majority of physical component domains, including Role Physical at Week 26 and Physical Component Score, Physical Functioning, and General Health Perception at both Week 26 and Week 52. At Week 26, the Physical Component Score (PCS) improved 4.445 in the avacopan group compared to 1.344 in the prednisone group (P=0.002), and at Week 52, the changes were 4.980 and 2.626, respectively (P=0.018). Notably, General Health Perception decreased (worsened) at Week 26 in the prednisone group (after the prednisone dosing period), whereas there was an increase (improvement) in the avacopan group: At Week 26, General Health Perception improved 3.12 in the avacopan group and deteriorated -2.89 in the prednisone group (P=0.002), and at Week 52, the changes were 5.84 and -0.17, respectively (P=0.002). The avacopan group scored higher in Role Physical at 52 weeks and in Bodily Pain, but differences did not reach statistical significance.

Figure 15: Health-Related QoL Score at Baseline as Measured by SF-36v2 (ITT Population)

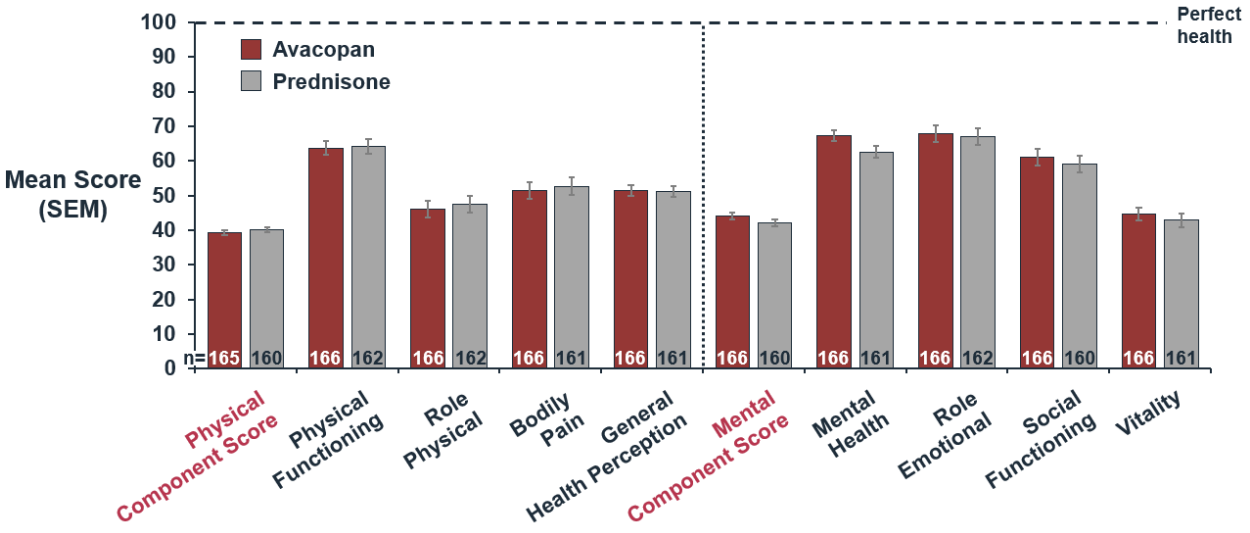
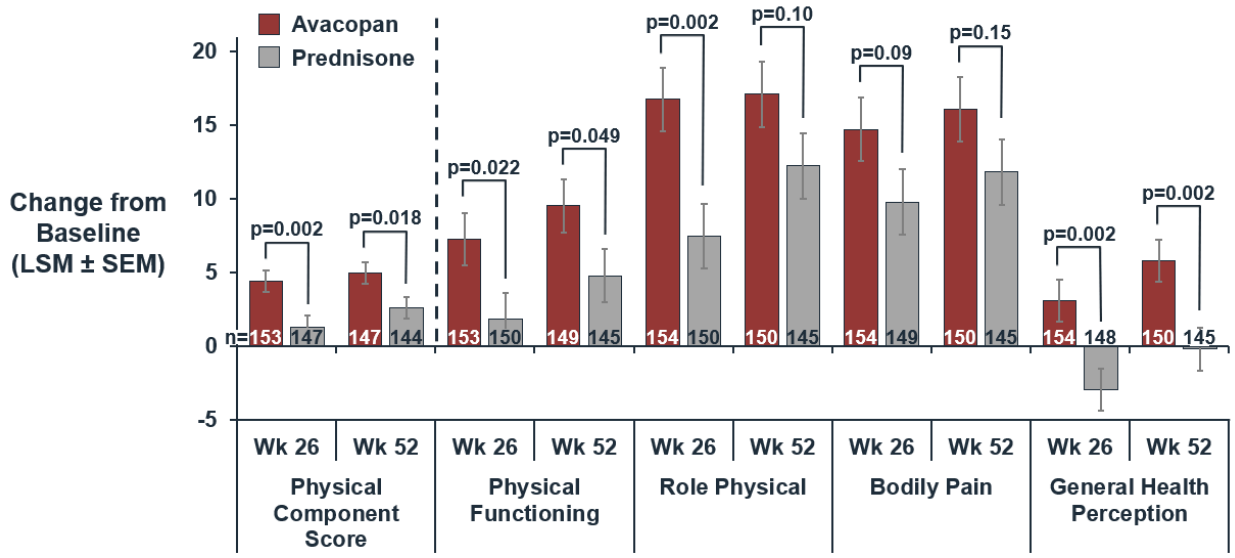
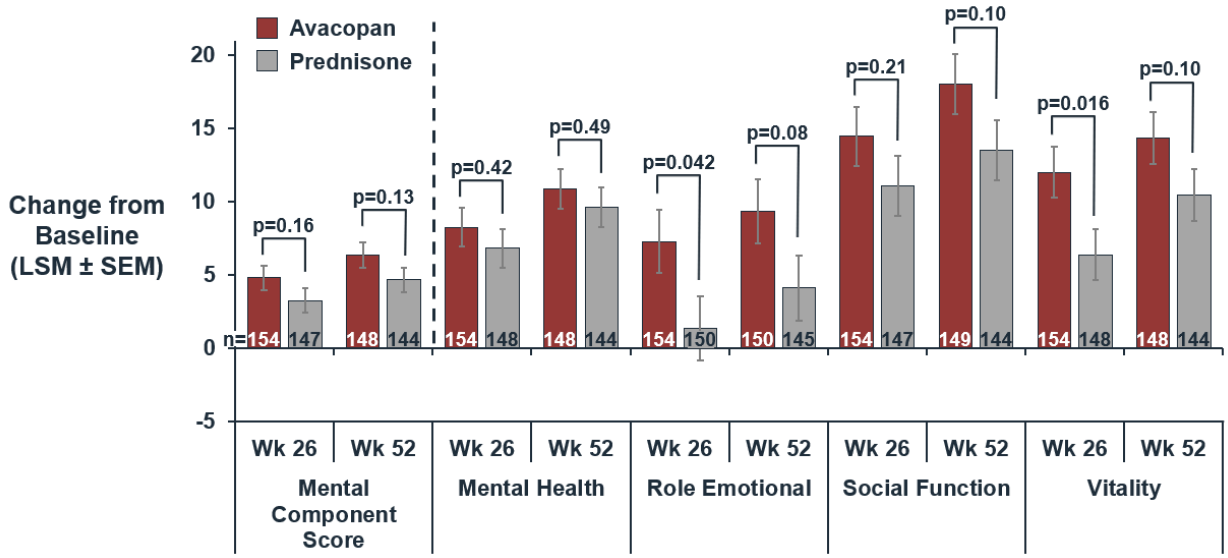


Figure 16: Health-Related QoL Score: SF-36v2 Change from Baseline in Component Score and Physical Domains for Avacopan Compared to Prednisone (ITT Population)



Regarding the Mental Component Score and mental domains, at Week 26, the changes in the Role Emotional and Vitality (measuring fatigue) domains were statistically significantly higher in the avacopan group compared to the prednisone group (Figure 17). All other domain changes were numerically higher in the avacopan group, but not statistically significant.

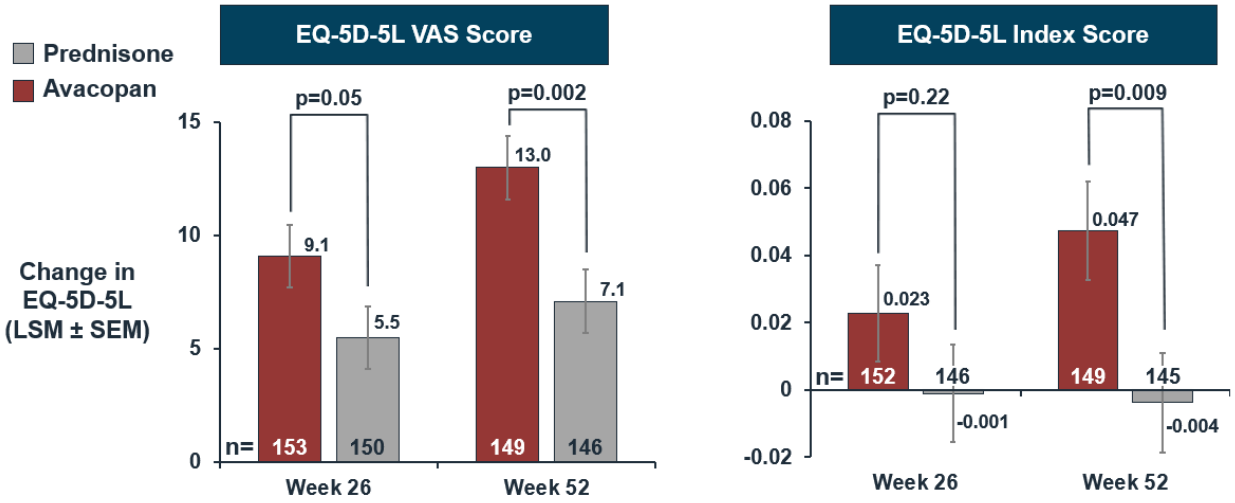
Figure 17: Health-Related QoL Score: SF-36v2 Change from Baseline Mental Component Score and Mental Domains for Avacopan Compared to Prednisone (ITT Population)



For over 25 years, the EQ-5D has been widely used in clinical trials, population studies and in real-world clinical settings. The EQ-5D instrument comprises a short descriptive system questionnaire and a visual analogue scale (EQ VAS) that are cognitively undemanding, taking only a few minutes for patients to complete. The questionnaire provides a simple descriptive profile of a respondent's health state. The EQ VAS provides an alternative way to elicit an individual's rating of their own overall current health. When the descriptive system profile is linked to a 'value set', a single summary index value for health status is derived that can be used in economic evaluations of healthcare interventions. A value set provides values (weights) for each health state description according to the preferences of the general population of a country/region. Value sets for the EQ-5D-5L and 3L versions are available in a large and growing number of countries. The EQ-5D, as a generic patient-reported outcome tool has been used in ANCA-associated vasculitis patients with nervous system involvement (Mullin et al., 2019).

Regarding the EQ-5D-5L, at Week 52, the avacopan group had significantly greater improvements from baseline compared to the prednisone group in both the Visual Analogue Scale (P=0.002; shown on the left in Figure 18) and on the Index Score (P=0.009; shown on the right in Figure 18). Overall, these significant changes in health-related quality of life demonstrate a clinically meaningful benefit for patients treated with avacopan.

Figure 18: Changes in EQ-5D-5L at Week 52 for Avacopan Compared to Prednisone (ITT Population)



VAS=visual analogue scale (0-100)

6.1.4.9 Birmingham Vasculitis Activity Score of 0 at Week 4

BVAS of 0 at Week 4 was observed in 68.9% of patients in the prednisone group compared to 62.7% in the avacopan group (not significantly different) for the ITT Population.

6.1.4.10 Vasculitis Damage Index

The Vasculitis Damage Index (VDI) is a validated instrument used to record cumulative organ damage as a result of ANCA-associated vasculitis (Exley et al., 1997). The VDI can only remain the same or increase over time since organ damage, once sustained, is permanent. Newly-diagnosed patients typically have a VDI score of zero because they have not yet sustained damage. It typically takes a number of years having ANCA-associated vasculitis to accumulate organ damage measurable with the VDI.

At baseline, the mean VDI score in the prednisone and avacopan groups were 0.72 and 0.66, respectively, reflective of a patient population with mostly newly diagnosed disease. Both treatment groups showed a similar mean increase in the LSM change from baseline to Week 52 in VDI (1.15 in the prednisone group and 1.17 in the avacopan group; not statistically different).

6.1.4.11 Rank Order of Testing of the Secondary Efficacy Endpoint

The GTI was the first secondary endpoint. For the remaining secondary endpoints, a rank order of testing was not specified in the Statistical Analysis Plan (SAP). The rationale was that these endpoints could not be studied to the full extent necessary in the early Phase 2 studies which were too small and/or too short in duration. Therefore, the likelihood of success of the outcome of the secondary endpoints could not be pre-determined, and prioritization was difficult to specify in the SAP. However, in several cases, data from these secondary efficacy endpoints were confirmatory for results observed in the two Phase 2 studies: (1) A greater increase in eGFR was also observed in Phase 2 study CL003_168 with 30 mg avacopan compared to the

other two treatment groups; (2) A faster improvement in UACR was also observed in Phase 2 study CL002_168 with avacopan compared to the prednisone control group; and (3) health-related quality of life improvement based on the SF-36 and EQ-5D-5L was also observed with avacopan compared to the prednisone control group in Phase 2 study CL002_168.

Therefore, results from the secondary endpoints provide independent and helpful information to support the primary efficacy endpoints and mechanism of action of avacopan. The results of the secondary endpoints would also be informative to prescribers and their patients.

6.1.5 Follow-Up Period Results and Treatment beyond 52 Weeks

The Phase 3 study included an 8-week follow-up period. Pertinent efficacy data from the 8-week follow-up period are summarized in Table 21.

There was a similar number of relapses during the follow-up period in the two treatment groups. This may indicate that when avacopan treatment is stopped, the relapse rate may increase, because the relapse rate was lower in the avacopan compared to the prednisone group during the 52-week treatment period (see Section 6.1.4.1). There was also a slight decrease from Week 52 to Week 60 in mean eGFR in the avacopan group, which again suggests that during the avacopan-free follow-up period, there may be some loss of the benefit gained with avacopan during the 52-week treatment period.

Regarding other secondary efficacy endpoints, health-related quality of life based on SF-36v2 and EQ-5D-5L, albuminuria, and urinary MCP-1, there did not appear to be a meaningful change between Week 52 and Week 60 values.

Table 21: Pertinent Efficacy Results from the 8-Week Follow-up Period of Phase 3 Study CL010_168

Parameter	Avacopan	Prednisone
Relapses (as Assessed by the Adjudication Committee), n (%)	6 (3.8%)	7 (4.5%)
SF-36v2 Physical Component Score		
Week 52		
n	147	144
Mean (SEM)	44.8 ± 0.80	43.1 ± 0.90
Week 60		
n	149	145
Mean (SEM)	45.0 ± 0.81	43.4 ± 0.90
EQ-5D-5L Visual Analogue Scale		
Week 52		
n	149	146
Mean (SEM)	78.5 ± 1.26	73.1 ± 1.68
Week 60		
n	149	147
Mean (SEM)	76.7 ± 1.48	73.8 ± 1.64
eGFR (mL/min/1.73 m^2)		
Week 52		
n	119	125
Mean (SEM)	53.2 ± 2.21	50.5 ± 1.98
Week 60		
n	119	122
Mean (SEM)	51.7 ± 2.10	51.0 ± 2.09

UACR (mg/g creatinine)		
Week 52		
n	109	114
Geometric mean	113.47	74.94
Week 60		
n	106	106
Geometric mean	104.29	81.62
U-MCP-1:creatinine ratio		
Week 52		
n	106	108
Geometric mean	252.10	274.64
Week 60		
n	100	109
Geometric mean	249.99	265.49

eGFR=estimated glomerular filtration rate; EQ-5D-5L=EuroQuality of Life-5 Domains-5 Levels; SEM=standard error of mean; SF 36v2=Short Form 36 version 2; UACR=urinary albumin:creatinine ratio; U-MCP-1=urinary monocyte chemoattractant protein-1

In summary, there is some evidence based on the relapse rate and eGFR that part of the benefit gained from avacopan treatment may be lost when the treatment is stopped at 52 weeks. Therefore, continued treatment with avacopan beyond 52 weeks may be indicated in patients who have benefited from avacopan treatment and who do not otherwise have safety or tolerability concerns.

There are encouraging case reports of avacopan treatment beyond 52 weeks, such as published recently (Ennis et al., 2020). This 19-year old patient with treatment-resistant GPA had severe, multi-relapsing disease. Avacopan 30 mg twice daily was started under a compassionate program. The patient was able to successfully reduce her glucocorticoid dose and reduce her immunosuppressive treatments without another flare. She had been on avacopan for 35 months, had no adverse events that required its discontinuation, and her disease is in sustained remission.

6.2 Supportive Phase 2 Study CL002_168

6.2.1 Investigational Plan

6.2.1.1 Overall Design

Supportive Phase 2 clinical Study CL002_168 was a prospective, randomized, double-blind, double-dummy, placebo-controlled clinical trial at 60 study centers in 11 countries in Europe, and enrolled 67 patients with active ANCA-associated vasculitis. There was a 12-week treatment period with a 12-week follow-up period.

Since this was the first study with avacopan in patients with ANCA-associated vasculitis, it was conducted in a step-wise manner, comprising 3 steps, to withdraw glucocorticoids gradually. In the first step, the prednisone dose given to patients in the avacopan group was reduced by two-thirds, and if successful, prednisone was removed completely from the avacopan group in the second step. The third step of the study was an expansion of enrollment to evaluate efficacy and safety more thoroughly. A detailed explanation of the study design and a study schema for Study CL002_168 are provided in Appendix 10.6.

The statistical analysis plan specified three study groups in the final analysis:

1. Full dose prednisone standard of care control group: patients received avacopan-matching placebo plus cyclophosphamide or rituximab plus a full starting dose of prednisone (60 mg once daily);
2. Avacopan plus low dose prednisone group: patients received avacopan 30 mg twice daily plus cyclophosphamide or rituximab plus a one-third starting dose of prednisone (20 mg once daily);
3. Avacopan plus no prednisone group: These patients received avacopan 30 mg twice daily plus cyclophosphamide or rituximab plus prednisone-matching placebo.

The statistical analysis plan for Study CL002_168 is described in detail in Appendix 10.13.

The prednisone dose was tapered as shown in Table 22.

Table 22: Oral Prednisone Tapering Schedule in the Three Study Groups in Clinical Trial CL002_168

Study Days	Full Dose Prednisone Control Group[a]	Avacopan Group Receiving Reduced Prednisone Dose[b]	Avacopan Group Receiving No Prednisone
	Daily Prednisone Dose		
1 to 7	60 mg	20 mg	0
8 to 14	45 mg	15 mg	0
15 to 21	30 mg	10 mg	0
22 to 28	25 mg	10 mg	0
29 to 35	25 mg	10 mg	0
36 to 42	25 mg	10 mg	0
43 to 49	20 mg	5 mg	0
50 to 56	20 mg	5 mg	0
57 to 63	15 mg	5 mg	0
64 to 70	15 mg	5 mg	0
71 to 77	10 mg	5 mg	0
78 to 84	10 mg	5 mg	0
85 to 98	10 mg	5 mg	0
99 to 140	5 mg	0	0
141 to 168	0	0	0

[a] For patients weighing at least 55 kg; for those < 55 kg, the starting prednisone dose was 45 mg/day
[b] For patients weighing at least 55 kg; for those < 55 kg, the starting prednisone dose was 15 mg/day

6.2.1.2 Selection of Study Population

Diagnosis and Main Criteria for Inclusion: Patients were to have a clinical diagnosis of granulomatosis with polyangiitis (GPA), microscopic polyangiitis or renal limited vasculitis, consistent with Chapel Hill consensus definitions (Jennette et al., 2013). The main criteria for inclusion were male and postmenopausal or surgically sterile female patients, aged at least 18 years, with new or relapsed ANCA-associated vasculitis where treatment with cyclophosphamide or rituximab would be required.

Patients were excluded if they had severe disease (including rapidly progressive glomerulonephritis, alveolar hemorrhage leading to grade 3 hypoxia, rapid-onset mononeuritis multiplex, or central nervous system involvement), any other autoimmune disease, coagulopathy

or bleeding disorder, had received cyclophosphamide within 12 weeks, rituximab within 12 months prior to screening (or 6 months with B-cell reconstitution, CD19 count > $0.01x10^9$/L), cumulative dose of intravenous glucocorticoids greater than 3 g within 12 weeks, or oral glucocorticoids of more than 10 mg per day prednisone equivalent for more than 6 weeks prior to screening.

A complete list of eligibility criteria for Study CL002_168 is provided in Appendix 10.11.

6.2.1.3 Randomization and Treatment

After screening, patients were stratified based on having newly diagnosed or relapsing disease (all three steps), and by PR3 or MPO-ANCA, and cyclophosphamide or rituximab treatment (step 3).

- In step 1, 12 patients were randomly assigned in a 2 to 1 ratio to receive 30 mg avacopan twice daily plus 20 mg prednisone, or avacopan-matching placebo plus prednisone.
- In step 2, 14 patients were randomly assigned in a 2 to 1 ratio to receive 30 mg avacopan twice daily without prednisone or avacopan-matching placebo plus 60 mg prednisone.
    - All patients in steps 1 and 2 received cyclophosphamide intravenously at 15 mg/kg up to 1.2 g on Day 1 and Weeks 2, 4, 8, and 12, followed by oral azathioprine at a target dose of 2 mg/kg/day from week 14 to 24.
- In step 3, 41 patients were randomly assigned (1:1:1) to receive 30 mg avacopan twice daily plus 20 mg prednisone, 30 mg avacopan twice daily plus placebo prednisone, or avacopan-matching placebo plus 60 mg prednisone.
    - All patients in step 3 received either cyclophosphamide followed by azathioprine as described above, or intravenous rituximab 375 mg/m^2/week for 4 weeks.

6.2.2 Study Patients

6.2.2.1 Disposition

Disposition of patients enrolled in Study CL002_168 is shown in Table 23 and a consort diagram of patient flow through the study is shown in Appendix 10.12.

A total of 67 patients were randomized and received at least one dose of study medication. This comprised the All Patients Randomized Population and also the Safety Population.

A total of 63 patients were included in the ITT population, defined as all patients who were randomized, received at least one dose of study drug, and who had at least one post baseline, on-treatment BVAS. Four patients, three in the full dose prednisone group and one in the avacopan plus no prednisone group, did not have any post baseline, on-treatment BVAS assessment, and were excluded from the ITT population according to the pre-specified statistical analysis plan.

Four patients discontinued during the 12-week treatment period: two patients in the full dose prednisone group withdrew due to informed consent withdrawal, and two patients in the

avacopan plus no prednisone group withdrew early, one due to an AE and another due to Investigator decision.

A similar number of patients across treatment groups withdrew during the 12-week follow-up period.

Table 23: Patient Disposition in Study CL002_168

	Full Dose Prednisone Control (N=23)	Avacopan + Low Dose Prednisone (N=22)	Avacopan + No Prednisone (N=22)	All Avacopan (N=44)
Randomized	23	22	22	44
ITT Population[a]	20	22	21	43
Safety Population[b]	23	22	22	44
Completed Week 12	21	22	20	42
Early withdrawal pre-Week 12	2	0	2	2
Early withdrawal reason				
Patient withdrew consent	2	0	0	0
Adverse event	0	0	1	1
Physician decision	0	0	1	1
Early withdrawal after Week 12	3	3	2	5
Patient withdrew consent	1	0	1	1
Adverse event	2	2	1	3
Other[c]	0	1	0	1

BVAS=Birmingham Vasculitis Activity Score; ITT=intent-to-treat

[a] ITT population, defined as all patients who were randomized, received at least one dose of study drug, and who had at least one post baseline, on-treatment BVAS score.

[b] Safety population, defined as all patients randomized and receiving at least one dose of study drug (Also referred to as the All Patients Randomized Population)

[c] Rescue medication

6.2.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics of patients enrolled in Study CL002_168 are summarized in Table 24.

The characteristics of treatment groups were relatively well balanced at baseline. The median duration of ANCA disease was 0 to 1 month across groups, which is consistent with the finding that most patients (68.2 to 78.3%) had newly diagnosed disease. This is consistent with Phase 3 Study CL010_168. There was a relatively equal distribution of newly diagnosed vs. relapsing disease, anti-MPO and anti-PR3 ANCA positivity, and GPA versus MPA disease across treatment groups. The mean BVAS, VDI, and eGFR were relatively similar across the three groups.

Table 24: Demographics and Baseline Characteristics in Study CL002_168

Category	Full Dose Prednisone Control (N=23)	Avacopan + Low Dose Prednisone (N=22)	Avacopan + No Prednisone (N=22)	All Avacopan (N=44)
Age in years, mean ± SD	59.1 ± 13.98	57.0 ± 14.22	57.4 ± 14.00	57.2 ± 13.95
Sex, Male/Female (n / n)	17 / 6	14 / 8	16 / 6	30 / 14
Race, White (Caucasian) (n)	23	22	22	44
Duration of ANCA disease in months, median (range)	0 (0-162)	0 (0-61)	1 (0-108)	0 (0-108)
BMI, kg/m^2, mean ± SD	27.29 ± 7.094	24.93 ± 4.049	26.53 ± 4.655	25.73 ± 4.384
ANCA-Associated Vasculitis Status				
Newly Diagnosed, n (%)	18 (78.3)	15 (68.2)	16 (72.7)	31 (70.5)
Relapsed Disease, n (%)	5 (21.7)	7 (31.8)	6 (27.3)	13 (29.5)
ANCA Type				
Anti-MPO positive, n (%)	10 (43.5)	12 (54.5)	13 (59.1)	25 (56.8)
Anti-PR3 positive, n (%)	11 (47.8)	10 (45.5)	8 (36.4)	18 (40.9)
Both anti-MPO and anti-PR3 positive, n (%)	1 (4.3)	0 (0)	0 (0)	0 (0)
ANCA equivocal or negative	1 (4.3)	0 (0)	1 (4.5)	1 (2.3)
ANCA Disease Type				
GPA, n (%)	10 (43.5)	11 (50.0)	12 (54.5)	23 (52.3)
MPA, n (%)	10 (43.5)	9 (40.9)	9 (40.9)	18 (40.9)
Renal limited vasculitis	2 (8.7)	2 (9.1)	1 (4.5)	3 (6.8)
Unknown	1 (4.3)	0 (0)	0 (0)	0 (0)
BVAS, mean ± SD	13.2 ± 5.80	14.3 ± 5.98	13.8 ± 6.38	14.0 ± 6.11
VDI, mean ± SD	1.2 ± 1.35	0.9 ± 1.46	0.5 ± 1.19	0.7 ± 1.33
eGFR (MDRD), mL/min/1.73 m^2, mean ± SD	47.6 ± 15.08	52.5 ± 26.70	54.7 ± 19.64	53.6 ± 23.19

N=number of patients in the in each treatment group; n=number of patients with applicable characteristic; %=100*n/N; ANCA=anti-neutrophil cytoplasmic autoantibody; BMI=body mass index; BVAS=Birmingham Vasculitis Activity Score; eGFR=estimated glomerular filtration rate; GPA=granulomatosis with polyangiitis; MDRD=Modification of Diet in Renal Disease (study equation); MPA=microscopic polyangiitis; MPO=myeloperoxidase; PR3=proteinase 3; SD=standard deviation; VDI=Vasculitis Damage Index.

6.2.3 Primary Efficacy Endpoint - Patients Achieving Disease Response at Week 12

The primary efficacy endpoint was the proportion of patients 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.

Since the study was Phase 2, per protocol, if the lower bound of the 2-sided 90% CI for the difference (avacopan minus full dose prednisone group) was above -0.20 (i.e., -20 percentage points), then the respective avacopan group was considered not inferior to the full dose prednisone group. Comparisons were also tested for superiority.

Results for the primary endpoint, BVAS response at Week 12, in the ITT population are summarized in Table 25.

The primary efficacy endpoint for the study was met. The avacopan group overall, as well as both the avacopan plus low dose prednisone group and the avacopan plus no prednisone group, had numerically higher BVAS response rates compared to the full dose prednisone group, and both avacopan groups were statistically non-inferior to the full dose prednisone group.

Table 25: BVAS Response at Week 12 in Study CL002_168 (ITT Population)

	Full Dose Prednisone Control	Avacopan + Low Dose Prednisone	Avacopan + No Prednisone	All Avacopan
BVAS Response[(1)], n / N (%)	14 / 20 (70.0)	19 / 22 (86.4)	17 / 21 (81.0)	36 / 43 (83.7)
Difference in percentage vs. control	---	16.4	11.0	13.7
Two-sided 90% CI for Difference, avacopan minus control	---	-4.3, 37.1	-11.0, 32.9	-5.5, 33.0
Non-inferiority P-value for avacopan vs. control	---	0.0019	0.0102	0.0020
Superiority P-value for avacopan vs. control	---	0.0969	0.2061	0.1203

N=number of patients in the in each treatment group; n=number of patients with response; %=100*n/N; BVAS=Birmingham Vasculitis Activity Score; CI=confidence interval

[a] BVAS response defined as a decrease from baseline of at least 50%, and no worsening in any organ system

6.2.4 Secondary Endpoints

The efficacy of avacopan was supported by several secondary endpoints, including percent change from baseline in BVAS, albuminuria, renal response, urinary MCP-1:creatinine ratio, and health-related quality of life (Jayne et al., 2017).

6.3 Supportive Phase 2 Study CL003_168

6.3.1 Investigational Plan

6.3.1.1 Overall Design

Study CL003_168 was primarily a safety study. In this study, avacopan was given on top of full dose prednisone plus cyclophosphamide or rituximab. The study was conducted in patients with ANCA-associated vasculitis in the USA and Canada.

The target enrollment of the study was 10 to 15 patients per treatment group (30 to 45 in total for the three treatment groups). This clinical trial enrolled 42 patients with ANCA-associated vasculitis.

The primary safety objective of this study was to evaluate the safety and tolerability of avacopan in patients with ANCA-associated vasculitis on standard of care glucocorticoids plus cyclophosphamide or rituximab treatment. The primary efficacy objective was to evaluate the efficacy of avacopan based on the BVAS. Because of the relatively small size of the trial, the statistical analysis plan stated prospectively that efficacy results based on BVAS response would only be summarized with descriptive statistics.

This randomized, double-blind, placebo-controlled clinical trial included three treatment groups:

1. Full dose prednisone control group: These patients received avacopan-matching placebo plus cyclophosphamide or rituximab plus a full starting dose of prednisone (60 mg/day);
2. Low dose avacopan group: These patients received avacopan 10 mg twice daily plus cyclophosphamide or rituximab plus a full starting dose of prednisone (60 mg/day);

3. High dose avacopan group: These patients received avacopan 30 mg twice daily plus cyclophosphamide or rituximab plus a full starting dose of prednisone (60 mg/day).

The prednisone tapering schedule for all three treatment groups was the same as the tapering schedule for the control group in Study CL002_168 (Table 22). The cyclophosphamide regimen was 15 mg/kg IV up to a dose of 1.2 g every 2 to 4 weeks and the rituximab regimen was 375 mg/m^2 IV weekly for 4 weeks, the same as in Study CL002_168.

There was a 12-week follow-up period for all patients after the 12-week treatment period. During the follow-up period, patients receiving cyclophosphamide were switched to azathioprine at a target dose of 2 mg/kg/day, starting at Week 15. Patients receiving rituximab background treatment did not receive any additional treatment during the follow-up period.

The statistical analysis plan for Study CL003_168 is described in detail in Appendix 10.16.

6.3.1.2 Selection of Study Population

Patients were to have a clinical diagnosis of GPA, MPA, or renal limited vasculitis, consistent with Chapel Hill consensus definitions (Jennette et al., 2013). The main criteria for inclusion included male and female patients, aged at least 18 years, with new or relapsed ANCA-associated vasculitis where treatment with cyclophosphamide or rituximab would be required.

Patients were excluded if they had severe disease (including rapidly progressive glomerulonephritis, alveolar hemorrhage leading to grade 3 hypoxia, rapid-onset mononeuritis multiplex, or central nervous system involvement), any other autoimmune disease, coagulopathy or bleeding disorder, had received cyclophosphamide within 12 weeks, rituximab within 12 months prior to screening (or 6 months with B-cell reconstitution, CD19 count > 0.01x10^9/L), cumulative dose of intravenous glucocorticoids greater than 3 g within 12 weeks, or oral glucocorticoids of more than 10 mg per day prednisone equivalent for more than 6 weeks prior to screening.

A complete list of eligibility criteria for Study CL003_168 is provided in Appendix 10.14.

6.3.1.3 Treatments

The study comprised 3 groups:

- Group A: Avacopan 10 mg twice daily plus cyclophosphamide/rituximab plus prednisone,
- Group B: Avacopan 30 mg twice daily plus cyclophosphamide/rituximab plus prednisone, and
- Group C: Placebo twice daily plus cyclophosphamide/rituximab plus prednisone.

All patients received either cyclophosphamide intravenously at 15 mg/kg up to 1.2 g on Day 1 and Weeks 2, 4, 8, and 12, followed by oral azathioprine at a target dose of 2 mg/kg/day from week 14 to 24, or rituximab 375 mg/m^2 once weekly IV for 4 weeks. Twice daily dosing of avacopan or placebo continued for 84 days.

All patients received prednisone typically at a starting dose of 60 mg prednisone per day, which was tapered to 0 mg by the end of Week 20.

6.3.2 Study Patients

6.3.2.1 Disposition

Patient disposition for Study CL003_168 is shown in Table 26 and a consort diagram of patient flow through Study CL003_168 is shown in Appendix 10.15.

A total of 42 patients were randomized and received at least one dose of study medication; this comprised the Safety Population. A total of 40 patients were included in the ITT population. Two patients included in the Safety Population, including one in the 10 mg avacopan twice daily group and one in the 30 mg avacopan twice daily group, did not have any post baseline, on-treatment BVAS assessment, and therefore were excluded from the ITT population according to the pre-specified statistical analysis plan.

Two patients discontinued during the 12-week treatment period. One patient each in the 10 mg and 30 mg avacopan twice daily groups withdrew early due to an AE. No patients withdrew during the 12-week follow-up period.

Table 26: Patient Disposition in Study CL003_168

	Full Dose Prednisone Control (N=13)	Full Dose Prednisone + 10 mg Avacopan Twice Daily (N=13)	Full Dose Prednisone + 30 mg Avacopan Twice Daily (N=16)	All Avacopan (N=29)
Randomized	13	13	16	29
ITT Population[a]	13	12	15	27
Safety Population[b]	13	13	16	29
Completed Week 12	13	12	15	27
Early withdrawal pre-Week 12	0	1	1	2
Early withdrawal reason				
Adverse event	0	1	1	2
Early withdrawal after Week 12	0	0	0	0

ANCA=anti-neutrophil cytoplasmic autoantibody; BVAS=Birmingham Vasculitis Activity Score; ITT=intent-to-treat

[a] ITT population, defined as all patients who were randomized, received at least one dose of study drug, and who had at least one post baseline, on-treatment BVAS score. N=40

[b] Safety population, defined per protocol as all patients randomized and receiving at least one dose of study drug (Also referred to as the All Patients Randomized Population) N=42

6.3.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics of patients enrolled in Study CL003_168 are summarized in Table 27.

Table 27: Demographics and Baseline Characteristics in Study CL003_168 in ANCA-Associated Vasculitis (Safety Population)

Category	Full Dose Prednisone Control (N=13)	Full Dose Prednisone + 10 mg Avacopan Twice Daily (N=13)	Full Dose Prednisone + 30 mg Avacopan Twice Daily (N=16)	All Avacopan (N=29)
Age (years), Mean ± SD	58.5 ± 15.42	60.0 ± 10.17	55.3 ± 13.81	57.4 ± 12.33
Sex, n (%)				
Male	4 (30.8)	8 (61.5)	7 (43.8)	15 (51.7)
Female	9 (69.2)	5 (38.5)	9 (56.3)	14 (48.3)
Race, n (%)				
Black or African American	0	2 (15.4)	1 (6.3)	3 (10.3)
White	13 (100)	11 (84.6)	14 (87.5)	25 (86.2)
Other	0	0	1 (6.3)	1 (3.4)
Duration of ANCA disease in months, median (range)	1.0 (0-95)	1.0 (0-347)	2.5 (0-170)	1.0 (0-347)
BMI, kg/m^2, mean ± SD	31.0 ± 12.51	27.6 ± 8.91	31.5 ± 7.59	29.8 ± 8.29
ANCA-Associated Vasculitis Status, n (%)				
Newly diagnosed	8 (61.5)	10 (76.9)	9 (56.3)	19 (65.5)
Relapsed	5 (38.5)	3 (23.1)	7 (43.8)	10 (34.5)
ANCA Type, n (%)				
Proteinase 3 positive	6 (46.2)	7 (53.8)	8 (50.0)	15 (51.7)
Myeloperoxidase positive	7 (53.8)	6 (46.2)	8 (50.0)	14 (48.3)
Immunosuppressant Treatment, n (%)				
Rituximab	12 (92.3)	13 (100.0)	14 (87.5)	27 (93.1)
Cyclophosphamide IV	1 (7.7)	0	2 (12.5)	2 (6.9)
ANCA Disease Type, n (%)				
Granulomatosis with polyangiitis	9 (69.2)	8 (61.5)	12 (75.0)	20 (69.0)
Microscopic polyangiitis	3 (23.1)	4 (30.8)	4 (25.0)	8 (27.6)
Renal-limited	1 (7.7)	1 (7.7)	0	1 (3.4)
BVAS, mean ± SD	15.0 ± 4.45	15.8 ± 8.84	15.1 ± 6.43	15.4 ± 7.47
VDI, mean ± SD	1.2 ± 1.77	0.8 ± 2.49	0.6 ± 1.15	0.7 ± 1.83
eGFR, mean ± SD	60.1 ± 24.25	56.4 ± 26.75	61.4 ± 31.09	59.1 ± 28.83

N=number of patients in the in each treatment group; n=number of patients with applicable characteristic; %=100*n/N; ANCA=anti-neutrophil cytoplasmic autoantibodies; BMI=body mass index; BVAS=Birmingham Vasculitis Activity Score; eGFR=estimated glomerular filtration rate; IV=intravenous; SD=standard deviation; VDI=Vasculitis Damage Index

6.3.3 Birmingham Vasculitis Activity Score (BVAS) Results

All treatment groups in Study CL003_168 received full dose prednisone as a component of their standard of care treatment. Therefore, as anticipated, the response rate in the ITT Population, based on a BVAS decrease from baseline to Week 12 of at least 50% and no worsening in any organ system, was high across treatment groups: 23 of 27 patients (85.2%) receiving avacopan, compared to 11 of 13 patients (84.6%) in the control group. Eleven of 12 patients, and 12 of 15 patients in the 10 mg and 30 mg avacopan twice daily groups, respectively, had a BVAS response at Week 12.

A BVAS of 0 at Week 4, was achieved in 6 of 27 patients (22.2%) in the all avacopan group, compared to 2 of 13 patients (15.4%) in the control group. One of 12, and 5 of 15 patients in the 10 mg and 30 mg avacopan twice daily groups, respectively, had a BVAS of 0 at Week 4.

6.3.4 Renal Endpoints

In patients with renal ANCA-associated vasculitis (based on BVAS), the mean ± standard error of mean (SEM) change from baseline to Week 12 in eGFR was 6.2 ± 7.0 mL/min/1.73 m^2 in the 30 mg avacopan twice daily group, compared to 1.3 ± 3.5 and 2.0 ± 3.6 mL/min/1.73 m^2 in the 10 mg avacopan twice daily group and the control group, respectively.

Renal response, defined as an improvement from baseline to Week 12 in eGFR, hematuria, and albuminuria, was observed in 5 of 8 patients (62.5%) in the 30 mg avacopan twice daily group, compared to 2 of 5 patients (40.0%) in the 10 mg avacopan twice daily group and 1 of 6 patients (16.7%) in the control group.

6.4 Efficacy Conclusions

6.4.1 Efficacy Conclusions for Pivotal Phase 3 Study CL010_168

Primary Endpoints

Study CL010_168 met both of its primary endpoints, remission at Week 26 and sustained remission at Week 52. The avacopan group was non-inferior to the prednisone group with respect to the incidence of patients who achieved clinical remission at Week 26 and superior with regard to those who achieved sustained remission at Week 52.

- At Week 26, 70.1% (115/164) of patients in the prednisone group achieved remission compared to 72.3% (120/166) of patients in the avacopan group.
- At Week 52, 54.9% (90/164) of patients in the prednisone group achieved sustained remission compared to 65.7% (109/166) of patients in the avacopan group.
- For each comparison, the lower limit of the one-sided confidence interval for the difference in the percentage between the avacopan and the prednisone group exceeded the pre-specified non-inferiority margin of -20%, and the non-inferiority tests were highly statistically significant (P< 0.0001).

- The superiority test comparing the sustained remission rates at Week 52 between the avacopan group and the prednisone group was also statistically significant (P=0.0066).
- The efficacy observed was generally consistent across pertinent subgroups, i.e., those with newly diagnosed and relapsed disease, PR3 and MPO ANCA, GPA and MPA, those receiving cyclophosphamide and those receiving rituximab.

Secondary Endpoints

Study CL010_168 met the majority of its secondary endpoints.

- There were fewer ANCA-associated vasculitis relapses in the avacopan group compared to the prednisone group, with an estimated 54% reduction in risk of relapse in the avacopan group compared to the prednisone group.
- Glucocorticoid toxicity, as measured by the GTI-CWS as well as the GTI-AIS was reduced in the avacopan group compared to the prednisone group at both measured time points, Week 13 and Week 26.
- Health-related quality of life, as measured by the SF-36v2, as well as the EQ-5D-5L instrument, showed greater improvement in the avacopan group compared to the prednisone group. This was particularly evident in the physical component, but overall health also appeared to improve with avacopan whereas it largely remained unchanged in patients receiving prednisone.
- Renal function, based on eGFR improved more in the avacopan group compared to the prednisone group. This improvement was particularly evident in patients with Stage 4 kidney disease, i.e., a baseline eGFR < 30 mL/min/1.73 m^2.
- Albuminuria, based on UACR improved earlier in the avacopan group compared to the prednisone group. Decreasing albuminuria early may be beneficial in preserving renal function.
- Renal inflammation, as measured by urinary MCP-1:creatinine ratio improved more in the avacopan versus the prednisone group at Week 13, and to the same extent thereafter.
- The proportion of patients with BVAS=0 at Week 4 was similar between groups.
- Vasculitis Damage Index increased similarly in both treatment groups.

6.4.2 Efficacy Conclusions for Supportive Phase 2 Studies

Supportive data from the Phase 2 studies included the following:

- Study CL002_168 met its primary endpoint based on BVAS response at Week 12: The two avacopan treatment groups were non-inferior to the full dose prednisone group in terms of BVAS response at Week 12. Secondary endpoint results support the efficacy of avacopan.
- Results from Study CL003_168, in which avacopan, either 10 mg or 30 mg given twice daily, was given on top of full dose prednisone plus either rituximab or

cyclophosphamide showed, that the clinical response was high in all three treatment groups. Several secondary efficacy variables showed evidence of efficacy with avacopan treatment, including early remission, eGFR, and renal response.

7 CLINICAL SAFETY

Summary

- Regarding overall AEs in Phase 3 Study CL010_168:
  - Adverse events were reported in 98.2% (2139 events) of patients in the prednisone group compared to 98.8% (1779 events) in the avacopan group.
  - The incidence of SAEs was 45.1% (166 events) in the prednisone group vs. 42.2% (116 events) in the avacopan group.
  - Life-threatening SAEs were observed in 8.5% (22 events) of patients in the prednisone group and 4.8% (8 events) in the avacopan group.
  - There were 4 deaths in the prednisone group compared to 2 in the avacopan group.
- The incidence of AEs and SAEs assessed as possibly related to glucocorticoids was lower in the avacopan group compared to the prednisone group.
- Examining AEs of interest in Study CL010_168:
  - There were fewer events of infection and serious infection in the avacopan compared to the prednisone group. There were no *Neisseria meningitidis* infections in the avacopan clinical trials.
  - Adverse events of hepatic function test abnormalities were reported in 13.3% of patients in the avacopan group (5.4% serious) and 11.6% of patients in the prednisone group (3.7% serious).
  - Avacopan did not appear to increase the risk of leukopenia (neutropenia or lymphopenia) compared to prednisone; there were lower incidences of AEs of neutropenia or lymphopenia in the avacopan group (18.7%, with 2.4% serious) compared to the prednisone group (23.8%, with 4.9% serious).
  - Hypersensitivity events occurred in a similar percentage of patients in each treatment group. One SAE of angioedema was reported in the avacopan group and none in the prednisone group. Study medication was withdrawn. The patient recovered without sequelae.
- Results from the Phase 2 studies were generally consistent with results from the Phase 3 study.
- Overall safety conclusions:
  - Avacopan had a favorable safety profile based on the overall adverse event profile, glucocorticoid-related AEs, infection incidence, and WBC count adverse events.
  - Avacopan provides a lower toxicity profile compared to glucocorticoid treatment.

7.1 Treatment Exposure

Overall, the avacopan clinical development program included 1017 patients who received at least one dose of avacopan, with 239 patients in the Phase 2 and Phase 3 well-controlled studies in

patients with ANCA-associated vasculitis (Table 28). There were 212.3 patient-years of exposure in the Phase 2 and 3 studies in ANCA-associated vasculitis. The 166 patients in Phase 3 Study CL010_168 are the primary focus of the overview of clinical safety presented in this document. This study contains the largest population of patients with ANCA-associated vasculitis studied with avacopan for the longest period of time (12 months).

Avacopan has also been studied in patients with complement 3 glomerulopathy (N=57 patients; 28 receiving avacopan 30 mg twice daily for up to 52 weeks), hidradenitis suppurativa (N=398 patients; 268 receiving avacopan 10 mg or 30 mg twice daily for up to 36 weeks), IgA nephropathy (N=7, all receiving avacopan 30 mg twice daily for up to 12 weeks), and atypical hemolytic uremic syndrome (N=6, all receiving avacopan 30 mg twice daily for up to 2 weeks).

Table 28: Overall Avacopan Safety Exposure

Study	Patients Receiving Avacopan
Clinical pharmacology studies	206
Phase 2/3 Controlled studies	239
CL002_168	44
CL003_168	29
CL010_168	166
Compassionate Use/Uncontrolled studies	23
Other indications*	310
Total	1017

*HS and C3G Studies are ongoing

7.2 Overall Safety Profile

Phase 3 study CL010_168 was the largest study with the longest treatment duration in the avacopan development program. The Phase 2 studies were smaller, with an avacopan treatment period of only 12 weeks. Also, in one of the two Phase 2 studies (CL003_168), avacopan was tested in combination with a full dose of glucocorticoids. This design was different from the Phase 3 study, where avacopan was tested without the full dose of glucocorticoids. Therefore, the Phase 3 study made the largest contribution to understanding of the safety profile of avacopan.

Nevertheless, an integrated analysis across all Phase 2 and 3 studies in ANCA-associated vasculitis was performed. An overview of this integrated analysis is shown in Table 29.

Results from the integrated analysis showed that there was a similar incidence of AEs, severe AEs, SAEs, and withdrawal of study medication due to AEs in the two treatment groups. There was a lower incidence of life-threatening AEs and deaths in the avacopan compared to the prednisone group.

Table 29: Avacopan AE Overview Across All Phase 2 and 3 Studies in ANCA-Associated Vasculitis

	Avacopan (N=239) Patients n (%)	Prednisone (N=200) Patients n (%)
Adverse event (AE)	233 (98%)	195 (97%)
Severe AE	51 (22%)	45 (22%)
Serious AE	94 (40%)	82 (39%)
Life-threatening	10 (4%)	14 (6%)
Death	2 (1%)	4 (2%)
AEs leading to study medication discontinuation	35 (15%)	32 (16%)

n=number of subjects with at least one event. % is calculated as study-size adjusted percentages.
Separate weights are used for the three studies

7.3 Adverse Events: Pivotal Phase 3 Study CL010_168

7.3.1 Common Adverse Events

Adverse events were reported in 98.2% of patients (2139 events) in the prednisone group compared to 98.8% (1779 events) in the avacopan group (Table 30). The incidence of SAEs was 45.1% (166 events) in the prednisone group vs. 42.2% (116 events) in the avacopan group. Life-threatening SAEs were observed in 8.5% (22 events) of patients in the prednisone group and 4.8% (8 events) in the avacopan group. There were 4 deaths in the prednisone group (death of unknown cause, acute myocardial infarction, infectious pleural effusion, and generalized fungal infection) and 2 in the avacopan group (pneumonia and worsening of GPA). The percentage of patients who discontinued study medication due to an AE was similar between treatment arms.

Table 30: Study CL010_168: Avacopan Adverse Event Overview

	Avacopan (N=166)		Prednisone (N=164)	
	Patients n (%)	Events n	Patients n (%)	Events n
Adverse event (AE)	164 (98.8%)	1779	161 (98.2%)	2139
Severe AE	39 (23.5%)	71	41 (25.0%)	94
Serious AE (SAE)	70 (42.2%)	116	74 (45.1%)	166
Life-threatening	8 (4.8%)	8	14 (8.5%)	22
Death	2 (1.2%)		4 (2.4%)	
AEs leading to study medication discontinuation	27 (16.3%)		28 (17.1%)	

The AEs reported in at least 5% of patients in either treatment group are presented in Table 31. Nausea, headache, vomiting, and rash were reported more commonly in the avacopan group compared to the prednisone group (≥ 2% higher). Nausea and vomiting were reported predominantly in patients in the cyclophosphamide stratum. Only 1 patient discontinued study medication due to nausea and vomiting. Regarding rash, in the Phase 2 and Phase 3 studies combined, the incidence of rash was similar in the two treatment groups, with 22% in the avacopan group and 23% in the prednisone group.

Those AEs with a patient incidence ≥ 2% higher in the prednisone group compared with the avacopan group for AEs ≥ 5% in either treatment group were edema peripheral, arthralgia, anti-neutrophil cytoplasmic autoantibody positive vasculitis (worsening of vasculitis), nasopharyngitis, muscle spasms, back pain, myalgia, pyrexia, epistaxis, anemia, insomnia, hypercholesterolemia, urinary tract infection, alopecia, lymphopenia, oropharyngeal pain, bronchitis, dyspepsia, Cushingoid, and weight increased. Several of these AEs are likely related to glucocorticoid use.

Table 31: Study CL010_168: Most Commonly Reported AEs (≥ 5% of Patients)

	Avacopan (N=166)		Prednisone (N=164)		Total (N=330)	
Preferred Term	**Patients n (%)**	**Events n**	**Patients n (%)**	**Events n**	**Patients n (%)**	**Events n**
Any Treatment-Emergent Adverse Event	164 (98.8)	1779	161 (98.2)	2139	325 (98.5)	3918
Nausea	39 (23.5)	54	34 (20.7)	46	73 (22.1)	100
Edema peripheral	35 (21.1)	39	40 (24.4)	56	75 (22.7)	95
Headache	34 (20.5)	43	23 (14.0)	30	57 (17.3)	73
Arthralgia	31 (18.7)	42	36 (22.0)	48	67 (20.3)	90
Hypertension	30 (18.1)	36	29 (17.7)	31	59 (17.9)	67
Anti-neutrophil cytoplasmic antibody positive vasculitis[a]	26 (15.7)	30	34 (20.7)	46	60 (18.2)	76
Cough	26 (15.7)	31	26 (15.9)	29	52 (15.8)	60
Diarrhea	25 (15.1)	33	24 (14.6)	31	49 (14.8)	64
Nasopharyngitis	25 (15.1)	38	30 (18.3)	46	55 (16.7)	84
Vomiting	25 (15.1)	29	21 (12.8)	27	46 (13.9)	56
Upper respiratory tract infection	24 (14.5)	28	24 (14.6)	33	48 (14.5)	61
Rash	19 (11.4)	26	13 (7.9)	17	32 (9.7)	43
Muscle spasms	18 (10.8)	23	37 (22.6)	47	55 (16.7)	70
Fatigue	17 (10.2)	19	15 (9.1)	15	32 (9.7)	34
Back pain	16 (9.6)	16	22 (13.4)	22	38 (11.5)	38
Myalgia	16 (9.6)	17	22 (13.4)	25	38 (11.5)	42
Pyrexia	15 (9.0)	18	19 (11.6)	25	34 (10.3)	43
Epistaxis	14 (8.4)	21	21 (12.8)	30	35 (10.6)	51
Anemia	13 (7.8)	13	18 (11.0)	19	31 (9.4)	32
Insomnia	13 (7.8)	13	25 (15.2)	27	38 (11.5)	40
Pain in extremity	13 (7.8)	13	13 (7.9)	13	26 (7.9)	26
Hypercholesterolemia	12 (7.2)	13	20 (12.2)	21	32 (9.7)	34
Leukopenia	12 (7.2)	15	14 (8.5)	20	26 (7.9)	35
Urinary tract infection	12 (7.2)	19	23 (14.0)	33	35 (10.6)	52
Abdominal pain upper	11 (6.6)	12	10 (6.1)	13	21 (6.4)	25
Constipation	11 (6.6)	11	11 (6.7)	11	22 (6.7)	22
Dizziness	11 (6.6)	14	10 (6.1)	10	21 (6.4)	24
Pneumonia	11 (6.6)	12	11 (6.7)	11	22 (6.7)	23
Blood creatinine increased	10 (6.0)	10	8 (4.9)	10	18 (5.5)	20

Preferred Term	Avacopan (N=166)		Prednisone (N=164)		Total (N=330)	
	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
Pruritus	10 (6.0)	15	10 (6.1)	11	20 (6.1)	26
Sinusitis	10 (6.0)	10	12 (7.3)	12	22 (6.7)	22
Paresthesia	9 (5.4)	10	7 (4.3)	8	16 (4.8)	18
Dyspnea	8 (4.8)	11	11 (6.7)	14	19 (5.8)	25
Alopecia	7 (4.2)	7	12 (7.3)	12	19 (5.8)	19
Increased tendency to bruise	7 (4.2)	7	10 (6.1)	11	17 (5.2)	18
Lymphopenia	6 (3.6)	7	18 (11.0)	27	24 (7.3)	34
Oropharyngeal pain	6 (3.6)	7	12 (7.3)	12	18 (5.5)	19
Bronchitis	5 (3.0)	7	10 (6.1)	11	15 (4.5)	18
Dyspepsia	5 (3.0)	6	10 (6.1)	12	15 (4.5)	18
Cushingoid	3 (1.8)	3	9 (5.5)	9	12 (3.6)	12
Tremor	2 (1.2)	2	10 (6.1)	11	12 (3.6)	13
Weight increased	1 (0.6)	1	17 (10.4)	19	18 (5.5)	20

Note: An AE was considered treatment-emergent if the start date/time of the event was on or after the date/time of first dose of study medication. Adverse events were coded using MedDRA (version 19.1).
[a] Worsening of vasculitis is reported as the Preferred Term of "anti-neutrophil cytoplasmic antibody-positive vasculitis."

7.4 Deaths

No deaths occurred in the Phase 1 or Phase 2 studies. There were 7 deaths in the Phase 3 study, with 1 death occurring during the screening period (myocardial infarction). There were 4 patient deaths in the prednisone group and 2 deaths in the avacopan group (Table 32).

The AEs leading to death for the 2 patients in the avacopan group were granulomatosis with polyangiitis and pneumonia. Additional details regarding these patient deaths are as follows:

- Patient 1: A 70-year-old male with newly diagnosed PR3-positive GPA who died on Day 315 from severe worsening of morbus Wegener (GPA). The last dose of avacopan was taken on Day 236, 79 days before his death.
- Patient 2: The second avacopan patient was a 70-year-old woman with newly diagnosed, MPO-positive MPA, who died from broncho-pneumonia with *Aspergillus* superinfection on Day 160. Her last dose of avacopan was on Day 50.

Both events were assessed by the Investigator as probably not related to study medication.

Table 32: Study CL010_168: Deaths During Study

Patient	AE Leading to Death Preferred Term	Study Day of Last Dose of Study Drug	Study Day of Death
Avacopan			
1	Granulomatosis with polyangiitis	236	315
2	Pneumonia	50	160

Patient	AE Leading to Death Preferred Term	Study Day of Last Dose of Study Drug	Study Day of Death
Prednisone			
1	Death (unknown cause)	319	359
2	Acute myocardial infarction	113	160
3	Infectious pleural infusion	94	108
4	Diarrhea, Vomiting, Fungal infection	16	34

7.5 Serious Adverse Events: Pivotal Phase 3 Study CL010_168

Overall, 166 SAEs were reported in 74 patients in the prednisone group and 116 SAEs were reported by 70 patients in the avacopan group (Table 33). The most common SAE was anti-neutrophil cytoplasmic antibody positive vasculitis (worsening), including terms of granulomatosis with polyangiitis and microscopic polyangiitis, with 14.0% in the prednisone group and 10.2% in the avacopan group. This finding is consistent with the efficacy results.

SAEs of pneumonia (as a preferred term) occurred in 4.8% in the avacopan group compared to 3.7% in the prednisone group; when all AE terms indicating pneumonia were combined (i.e., pneumonia, pneumonia bacterial, atypical pneumonia, pneumonia cytomegaloviral, pneumonia haemophilus, lower respiratory tract infection), the incidence was approximately the same in the two treatment groups: 5.5% in the prednisone group and 5.4% in the avacopan group.

Regarding the cases of acute kidney injury, all cases resolved, and none were considered related to study medication by the Investigators.

Table 33: Study CL010_168: Incidence of SAEs (≥ 1% in Either Treatment Group)

Preferred Term	Avacopan (N=166)		Prednisone (N=164)	
	Patients n (%)	Events n	Patients n (%)	Events n
Any Serious Treatment-Emergent Adverse Event	70 (42.2)	116	74 (45.1)	166
Anti-neutrophil cytoplasmic auto-antibody positive vasculitis, granulomatosis with polyangiitis, or microscopic polyangiitis	17 (10.2)	17	23 (14.0)	28
Pneumonia	8 (4.8)	9	6 (3.7)	6
Acute kidney injury	3 (1.8)	3	1 (0.6)	2
Urinary tract infection	3 (1.8)	3	2 (1.2)	2
Angina pectoris	2 (1.2)	2	0 (0.0)	0
Cardiac failure	2 (1.2)	2	0 (0.0)	0
Device-related infection	2 (1.2)	2	0 (0.0)	0
Drug hypersensitivity	2 (1.2)	2	2 (1.2)	3
Hepatic enzyme increased	2 (1.2)	2	3 (1.8)	3
Hepatic function abnormal	2 (1.2)	2	0 (0.0)	0
Hyperglycemia	2 (1.2)	2	1 (0.6)	1
Influenza	2 (1.2)	2	1 (0.6)	1
Pyrexia	2 (1.2)	3	3 (1.8)	3
Acute myocardial infarction	1 (0.6)	1	2 (1.2)	2
Agranulocytosis	1 (0.6)	1	2 (1.2)	2

Preferred Term	Avacopan (N=166)		Prednisone (N=164)	
	Patients n (%)	Events n	Patients n (%)	Events n
Blood creatinine increased	1 (0.6)	1	2 (1.2)	2
Lymphopenia	1 (0.6)	1	3 (1.8)	3
Pulmonary alveolar hemorrhage	1 (0.6)	1	2 (1.2)	2
Anemia	0 (0.0)	0	2 (1.2)	2
Dehydration	0 (0.0)	0	2 (1.2)	2
Diarrhea	0 (0.0)	0	3 (1.8)	3
Epistaxis	0 (0.0)	0	2 (1.2)	2
Glomerulonephritis	0 (0.0)	0	2 (1.2)	2
Herpes zoster	0 (0.0)	0	2 (1.2)	2
Infectious pleural effusion	0 (0.0)	0	2 (1.2)	2
Large intestine polyp	0 (0.0)	0	2 (1.2)	2
Microscopic polyangiitis	0 (0.0)	0	2 (1.2)	2
Mononeuropathy multiplex	0 (0.0)	0	2 (1.2)	2
Neutropenia	0 (0.0)	0	2 (1.2)	2
Pneumonia bacterial	0 (0.0)	0	2 (1.2)	2
Prostate cancer	0 (0.0)	0	2 (1.2)	2
Pulmonary embolism	0 (0.0)	0	3 (1.8)	3
Respiratory syncytial virus infection	0 (0.0)	0	2 (1.2)	2
Thrombocytopenia	0 (0.0)	0	2 (1.2)	2
Vomiting	0 (0.0)	0	2 (1.2)	2

7.6 Adverse Events Leading to Discontinuation: Pivotal Phase 3 Study CL010_168

The protocol included criteria for pausing or stopping study medication for certain adverse events, including hepatic enzyme elevations, WBC count decreases, and creatine phosphokinase increases. These criteria are presented in Appendix 10.8.

The overall incidence of AEs leading to discontinuation of study medication were similar between treatment groups (Table 34), indicating that the AE profile is manageable and allows most patients to remain on study treatment. The most common AE leading to study medication discontinuation was anti-neutrophil cytoplasmic antibody positive vasculitis (worsening), with 4.9% in the prednisone group and 2.4% in the avacopan group.

The two cases of latent tuberculosis, not related to study medication, were identified based on screening results, which violated an exclusion criterion of the study. Study medication was stopped in both patients on Day 7. Therefore, there is no association of avacopan with latent tuberculosis in these cases.

Table 34: Study CL010_168: AEs Leading to Study Medication Discontinuation

AE ≥ 2 Patients	Avacopan (N=166)	Prednisone (N=164)
Any AE leading to discontinuation of study medication	27 (16.3)	28 (17.1)
Anti-neutrophil cytoplasmic antibody positive vasculitis	4 (2.4)	8 (4.9)
Hepatic function abnormal	3 (1.8)	0 (0.0)
Latent tuberculosis	2 (1.2)	0 (0.0)
Hepatic enzyme increased	1 (0.6)	2 (1.2)
Lymphopenia	0 (0.0)	3 (1.8)
Thrombocytopenia	0 (0.0)	2 (1.2)

7.7 Glucocorticoid Toxicity

The incidence of pre-identified AEs considered possibly related to glucocorticoid use based on EULAR search term criteria, a list of AEs recommended for monitoring in patients receiving glucocorticoid therapy (Duru et al., 2013), was significantly lower in the avacopan group (66.3%) compared to the prednisone group (80.5%) (Table 35). The 95% confidence intervals around the group differences of the adverse event terms that were clustered according to EULAR terms indicated that the incidence of dermatological and endocrine/metabolic events was higher in the prednisone group compared with the avacopan group. When evaluating individual adverse events, the difference between treatment groups was mainly due to adverse events of weight increase, insomnia, hyperlipidemia, adrenal insufficiency, blood glucose increase, and irritability. These are likely related to glucocorticoid use.

The incidence of SAEs considered possibly related to prednisone by the Investigators was 14.6% in the prednisone group compared with 6.6% in the avacopan group, mostly due to a higher incidence of infection-related events in the prednisone group compared to the avacopan group.

Table 35: Study CL010_168: Incidence of Glucocorticoid Toxicity Adverse Events

Category	Avacopan (N=166) n (%)	Prednisone (N=164) n (%)	Difference (%)	Difference (95% CI)
Any AE of Glucocorticoid use*	110 (66.3%)	132 (80.5%)	-14.2	-23.7, -3.8
Cardiovascular	72 (43.4%)	85 (51.8%)	-8.5	-19.2, 2.6
Dermatological	14 (8.4%)	28 (17.1%)	-8.6	-16.2, -1.0
Endocrine/Metabolic	23 (13.9%)	48 (29.3%)	-15.4	-24.3, -6.0
Gastrointestinal	3 (1.8%)	4 (2.4%)	-0.6	-4.6, 3.1
Infectious	22 (13.3%)	25 (15.2%)	-2.0	-9.9, 5.7
Musculoskeletal	19 (11.4%)	21 (12.8%)	-1.4	-8.7, 5.9
Ophthalmological	7 (4.2%)	12 (7.3%)	-3.1	-8.7, 2.1
Psychological	27 (16.3%)	39 (23.8%)	-7.5	-16.5, 1.3

*Adverse Events Considered Possibly Related to Glucocorticoids Based on EULAR Criteria

7.8 Creatine Phosphokinase (CPK) Increases

Adverse events of increased blood creatine phosphokinase occurred in 1 (0.6%) patient in the prednisone group and 6 (3.6%) patients in the avacopan group. A listing of these patients is presented in Table 36. Two of the 6 patients in the avacopan group had Grade 3 creatine phosphokinase elevations (>5-fold the upper limit of normal [ULN] to 10-fold the ULN). One of these two patients was taking pravastatin and the other colchicine. The other four patients had Grade 1 or 2 events. None of the AEs of increased creatine phosphokinase were serious, and there were no cases of rhabdomyolysis, myositis, or cardiac events associated with these creatine phosphokinase increases. In 4 of 6 cases, avacopan was continued throughout the event with no consequences.

Table 36: Study CL010_168: Listing of Patients with Adverse Events of Blood Creatine Phosphokinase Increased

Subject Number / Age / Sex	Start Day of Adverse Event	Severity	Highest CPK CTCAE Grade	TEAEs in Proximity to CPK Elevation	Outcome	Action Taken with Study Medication	Relatedness per Investigator
Prednisone Group							
1 / 67 / M	Day 28	Moderate	1	Muscle spasms, blepharitis, blood lactate dehydrogenase increased	Resolved Day 92	None	Possibly related
Avacopan Group							
2 / 77 / M	Day 225	Mild	2	Bone pain, anxiety, rash, ear discomfort	Ongoing	None	Possibly related
3 / 43 / M	Days 92, 246	Mild, mild	3	Viral upper respiratory tract infection, myalgia, fatigue	Resolved Day 99, resolved Day 261	Interrupted for both events	Probably not related, possibly related
4 / 74 / F	Day 49	Moderate	2	Painful dry nose, joint pains, worse dry cough, painful dry eyes	Resolved Day 141	None	Possibly related
5 / 49 / M	Day 30	Severe	3	Amylase increased, lipase increased	Ongoing	Discontinued	Probably not related
6 / 51 / M	Day 93, 276	Mild, mild	1	Back pain	Resolved Day 225, ongoing	None for both events	Probably not related, probably not related
7 / 74 / M	Day 113	Mild	1	Blood lactate dehydrogenase increased, diarrhea	Ongoing	None	Probably not related

CPK=creatine phosphokinase; CTCAE=Common Terminology Criteria of Adverse Event; F=female; M=male; ULN=upper limit of normal
* CTCAE Grade:
Grade 1: >ULN – 2.5 x ULN
Grade 2: >2.5 x ULN – 5 x ULN
Grade 3: >5 x ULN – 10 x ULN

7.9 Pre-Specified Adverse Events of Interest: Pivotal Phase 3 Study CL010_168

Pre-specified AEs of interest included:

- Infection

- Hepatic Events
- WBC Abnormalities (Neutropenia/Lymphopenia)
- Hypersensitivity

7.9.1 Infection

A lower incidence of AEs of infection, SAEs of infection, opportunistic infections, AEs leading to study withdrawal, life-threatening AEs, and infections resulting in death were observed in the avacopan group compared to the prednisone group (Table 37). Serious AEs of infection were reported in 15.2% of patients in the prednisone group (31 events) compared to 13.3% of the avacopan group (25 events). There was an approximately 25% higher number of infection events and 24% higher number of serious infection events reported in the prednisone group compared to the avacopan group. The incidence of severe AEs of infection was similar between the treatment groups (6.1% in the prednisone group and 7.2% in the avacopan group). Among the most common AEs of infection, the incidence rates were generally higher in the prednisone group.

When all AE terms of "pneumonia" were considered (i.e., pneumonia, pneumonia bacterial, atypical pneumonia, pneumonia cytomegaloviral, pneumonia haemophilus, lower respiratory tract infection), serious pneumonia was reported in 5.5% in the prednisone group and 5.4% in the avacopan group. Serious herpes zoster, infectious pleural effusion, and respiratory syncytial virus infection were each reported in 2 patients (1.2%) in the prednisone group and none in the avacopan group.

Two device-related serious infections were reported in the avacopan group: one patient had a permcath infection and another had a central venous catheter-related infection. Neither infection was considered related to avacopan by the Investigator, and both resolved with no action taken regarding study medication.

No *Neisseria meningitidis* infections were observed.

Table 37: Study CL010_168: Incidence of Infections

Category	Avacopan (N=166) n (%)	Prednisone (N=164) n (%)
Any Treatment-Emergent Infection Number of Events	113 (68.1) 233 events	124 (75.6) 291 events
Any Serious Treatment-Emergent Infection Number of Events	22 (13.3) 25 events	25 (15.2) 31 events
Any Severe Treatment-Emergent Infection	12 (7.2)	10 (6.1)
Any Treatment-Emergent Infection Leading to Study Withdrawal	4 (2.4)	5 (3.0)
Any Treatment-Emergent Life-threatening Infection	1 (0.6)	2 (1.2)
Any Treatment-Emergent Infection Leading to Death	1 (0.6)	2 (1.2)
Most common AEs of infection (≥ 5% in any treatment group)		
Nasopharyngitis	25 (15.1)	30 (18.3)
Upper respiratory tract infection	24 (14.5)	24 (14.6)
Urinary tract infection	12 (7.2)	23 (14.0)
Pneumonia	11 (6.6)	11 (6.7)
Sinusitis	10 (6.0)	12 (7.3)
Bronchitis	5 (3.0)	10 (6.1)
Most common serious AEs of infection (≥ 1% [2 patients] in any treatment group)		

Category	Avacopan (N=166) n (%)	Prednisone (N=164) n (%)
Pneumonia	8 (4.8)	6 (3.7)
Urinary tract infection	3 (1.8)	2 (1.2)
Device related infection	2 (1.2)	0 (0)
Influenza	2 (1.2)	1 (0.6)
Herpes zoster	0 (0)	2 (1.2)
Infectious pleural effusion	0 (0)	2 (1.2)
Pneumonia bacterial	0 (0)	2 (1.2)
Respiratory syncytial virus infection	0 (0)	2 (1.2)

The incidence of any serious opportunistic infection was higher in the prednisone group, at 6.7%, compared to 3.6% in the avacopan group (Table 38). Serious fungal infections occurred in 4 patients in the prednisone group and 2 in the avacopan group.

Table 38: Study CL010_168: Serious Opportunistic Infections

Category	Avacopan (N=166) n (%)	Prednisone (N=164) n (%)
Any Serious Opportunistic Infection	6 (3.6%) 8 events	11 (6.7%) 12 events
Fungal infection, including Aspergillus, Cryptococcus, or Candida	2 (1.2%)	4 (2.4%)
Respiratory syncytial virus	1 (0.6%)*	2 (1.2%)
Herpes zoster	0 (0%)	2 (1.2%)
Ophthalmic Herpes simplex	0 (0%)	1 (0.6%)
Cytomegalovirus pneumonia	0 (0%)	1 (0.6%)
Metapneumovirus	0 (0%)	1 (0.6%)
Pneumonia with Chlamydia positive culture	1 (0.6%)	0 (0%)
Campylobacter gastroenteritis	1 (0.6%)	0 (0%)
Hepatitis B reactivation	1 (0.6%)	0 (0%)

* Identified from nasopharyngeal swabs; 3 blood cultures negative.

7.9.2 Hepatic Events

Transaminase increases are common in patients with ANCA-associated vasculitis treated with cyclophosphamide/azathioprine plus glucocorticoids or rituximab plus glucocorticoids, without avacopan. Alanine aminotransferase (ALT) increases were reported in 15.2% of patients in the rituximab group and 22.5% of subjects in the cyclophosphamide group in the RAVE study (clinicaltrials.gov NCT00104299). Aspartate aminotransferase (AST) increases were reported in 11.1% of patients in the rituximab group and 16.3% of patients in the cyclophosphamide group in the RAVE study. All patients in this study received pneumocystis prophylaxis for *Pneumocystis jerovecii*, typically co-trimoxazole, which has known hepatic liabilities.

In study CL010_168, there were 19 patients (11.6%) in the prednisone group and 22 patients (13.3%) in the avacopan group who had hepatic function test abnormality AEs over the course of the study (Table 39). Hepatic function test SAEs were reported for 6 (3.7%) patients in the prednisone group and 9 (5.4%) patients in the avacopan group. A listing of all patients with hepatic function test SAEs are provided in Table 40.

The age range was 54 to 81 years among patients with SAEs in the avacopan group, and 8 of 9 patients were female. Six of 9 patients received IV cyclophosphamide. The median time to the event was 50 days (range 23 to 131 days). Alkaline phosphatase was initially elevated in 8 of 9 patients.

Of the SAEs, Grade 4 elevations in ALT or AST (> 20x the upper limit of normal [ULN]) occurred in 2 patients in the prednisone group (Patients 2 and 4) and 1 patient in the avacopan group (Patient 8). The rest of the cases were Grade 2 or 3. Bilirubin increases occurred in 1 patient (Patient 4) in the prednisone group and 2 in the avacopan group (Patients 8 and 15), described below.

- Patient 8 in the avacopan group, a 62-year old woman with a medical history of hepatitis A, Epstein Barr virus, cytomegalovirus infection, had an adverse event of diarrhea on Day 65, followed by a gradual increase in transaminases starting on Day 113. Study medication was stopped on Day 147. Liver enzymes continued to increase after avacopan was stopped and peaked on Day 161. The patient had serious adverse events of agranulocytosis with neutropenia on Day 155, and monocytes were elevated. A viral etiology could not be excluded. The patient received approximately 18 different medications over the course of the study; these include co-trimoxazole, acetaminophen, carvidelol, telmisartan, metformin, esomeprazole, and Inegy (ezetimibe/simvastatin), and repaglinide at the time of the event. The hepatic function disorder resolved on Day 225.
- Patient 15 in the avacopan group, an 81-year old woman had transaminase and alkaline phosphatase elevations starting on Day 43. Study medication was stopped on Day 43. Bilirubin was slightly elevated on Day 44 (1.7 mg/dL; reference range 0.4-1.5 mg/dL). Hepatitis B DNA assay was positive on Day 50. The event resolved by Day 113.

Study medication was interrupted on Day 37 in Patient 9 in the avacopan group, but was re-started on Day 43, prior to normalization of the liver enzymes. Liver enzymes increased and study medication was stopped on Day 50. The patient also had adverse events of diarrhea, cholestasis, and pancreatic failure.

All patients with hepatic events recovered with withdrawal of study medication and other potentially hepatotoxic drugs.

Due to the serious and life-threatening nature of ANCA-associated vasculitis, these patients are frequently monitored as part of routine medical practice. This includes liver function test measurements. Therefore, liver function test abnormalities can be detected early and appropriate action taken.

In summary, the adverse event rate of liver function test abnormalities in Phase 3 study CL010_168 was not higher than other studies such as RAVE. The events in the 9 patients with SAEs in the avacopan group occurred within 20 weeks of starting treatment, occurred mostly in women, and two-thirds were also receiving IV cyclophosphamide. Confounding factors were present in all 9 patients. All patients recovered. None of the AEs resulted in hepatic failure and there were no fatal hepatic events.

Table 39: Study CL010_168: Summary of Hepatic Function Test Abnormalities

Category	Avacopan (N=166) n (%)	Prednisone (N=164) n (%)
Any AE of Hepatic Function Test Abnormalities	22 (13.3%)	19 (11.6%)
Study medication paused or discontinued due to AE	9 (5.4%)	5 (3.0%)
Any serious AE	9 (5.4%)	6 (3.7%)

Table 40: Study CL010_168: Listing of All Patients with Serious Hepatic Function Test Adverse Events

Patient Number / Age / Sex	Treatment Group / Stratum	Reported Adverse Event	Start Day	ALT / AST / ALP / Bilirubin Grade*	Relatedness (per Investigator)	Action Taken with Study Medication / Outcome	Confounding Factors
1 / 60 / M	Prednisone / RTX	Transaminitis	28	3 / 1 / N / N	Possibly related	Interrupted / Resolved	Co-trimoxazole
2 / 81 / F	Prednisone / RTX	Hepatic cytolysis	72	4 / 3 / 2 / N	Probably not related	NA / Resolved	Co-trimoxazole
3 / 76 / F	Prednisone / CYC IV	Worsening of increased AST, Worsening of increased ALT	10, 10	2 / 3 / N / N	Probably not related	None / Resolved	Co-trimoxazole; Baseline elevated ALT, AST; fatty liver
4 / 70 / M	Prednisone / RTX	Increase of liver enzymes	92	4 / 3 / 1 / 2	Probably not related	Discontinued / Resolved	Co-trimoxazole (+ rechallenge)
5 / 49 / F	Prednisone / RTX	Elevation of liver enzymes	28	3 / 2 / 1 / N	Probably not related	Discontinued / Resolved	Hepatic steatosis
6 / 63 / M	Prednisone / CYC IV	Worsening of hepatic enzymes increased	8	3 / 3 / N / N	Possibly related	NA / Resolved	Cholelithiasis; Common bile duct stone
7 / 65 / F	Avacopan / CYC IV	Elevated liver function tests	50	3 / 2 / 2 / N	Possibly related	Discontinued / Resolved	Cyclophosphamide, cephalexin
8 / 62 / F	Avacopan / RTX	Hepatic function disorder	114	4 / 4 / 1 / 4	Possibly related	Discontinued / Resolved	History Hep A, EBV, CMV; agranulocytosis; co-trimoxazole, ezetimibe/ simvastatin, metformin, acetaminophen, repaglinide
9 / 80 / F	Avacopan / RTX	Hepatic cytolysis	37	3 / 2 / 2 / N	Possibly related	Discontinued / Resolved	Co-trimoxazole, paracetamol; diarrhea, cholestasis, and pancreatic failure
10 / 54 /F	Avacopan / CYC IV	Cytolytic hepatitis, Cholestatic hepatitis	93, 93	3 / 3 / N / N	Possibly related	Discontinued / Resolved	Cyclophosphamide
11 / 81 / F	Avacopan / CYC IV	Azathioprine-induced liver toxicity	131	3 / 3 / 2 / N	Probably not related	None / Resolved	Azathioprine, co-trimoxazole; elevated ALT, AST at screening

Patient Number / Age / Sex	Treatment Group / Stratum	Reported Adverse Event	Start Day	ALT / AST / ALP / Bilirubin Grade*	Relatedness (per Investigator)	Action Taken with Study Medication / Outcome	Confounding Factors
12 / 68 / M	Avacopan / CYC IV	Elevated AST values >5XULN	50	2 / 3 / 1 / N	Probably not related	None / Resolved	Cyclophosphamide; Biliary tract dilatation; cholecystectomy
13 / 79 / F	Avacopan / CYC IV	Elevated liver enzymes	103	2 / 3 / 1 / N	Possibly related	Discontinued / Resolved	Co-trimoxazole, cyclophosphamide; elevated ALT, AST at baseline
14 / 68 / F	Avacopan / RTX	Alcoholic hepatic enzyme elevation	23	3 / 1 / 2 / N	Probably not related	None / Resolved	Alcohol, fatty liver, Hep B history
15 / 81 / F	Avacopan / CYC IV	Liver dysfunction	43	3 / 2 / 2 / 1	Possibly related	Discontinued / Resolved	Cyclophosphamide, Hep B DNA assay positive

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CMV=cytomegalovirus; CYC IV=cyclophosphamide intravenously; EBV=Epstein Barr virus; F=female; Hep A=hepatitis A; Hep B=hepatitis B; M=male; N=normal; NA=not applicable; RTX=rituximab; ULN=upper limit of normal

* CTCAE Grade:
ALT and AST:
Grade 1: >ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Grade 2: >3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Grade 3: >5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4: >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Bilirubin:
Grade 1: >ULN - 1.5 x ULN if baseline was normal; 1.0 - 1.5 x baseline if baseline was abnormal
Grade 2: >1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal
Grade 3: >3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal
Grade 4: >10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
ALP:
Grade 1: >ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal
Grade 2: >2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal
Grade 3: >5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4: >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

7.9.3 WBC Abnormalities (Neutropenia/Lymphopenia)

The incidence of AEs potentially associated with neutropenia or lymphopenia was lower in the avacopan group than in the prednisone group; 23.8% of patients in the prednisone group and 18.7% in the avacopan group, respectively, had AEs associated with low white blood cell counts (Table 41). Of these events, 8 patients in the prednisone group reported SAEs, compared to 4 patients in the avacopan group. A listing of these patients is presented in Table 42.

Based on central laboratory data, the majority of the white blood cell count AEs were grades 1 or 2. As anticipated based on the mechanism of action of rituximab and cyclophosphamide, lymphopenia was commonly observed in both treatment groups. Grade 3 lymphopenia events were observed in a similar number of patients in the two treatment groups. However, Grade 4 lymphopenia events occurred in 7.9% of patients in the prednisone group and 2.4% of patients in the avacopan group. Grade 3 or 4 neutropenia occurred at a similar incidence between treatment groups. There did not appear to be a greater risk of neutropenia or lymphopenia with avacopan treatment.

Table 41: Study CL010_168: Neutropenia and Lymphopenia Events

Category		Avacopan (N=166) n (%)	Prednisone (N=164) n (%)
Any AE of WBC count decrease		31 (18.7%)	39 (23.8%)
Any SAE of WBC count decrease		4 (2.4%)	8 (4.8%)
Leukopenia	Grade 3	1 (0.6%)	3 (1.8%)
	Grade 4	0 (0%)	0 (0%)
Lymphopenia	Grade 3	47 (28.3%)	49 (30.1%)
	Grade 4	4 (2.4%)	13 (8.0%)
Neutropenia	Grade 3	4 (2.4%)	2 (1.2%)
	Grade 4	0 (0%)	2 (1.2%)

Leukopenia Grade 3: <2 to 1 x 10^3/µL; Grade 4: <1 x 10^3/µL
Lymphopenia Grade 3: <0.5 to 0.2 x 10^3/µL; Grade 4: <0.2 x 10^3/µL
Neutropenia Grade 3: <1 to 0.5 x 10^3/µL; Grade 4: <0.5 x 10^3/µL

Table 42: Study CL010_168: Listing of All Patients with Serious Adverse Events Potentially Associated with Neutropenia or Lymphopenia

Subject Number / Age / Sex	Treatment Group / Stratum	Reported Adverse Events	Start Day	Relatedness (per Investigator)	Action taken with study medication	Outcome
1 / 59 / M	Prednisone / RTX	Neutropenia	91	No	NA	Resolved
2 / 57 / M	Prednisone / CYC IV	Bone marrow toxicity, Lymphopenia, Bone marrow suppression	141, 141, 155	No for all 3 events	None for all 3 events	Resolved, ongoing, resolved
3 / 65 / M	Prednisone / CYC PO	Low lymphocytes	24	No	None	Resolved
4 / 88 / M	Prednisone / RTX	Febrile agranulocytosis	115	Yes	None	Resolved
5 / 67 / F	Prednisone / RTX	Drug induced agranulocytosis	60	No	Interrupted	Resolved
6 / 81 / F	Prednisone / RTX	Lymphopenia	8	Yes	Discontinued	Resolved
7 / 68 / F	Prednisone / RTX	Lymphopenia, Neutropenia (secondary to rituximab versus febuxostat/colchicine toxicity)	7, 231	No for both events	None for both events	Resolved (both)
8 / 65 / F	Prednisone / CYC IV	Febrile neutropenia	148	No	None	Resolved
9 / 61 / M	Avacopan / RTX	Neutropenic fever	179	No	Discontinued	Resolved
10 / 62 / F	Avacopan / RTX	Agranulocytosis	155	Yes	NA	Resolved
11 / 43 / M	Avacopan / CYC IV	Lymphopenia	265	No	None	Resolved
12 / 66 / F	Avacopan / CYC PO	Neutropenic sepsis of unknown source	59	No	None	Resolved

CYC IV=cyclophosphamide intravenously; CYC PO=cyclophosphamide orally F=female; M=male; NA=not applicable; RTX=rituximab

7.9.4 Hypersensitivity

Patients with ANCA-associated vasculitis are often on multiple medications, which may cause hypersensitivity reactions. Hypersensitivity events occurred in a similar percentage of patients in each treatment group (Table 43). The majority of these events occurred in the Skin and

Subcutaneous Tissue Disorders system organ class. Rash was the most common hypersensitivity AE, observed in 7.9% of the prednisone group and 11.4% in the avacopan group. An analysis was done combining all terms in the Standardized MedDRA Query for hypersensitivity denoting skin rash in all Phase 2 and 3 studies. Results showed that the overall patient incidence of rash in the Phase 2 and Phase 3 studies combined was similar in the two treatment groups: 21.5% in the avacopan group and 22.7% in the prednisone group. Therefore, avacopan was not associated with a higher risk of skin rash.

Two hypersensitivity SAEs, angioedema and skin necrosis, were reported in the Skin and subcutaneous tissue disorders system organ class in the avacopan group. The patient with angioedema was a 35-year old man, who initially had urticaria on Day 32, a strange sensation when swallowing on Day 33, and a spreading itchy rash. Study medication was withdrawn, the patient was treated with glucocorticoids and anti-histamines, and he recovered without sequelae. The event of skin necrosis was not considered to be a hypersensitivity reaction to avacopan (necrotic ulcer left foot due to secondary infection of purpura). One additional patient had an AE of angioedema. Study medication was paused and the event resolved. Study medication was restarted and the event did not recur. The reported hypersensitivity events were manageable.

Table 43: Study CL010_168: Incidence of Hypersensitivity

Category	Avacopan (N=166) n (%)	Prednisone (N=164) n (%)
Any AE of Hypersensitivity*	68 (41.0%)	70 (42.7%)
Skin and Subcutaneous Tissue Disorders	51 (30.7%)	55 (33.5%)
Rash	19 (11.4%)	13 (7.9%)
Any serious AE	2 (1.2%)	0 (0%)

*Based on the Standardised MedDRA Query for hypersensitivity

7.10 Adverse Events: Pooled Phase 2 Studies

An overview of AEs in the pooled Phase 2 studies is presented in Table 44. When reviewing the pooled Phase 2 study data, it is important to keep in mind that:

- There are approximately 2-fold more patients in the avacopan group (73 patients) compared to the prednisone group (36 patients),
- The number of patients in Phase 2 was smaller (N=109) than in the Phase 3 study (N=330),
- The treatment period in the two Phase 2 studies was much shorter (12 weeks) compared to the Phase 3 study (52 weeks), and
- In one of the two Phase 2 studies (CL003_168), all patients in the avacopan groups also received a full dose of prednisone.

The proportion of patients with at least one AE was similar in the avacopan (94.5%) and prednisone (94.4%) groups. A majority of patients in both treatment groups experienced AEs with a maximum severity of mild or moderate. The proportion of patients with severe AEs, as

assessed by the Investigator, was 16.4% in the avacopan group and 11.1% in the prednisone group and life-threatening AEs were observed in 2 patients (2.7%) in the avacopan group (late onset neutropenia, considered related to rituximab by the Investigator, and sepsis, related to biliary tract stricture following a Whipple procedure) compared to 0 in the prednisone group. The incidence of AEs leading to discontinuation of study drug was 11% in both treatment groups.

Overall, 13 SAEs were reported by 8 patients (22.2%) in the prednisone group and 34 SAEs were reported by 24 patients (32.9%) in the avacopan group. Although the incidence of SAEs was higher in the avacopan group compared to the prednisone group, the only system organ classes (SOCs) with a ≥ 2% higher incidence of SAEs in the avacopan compared to the prednisone group were Vascular Disorders and Investigations. Within the Vascular Disorders SOC, vasculitis (worsening) was reported in 4 of 73 patients (5.5%) in the avacopan group compared to 1 of 36 (2.8%) in the prednisone group. However, when all adverse events of vasculitis (including renal vasculitis, vasculitis, microscopic polyangiitis, anti-neutrophil cytoplasmic antibody positive vasculitis [worsening]) were considered across both Phase 2 studies, vasculitis was reported in 4 of 73 patients (5.5%) in the avacopan group compared to 3 of 36 patients (8.3%) in the prednisone group. Within the Investigations SOC, C-reactive protein increase was reported in 2 of 73 patients (2.7%) in the avacopan group and none in the prednisone group. Neither of these two events in the avacopan group were considered related to study medication by the Investigators, no action was taken regarding study medication for the events, and the patients continued in the study.

No patients died during the Phase 2 studies.

Table 44: Overview of the Patient Incidence of Treatment-Emergent Adverse Events – Phase 2 Pooled Safety Population

Category	Avacopan (N=73) n (%)	Prednisone (N=36) n (%)
Treatment-emergent adverse event	69 (94.5)	34 (94.4)
Maximum severity of AE		
Mild	21 (28.8)	15 (41.7)
Moderate	34 (46.6)	15 (41.7)
Severe	12 (16.4)	4 (11.1)
Life-threatening	2 (2.7)	0 (0)
Death	0 (0)	0 (0)
Serious AE	24 (32.9)	8 (22.2)
AEs leading to study medication discontinuation	8 (11.0)	4 (11.1)

AE=adverse event; N=number of patients randomized to treatment group in the pooled Phase 2 Safety Population; n=number of patients in specified category.

7.11 Safety Conclusions

As a first-in-class, small molecule, selective C5aR inhibitor, avacopan appeared to be well tolerated by patients with ANCA-associated vasculitis.

To date, avacopan studies have included more than 1200 participants, 440 of whom had ANCA-associated vasculitis, with a total of 212.3 patient-years of exposure to avacopan.

In the largest avacopan clinical trial in ANCA-associated vasculitis, Phase 3 Study CL010_168, 331 patients were enrolled, of whom 166 patients received avacopan for up to 52 weeks.

- The prednisone group had a higher AE rate and SAE rate compared to the avacopan group.
- The percentage of patients experiencing an AE leading to discontinuation of study medication was similar in the two treatment groups (16.3% in the avacopan group and 17.1% in the prednisone group).
- Reduction in glucocorticoid toxicity as demonstrated by the GTI was consistent with a lower incidence of AEs and SAEs assessed as possibly related to glucocorticoids in the avacopan group compared to the prednisone group.
- Patients in the avacopan group had a lower rate of infections, serious infections, serious opportunistic infections, life-threatening infections, and fatal infections compared to the prednisone group.
- Hepatic function test abnormalities occurred in 13.3% of patients in the avacopan group and 11.6% of patients in the prednisone group. Hepatic function test SAEs were reported in 5.4% of patients in the avacopan group and 3.7% of patients in the prednisone group. Causality assessment was confounded by the presence of other known hepatotoxic drugs, such as co-trimoxazole, azathioprine, and alcohol, as well as potential viral etiologies.
- Avacopan did not appear to increase the risk of leukopenia (neutropenia or lymphopenia) compared to prednisone; there were lower incidences of AEs and SAEs of neutropenia and lymphopenia in the avacopan group compared to the prednisone group.
- Hypersensitivity events occurred in a similar percentage of patients in each treatment group (41.0% in the avacopan group and 42.7% in the prednisone group). One patient in the avacopan group had an SAE of angioedema, which resolved with withdrawal of study medication.
- There was a higher patient incidence of elevated creatine phosphokinase in the avacopan group compared to the prednisone group. These events were not serious and not associated with rhabdomyolysis, myositis, or cardiac events.

Results from the Phase 2 studies were generally consistent with results from the Phase 3 study.

8 BENEFIT-RISK CONCLUSIONS

8.1 Benefits

Results from the Phase 3 pivotal study showed clinically meaningful and statistically significant efficacy of avacopan in the treatment of patients with active ANCA-associated vasculitis.

Both pre-specified primary endpoints of remission at Week 26 and sustained remission at Week 52 in this Phase 3 study were met.

The majority of secondary efficacy endpoints were achieved with the avacopan group showing superiority compared to the prednisone group. There was a lower incidence of relapses in the avacopan group compared to the prednisone group. Statistically significant reduction in glucocorticoid-related toxicity, a common burden for patients being treated for ANCA-associated vasculitis, was observed in the avacopan group compared to the prednisone group based on the Glucocorticoid Toxicity Index (GTI) assessments. Reduction in glucocorticoid toxicity as demonstrated by the GTI was consistent with a lower incidence of adverse events and serious adverse events possibly related to glucocorticoids in the avacopan group compared to the prednisone group.

Greater improvements in health-related quality of life based on the Short Form 36 and EQ-5D-5L instruments were also observed in the avacopan group compared to the prednisone group.

Kidney function, as measured by estimated glomerular filtration rate, was improved more in the avacopan group compared to the prednisone group. Albuminuria improved earlier in the avacopan group compared to the prednisone group.

In summary, the avacopan group demonstrated superior efficacy compared to the prednisone group based on sustained remission at Week 52, relapse rate, health-related quality of life measurements, and renal function, coupled with lower toxicity associated with glucocorticoid use.

The results from Study CL010_168 are highly relevant clinically. Unmet needs in the treatment of patients with ANCA-associated vasculitis include high relapse rate, high toxicity often associated with high dose and chronic glucocorticoid use, limited efficacy of renal function (with renal impairment being one of the most common manifestations of ANCA-associated vasculitis), and poor health-related quality of life, including impaired physical function, fatigue, and poor general health status. Results from our Phase 3 study showed that avacopan treatment without daily prednisone dosing was effective in addressing these unmet needs:

- There was a high sustained remission rate at Week 52 with a low relapse rate,
- Significantly lower toxicity associated with glucocorticoids,
- Albuminuria was corrected rapidly and renal function (based on eGFR) improved continuously throughout the 52-week treatment period, and

- Health-related quality of life, especially the physical aspects, improved significantly more in the avacopan compared to the prednisone group.

8.2 Risks

Overall, the safety profile of avacopan is favorable, and avacopan was generally well tolerated in patients with ANCA-associated vasculitis. The incidence of SAEs, life-threatening adverse events, and deaths was numerically lower in the avacopan group compared to the prednisone group.

Overall, there was a higher number of SAEs in the prednisone group compared to avacopan (166 events reported by 74 patients [45.1%] in the prednisone group compared to 116 events in 70 patients [42.2%] in the avacopan group).

There were 4 deaths in the prednisone group (generalized fungal infection, infectious pleural effusion, death of unknown cause, and acute myocardial infarction) and 2 in the avacopan group (worsening of granulomatosis with polyangiitis and pneumonia). The 2 deaths in the avacopan group occurred while the patients were off avacopan for at least 79 days.

The incidence of infections overall, fatal infections, life-threatening infections, serious infections, and serious opportunistic infections was lower in the avacopan group compared to the prednisone group in Phase 3. There were no *Neisseria meningitidis* infections in the avacopan clinical trials.

Among the most common adverse events (≥ 5%), headache, nausea, and vomiting were observed more commonly in patients in the avacopan group. These were generally not serious and patients did not discontinue study medication for these AEs. Adverse events of creatine phosphokinase increase was observed more commonly in the avacopan group, but were not serious and were not associated with adverse clinical manifestations.

The incidence of SAEs of increased hepatic function tests was higher in the avacopan group compared to the prednisone group (5.4% vs 3.7%). Causality assessment was confounded by numerous concomitant factors, e.g., concomitant hepatotoxic drugs such as co-trimoxazole (given to patients for pneumocystis prophylaxis), azathioprine, alcohol, and potential viral etiologies. All these patients recovered. These events can be managed with close monitoring, which is already part of standard medical care of patients with ANCA-associated vasculitis.

One SAE of angioedema was observed in the avacopan group. Avacopan treatment was discontinued. The event resolved without sequelae.

There was a lower incidence of AEs and serious AEs associated with low WBC counts in the avacopan group compared with the prednisone group. Grade 4 lymphopenia and neutropenia were observed more commonly in the prednisone group compared with the avacopan group (8.0% vs 2.4%, respectively, for Grade 4 lymphopenia, and 1.2% vs 0%, respectively, for Grade 4 neutropenia).

The incidence of AEs and SAEs considered possibly related to prednisone by the Investigators was also higher in the prednisone group compared to the avacopan group.

In summary, several safety aspects showed a lower toxicity profile in the avacopan group compared to the prednisone group. The adverse events identified as having a higher incidence in the avacopan group compared to the prednisone group could be monitored readily to ensure safe administration of avacopan.

8.3 Benefit-Risk Assessment

Avacopan was shown to be an effective and safe treatment for patients with active ANCA-associated vasculitis and was also able to substantially reduce the need for daily glucocorticoid treatment. Superior efficacy was achieved with avacopan in several aspects, without glucocorticoid-associated toxicities, including having an impact on how a patient feels, functions, and survives. Avacopan offers a therapy that is an improvement in treatment in many areas of concern to physicians and patients and may provide a valuable asset in the armamentarium of treatments for patients with ANCA-associated vasculitis. Based on the nonclinical and clinical study results accumulated to date, the potential benefits of avacopan in patients with ANCA-associated vasculitis outweigh the potential risks. Given the status of ANCA-associated vasculitis as a serious, potentially organ- and life-threatening orphan disease, the discovery and development of avacopan as a potential treatment addresses important unmet patient needs.

8.4 Clinical Relevance of Results in CL010_168

The results from study CL010_168 are highly relevant clinically. Results showed that avacopan treatment without daily prednisone dosing was statistically not inferior to a daily prednisone tapering regimen regarding clinical remission of acute vasculitis signs and symptoms within the first 26 weeks. The Phase 3 data demonstrate that avacopan was effective in both the rituximab and the cyclophosphamide background medication strata. The safety profile of avacopan during the first 26 weeks was favorable compared to the prednisone group. This is clinically relevant because treating physicians and their patients have been expressing a need for alternatives to glucocorticoids for decades.

Secondly, results from study CL010_168 also showed that the avacopan group was statistically superior compared to the prednisone group in maintaining remission through Week 52. The data demonstrate that avacopan was effective in both the rituximab and the cyclophosphamide strata with the safety profile of avacopan during the last 26 weeks also favoring the avacopan group.

Of note, avacopan as a single agent (without any immunosuppressant treatment) was effective compared to placebo in maintaining remission (observed in the rituximab stratum). This is also highly relevant clinically, because it shows that once remission has been accomplished, remission could be maintained on avacopan alone.

Thirdly, results from the secondary endpoints pertaining to glucocorticoid toxicity, renal function, health-related quality of life, and relapses are consistent with the primary efficacy

endpoints. These results are also clinically relevant because none of the currently available treatments for ANCA-associated vasculitis have been shown to be effective in addressing glucocorticoid toxicity, renal function, or health-related quality of life.

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10 APPENDICES

The following appendices are provided in this section:

10.1 Birmingham Vasculitis Activity Score

The Birmingham Vasculitis Activity Score (BVAS) is used to capture vasculitis disease activity (Mukhtyar et al., 2009; Suppiah et al., 2011). There are 9 organ systems, plus an "Other" category in the BVAS. The individual items in the BVAS and scoring of these items are presented in Table 45. For study eligibility, a patient must have had at least one major item, at least 3 minor items, or at least the two renal items of hematuria and proteinuria. Major items are indicated in bold italics.

Table 45: Birmingham Vasculitis Activity Index Items with Scoring

Target Item	Description
General subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 3 (max score is 3 regardless if sum is above): Myalgia (1), Arthralgia or arthritis (1), Fever ≥ 38 (2), Weight loss ≥2 kg (2)
Cutaneous subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 6 (max score is 6 regardless if sum is above): Infarct (2), Purpura (2), Ulcer (4), ***Gangrene*** (6), Other skin vasculitis (2)
Mucous membranes/eyes subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 6 (max score is 6 regardless if sum is above): Mouth ulcers / granulomata (2), Genital ulcers (1), Adnexal inflammation (4), Significant proptosis (4), ***Scleritis / Episcleritis*** (2), Conjunctivitis / Blepharitis / Keratitis (1), Blurred vision (3), Sudden visual loss (6), Uveitis (6), ***Retinal changes*** (6)
ENT subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 6 (max score is 6 regardless if sum is above): Bloody nasal discharge / crusts / ulcers / granulomata (4), Paranasal sinus involvement (2), Subglottic stenosis (6), Conductive hearing loss (3), ***Sensorineural hearing loss*** (6)
Chest subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 6 (max score is 6 regardless if sum is above): Wheeze (2), Nodules or cavities (3), Pleural effusion / pleurisy (4), Infiltrate (4), Endobronchial involvement (4), ***Massive haemoptysis / alveolar haemorrhage*** (6), ***Respiratory failure*** (6)
Cardiovascular subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 6 (max score is 6 regardless if sum is above): Loss of pulses (4), Valvular heart disease (4), Pericarditis (3), Ischaemic cardiac pain (4), Cardiomyopathy (6), Congestive cardiac failure (6)
Abdominal subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 9 (max score is 9 regardless if sum is above): Peritonitis (9), Bloody diarrhoea (9), ***Ischaemic abdominal pain*** (6)
Renal subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 12 (max score is 12 regardless if sum is above): Hypertension (4), Proteinuria >1+ or >0.2 g/g creatinine (4), Haematuria ≥10 RBCs/hpf (6), Serum creatinine 125-249 µmol/L (4), Serum creatinine 250-499 µmol/L (6), Serum creatinine ≥500 µmol/L (8), ***Rise in serum creatinine >30% or fall in creatinine clearance >25%*** (6)
Nervous system subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 9 (max score is 9 regardless if sum is above): Headache (1), ***Meningitis*** (3), Organic confusion (3), Seizures (9), ***Cerebrovascular accident*** (9), ***Spinal cord lesion*** (9), ***Cranial nerve palsy*** (6), ***Sensory peripheral neuropathy*** (6), ***Mononeuritis multiplex*** (9)
Other	If RBC casts and/or glomerulonephritis is checked, it should be added to the Renal Organ System with a Score of 6. Haematuria is also in the Renal organ system (also given a score of 6). Only one or the other should be included in the Renal System.

Target Item	Description
	If additional Other Items are checked the applicable organ system and whether the item is major or minor is indicated. Minor items are given a score of 2 and Major items are given a Score of 4. The maximum score within an organ system is still applicable.
Total BVAS Score	Sum of all individual scores described above (General + Cutaneous + Mucous membranes / eyes + ENT + Chest + Cardiovascular + Abdominal + Renal + Nervous System)
Note: Major items are indicated in ***bold italics***.	

ENT=ear nose and throat

10.2 Glucocorticoid Toxicity Index

The GTI was developed to quantitatively capture glucocorticoid toxicity and the glucocorticoid-sparing ability of other therapies (Miloslavsky et al., 2017). The GTI version 2 was used in this study (McDowell et al., 2021). The index consists of the components listed in Table 46:

Table 46: The Glucocorticoid Toxicity Index with Scoring

Feature/Body System	Item Weight
Body Mass Index (BMI)	
Decrease of ≥5 BMI units	-36
Decrease of >2 but <5 BMI units	-21
No significant change in BMI (±2 BMI units)	0
Increase of >2 to <5 BMI units	21
Increase of 5 or more BMI units	36
Glucose tolerance	
Improvement in HbA1c AND decrease in medication	-44
Improvement in HbA1c OR decrease in medication	-32
No significant change	0
Increase in HbA1c OR increase in medication	32
Increase in HbA1c AND increase in medication	44
Blood pressure	
Improvement in BP AND decrease in medication	-44
Improvement in BP OR decrease in medication	-19
No significant change in blood pressure	0
Increase in BP OR increase in medication	19
Increase in BP AND increase in medication	44
Lipids	
Decrease in LDL AND decrease in medication	-30
Decrease in LDL OR decrease in medication	-10
No significant change in lipids	0
Increase in LDL OR increase in medication	10
Increase in LDL AND increase in medication	30
Steroid myopathy[1]	
Moderate weakness to none	-63
Moderate to Mild weakness	-54
Mild weakness to none	-9
No significant change	0
None to mild weakness	9
Mild to moderate weakness	54
None to Moderate weakness	63
Skin toxicity[1]	
Decrease in Skin Toxicity - Moderate to None	-26
Decrease in Skin Toxicity - Moderate to Mild	-18
Decrease in Skin Toxicity - Mild to None	-8
No significant change	0
Increase in Skin Toxicity - None to Mild	8
Increase in Skin Toxicity - Mild to Moderate	18
Increase in Skin Toxicity - None to Moderate	26
Neuropsychiatric (NP) toxicity[1]	
Decrease in NP Toxicity - Moderate to None	-74
Decrease in NP Toxicity - Moderate to Mild	-63
Decrease in NP Toxicity - Mild to None	-11
No significant change	0
Increase in NP Toxicity - None to Mild	11
Increase in NP Toxicity – Mild to Moderate	63
Increase in NP Toxicity - None to Moderate	74
Infection	

Feature/Body System	Item Weight
No significant infection	0
Oral/vaginal candidiasis or uncomplicated zoster	19
Grade 3, 4 or 5 infection	93

BMI=body mass index; BP=blood pressure; LDL=low density lipoprotein cholesterol; NP=neuropsychiatric

Weighting of Improvement and Worsening in Items of Glucocorticoid Toxicity

As indicated by a review of Table 46, the GTI 2.0 permits an improvement in glucocorticoid toxicity to be accorded the same absolute weight as a worsening of glucocorticoid toxicity. The GTI 2.0 accomplishes this through the GTI-AIS (Aggregate Improvement Score). The GTI-AIS scores improvement in glucocorticoid toxicity the same as a corresponding worsening of glucocorticoid toxicity.

Example: An increase in the body mass index (BMI) more than 5 BMI units to a BMI of greater than 25 is associated with an increase in the GTI score of +36 points. Conversely, a decrease in BMI of more than 5 BMI units towards a normal BMI is associated with an improvement in the score of -36 points.

Application of GTI Scoring

The GTI was measured at Week 13 and Week 26 in this clinical trial. Both the GTI-CWS and the GTI-AIS are calculated for each three-month interval, and then the interval scores are summed. If avacopan was effective at reducing glucocorticoid toxicity compared to the prednisone control group, both the GTI-CWS and the GTI-AIS would be lower in the avacopan treatment group than in the prednisone group.

Scoring of Domains That Have Sub-Items (the Skin and Neuropsychiatric Domains)

The Skin and Neuropsychiatric Domains both have Sub-Items:

- For the Neuropsychiatric Domain, these are Insomnia, Depression, Mania, and Cognitive Impairment.
- For the Skin Domain, these are Acneiform Rash, Easy Bruising, Hirsutism, Atrophy/Striae, and Erosions/tears/ulcerations.

Scoring of these Domains differs according to whether one is calculating the GTI-CWS or the GTI-AIS:

- With the GTI-CWS, only worsening is scored. Only the Item with the highest weight is scored for any GTI interval with the GTI-CWS. As an example, if neither insomnia nor depression were present at the baseline visit but there is now mild insomnia and moderate depression present at follow-up, then only the moderate depression is scored (+74 points).
- With the GTI-AIS, improvement as well as worsening can be recorded. Because it is conceivable that one Item might improve while another worsens, the Item of greatest improvement (highest absolute weight) and the Item of greatest worsening (highest weight) are recorded for given GTI interval.

Scoring of Infections

The GTI-CWS and GTI-AIS handle the scoring of infections differently, because these scores reflect reciprocal measures of glucocorticoid toxicity:

- In the CWS, the most severe infection in every GTI interval (usually three months) is scored.
- In the AIS, only the most severe infection occurring over the course of the 26 weeks is scored.

10.3 Estimated Glomerular Filtration Rate

Changes in kidney function were measured by the estimated glomerular filtration rate (eGFR). Calculation of eGFR was based on serum creatinine, per Modification of Diet in Renal Disease (MDRD) equation for adults (Levey et al., 2006), and modified Schwartz equation for adolescents (Schwartz et al., 2009).

- MDRD: eGFR (mL/min/1.73 m^2) = 175 x (serum creatinine in mg/dL)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African-American/Black)
- Modified Schwartz: eGFR = (0.413 x Height [in cm]) / Serum creatinine (in mg/dL)

Japan unique formula for eGFR in Japanese adults (Matsuo et al., 2009) is defined as follows:

- eGFR (mL/min/1.73 m^2) = 194 x (serum creatinine in mg/dL)$^{-1.094}$ x (Age)$^{-0.287}$ x (0.739 if female)

Normal glomerular filtration rate is 90 mL/min/1.73 m^2 or higher. There are five stages of kidney function based on the glomerular filtration rate (National Kidney, 2002):

- Stage 1 (normal or increased kidney function): GFR at least 90 mL/min/1.73 m^2
- Stage 2 (mild impairment): GFR 60 to 89 mL/min/1.73 m^2
- Stage 3 (moderate impairment): GFR 30 to 59 mL/min/1.73 m^2
- Stage 4 (severe impairment): GFR 15 to 29 mL/min/1.73 m^2
- Stage 5 (kidney failure): GFR <15 mL/min/1.73 m^2

The average annual decline in eGFR in patients with chronic kidney disease is approximately 1 mL/min/1.73 m^2 (Inker et al., 2019). There is no generally acceptable minimum clinically important difference for eGFR. However, it has been estimated that an effect size as small as 0.75 mL/min/1.73 m^2 per year predicts a clinical benefit on chronic kidney disease progress (Inker et al., 2019).

10.4 Pivotal Phase 3 Study CL010_168: Inclusion Requirements for Females of Childbearing Potential and Males with Partners of Childbearing Potential

The protocol for Pivotal Phase 3 Study CL010_168 specified the following criteria for inclusion of females of childbearing potential and males with partners of childbearing potential:

- Female patients of childbearing potential may have participated if adequate contraception was used during the study, and for at least 6 months after the last cyclophosphamide dose (if receiving cyclophosphamide) and at least 12 months after the last rituximab dose (if receiving rituximab).
- Male patients with partners of childbearing potential may have participated in the study if they had a vasectomy at least 6 months prior to randomization or if adequate contraception was used during the study, and for at least 6 months after the last cyclophosphamide dose (if receiving cyclophosphamide) and at least 12 months after the last rituximab dose (if receiving rituximab).
- Adequate contraception was defined as resulting in a failure rate of less than 1% per year (combined estrogen and progestogen [oral, intravaginal, or transdermal], or progestogen-only hormonal contraception [oral, injectable, or implantable], intra-uterine device, intra-uterine hormone releasing system, bilateral tubal occlusion, vasectomized partner, or true [absolute] sexual abstinence, i.e., in line with the preferred and usual lifestyle of the patient).
- For patients who received mycophenolate instead of azathioprine, a second form of birth control must have been used if the first form of birth control was hormonal contraception, such as progestogen-only hormonal contraception, because mycophenolate reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness; sperm donation for at least 6 months after the last cyclophosphamide dose (if receiving cyclophosphamide), and at least 12 months after the last rituximab dose (if receiving rituximab), must not have been performed.

10.5 Pivotal Phase 3 Study CL010_168: Setting Non-Inferiority Margin

10.5.1 Introduction

Avacopan is a C5a receptor inhibitor being developed for treatment of patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

The current standard of care treatment for patients with ANCA-associated vasculitis is cyclophosphamide or rituximab plus glucocorticoids (Jayne et al., 2003; Stone et al., 2010). These combination treatments result in disease remission in many patients with ANCA-associated vasculitis (Mukhtyar et al., 2008). However, it comes at a cost of serious side effects, including infection (de Lind van Wijngaarden et al., 2006; Goupil et al., 2013; Little et al., 2010; Weidner et al., 2004). Glucocorticoids are considered the culprit in many cases of treatment toxicity (Charlier et al., 2009; Goupil et al., 2013; McGregor et al., 2012). Therefore, there is an unmet medical need to find alternative treatment options.

ANCA-associated vasculitis is a serious disease which if left untreated invariably results in organ failure, eg, kidney failure and death (Booth et al., 2003; Harper et al., 2005; Little et al., 2010). Prior to the 1970's, glucocorticoids were the standard treatment for patients with ANCA-associated vasculitis. Due to severe toxicity including crippling myopathy, multiple vertebral fractures, poorly controlled diabetes mellitus, cataracts, and glaucoma, there was a need for new treatments. Cyclophosphamide as a treatment for ANCA-associated vasculitis (in addition to high dose glucocorticoids) was introduced in the 1970s (Fauci et al., 1971, 1979). However, cyclophosphamide introduced new toxicities including cancer, infertility, cystitis, bone marrow suppression, and infections (Langford, 2011).

Rituximab, as a replacement for cyclophosphamide, was introduced in the United States in 2011 and in Europe in 2013. The basis for the Regulatory approval was two clinical trials (Jones et al., 2010; Stone et al., 2010). The larger of the two studies, conducted in 197 patients with ANCA-associated vasculitis, showed that rituximab plus glucocorticoids was non-inferior to cyclophosphamide plus glucocorticoids in inducing disease remission at the end of a 6-month treatment period. The safety profile between the rituximab and cyclophosphamide arms was very similar. The incidence of serious and Grade 3 or higher adverse events was 80% in both groups. Grade 3 or higher infection incidence was 7% in both groups. Therefore, even though rituximab provided an alternative to cyclophosphamide, it did not address many of the therapy-related toxicity concerns.

Rituximab and cyclophosphamide are immunosuppressive drugs. Rituximab, an antibody against CD20, depletes B lymphocytes. Cyclophosphamide, a cytotoxic drug, was also shown to be relatively selective for B lymphocytes (Fauci et al., 1971). Glucocorticoids provide a non-specific anti-inflammatory component to the treatment regimens.

Avacopan, as a selective complement 5a receptor (C5aR) inhibitor, is a specific anti-inflammatory drug that does not broadly suppress the immune system like glucocorticoids. By blocking the C5aR, avacopan dampens the extent of C5a-medicated neutrophil accumulation and activation, resulting in reduced vasculitis (Xiao et al., 2014).

The clinical development strategy for avacopan as a specific anti-inflammatory drug is to replace the oral glucocorticoids, typically prednisone or prednisolone, in the treatment of patients with ANCA-associated vasculitis. Therefore, the plan is to test avacopan plus cyclophosphamide or rituximab against prednisone plus cyclophosphamide or rituximab in a Phase 3 clinical trial in patients with ANCA-associated vasculitis.

The FDA Guidance for Industry: Non-Inferiority Clinical Trials (Food and Drug Administration, 2016) and EMA Guideline on the Choice of the Non-Inferiority Margin (European Medicines Agency, 2005) were consulted and used as a basis for determining an appropriate study design as well as an appropriate non-inferiority margin.

10.5.2 Clinical Trial Design Considerations

A number of clinical trial designs have been considered for a Phase 3 study of avacopan in ANCA-associated vasculitis.

10.5.2.1 Placebo-Controlled Superiority Clinical Trial

In this traditional clinical trial design, avacopan is compared to placebo. Unfortunately, this clinical trial design that includes a placebo arm is not an ethical option in patients with ANCA-associated vasculitis, because of the life-threatening nature of the disease. Therefore, a placebo-controlled superiority clinical trial design is not an option for Phase 3.

10.5.2.2 Add-on to Standard of Care Superiority Clinical Trial

In this clinical trial design, the test drug is added to standard of care treatment, and tested against placebo plus standard of care.

This could be a viable treatment option if the remission rate is reasonably low to allow superiority to be demonstrated in a reasonably sized clinical trial. The remission rates achieved with standard of care regimens, cyclophosphamide plus glucocorticoids or rituximab plus glucocorticoids, are up to 94% and 100%, respectively (see Table 47 and Table 48). The estimated average remission rates across all studies conducted with cyclophosphamide plus glucocorticoids is 74.6% (Table 50) and with rituximab plus glucocorticoids is 73.1% (Table 51). Therefore, to conduct a successful add-on study with the goal of demonstrating superiority of the avacopan add-on group versus standard of care control would require a very large clinical trial to demonstrate superiority. For example, assuming a clinical remission rate at 6 months (26 weeks) of 70% for the control group, a sample size of ~460 patients per treatment group (~920 in total) would be required to demonstrate a 10% higher clinical remission rate (with power of 90%, alpha 0.05, and dropout rate of 10%) in the test group. Since ANCA-associated vasculitis is an orphan disease, we estimate that enrollment for a 920-patient study with 200 study centers worldwide would take at least 6 years, based on enrollment rates observed in our Phase 2 studies with avacopan. This is clearly not feasible.

10.5.2.3 Non-Responder Clinical Trial

In this clinical trial design, patients who are non-responders to current standard of care treatment are enrolled.

As indicated above, the clinical remission rate with current standard of care is high. Therefore, a low percentage of patients do not respond to the treatment. Even though certain situations or conditions may be indicators of a higher likelihood of treatment resistance, there are no predictive markers that would clearly distinguish responders from non-responders.

Patients with relapsing disease may be less responsive to cyclophosphamide than rituximab treatment (Stone et al., 2010). Also, there are patients for whom cyclophosphamide or rituximab is contra-indicated or for whom these are not ideal treatment options. For example, cyclophosphamide is not ideal in young patients who want to maintain their fertility, or patients with a history of cancer. Unfortunately, this is a small group of patients, which would make enrollment extremely challenging.

Also, the primary goal of the avacopan clinical development program is to provide a potentially safer therapy that maintains the efficacy profile of current therapy.

Therefore, a clinical trial in patients who do not benefit from current treatment is not feasible in an orphan setting such as ANCA-associated vasculitis, and deviates from the primary goal of the development plan.

10.5.2.4 Early Escape, Rescue Treatment, Randomized Withdrawal Trial

In these designs, all patients are treated with the test drug. Early escape or rescue treatment is incorporated for patients who do not respond adequately to the test drug. In a randomized withdrawal study design, all patients receive the test drug initially. After inducing remission, patients are randomly assigned to placebo or test drug for a further treatment period. Time to relapse is then assessed in the two treatment groups and compared.

There are currently insufficient data to justify single agent avacopan treatment of patients with ANCA-associated vasculitis. Therefore, avacopan would need to be given in combination with other therapies to treat patients with active disease. This could compromise the assessment of efficacy in a randomized withdrawal study design, since it might be difficult to separate the avacopan and the other treatment contribution to the efficacy signal. There is also no data at this time to provide confidence that avacopan would be effective in the maintenance setting. Therefore, these study designs are not considered viable options for avacopan for this stage of clinical development.

10.5.2.5 Non-Inferiority Clinical Trial

In this design, the test drug is tested against an active control, with or without background standard of care treatment.

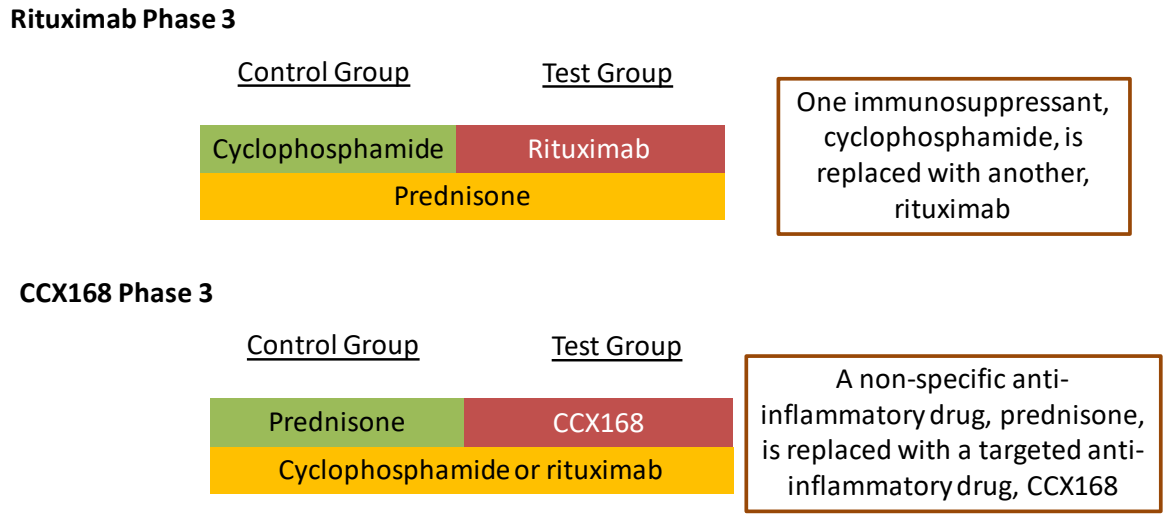
Since none of the other clinical trial designs are considered feasible, the option of a non-inferiority clinical trial was considered carefully. As stated, the goal of the clinical development plan for avacopan is to show that avacopan can be used instead of oral glucocorticoids as part of standard of care treatment of patients with ANCA-associated vasculitis.

The strategy of trading one of the components of standard of care treatment of ANCA-associated vasculitis was followed for the rituximab clinical development program. In that case, the goal was to demonstrate that rituximab could be traded for cyclophosphamide as part of the standard of care treatment of ANCA-associated vasculitis. In the large rituximab clinical trial (Stone et al., 2010), clinical remission (based on a BVAS of zero, and successful glucocorticoid tapering) at 6 months was the primary endpoint. The pre-specified non-inferiority margin for comparison of rituximab plus prednisone vs. cyclophosphamide plus prednisone was 20 percentage points. The study showed non-inferiority of the test group compared to the control group.

In avacopan Phase 2 clinical trial CL002_168 in patients with ANCA-associated vasculitis, avacopan plus cyclophosphamide or rituximab was shown to be non-inferior to prednisone plus cyclophosphamide or rituximab with regard to the primary endpoint of proportion of patients with clinical response based on BVAS. Since the treatment period in study CL002_168 was 12 weeks instead of 26 weeks, BVAS response rather than BVAS remission was used as the primary endpoint in study CL002_168.

In the Phase 3 clinical trial with avacopan, clinical remission at 6 months based on a BVAS of zero, and successful glucocorticoid tapering as the primary endpoint (similar to the rituximab study) is one of the primary endpoints. All patients in the avacopan Phase 3 study will receive either cyclophosphamide or rituximab, which is part of the standard of care treatment of ANCA-associated vasculitis. A comparison of the rituximab study design and the Phase 3 avacopan study design is shown in Figure 19.

Figure 19: A Comparison of the Treatment Groups in the Phase 3 Rituximab and the Proposed Phase 3 Avacopan Clinical Trials



In the following sections, all clinical trials previously conducted with cyclophosphamide, rituximab, or glucocorticoids are summarized. M1, the entire assumed treatment effect of prednisone, is estimated from these clinical trials. A justification for M2, the largest clinically acceptable difference of avacopan compared to prednisone, is also provided. This forms the basis for recommendation of the non-inferiority margin for the Phase 3 clinical trial of avacopan.

10.5.3 Previous Clinical Trials

Two strategies were followed to identify all clinical trials conducted with cyclophosphamide, rituximab, or glucocorticoids in ANCA-associated vasculitis:

1. PubMed literature searches were conducted using the search terms “cyclophosphamide” AND “vasculitis” AND “clinical trial”, “rituximab” AND “vasculitis” AND “clinical trial”, and “steroid” AND “clinical trial”, “rituximab” AND “vasculitis”;
2. Results from the literature searches were sent to a renowned ANCA-associated vasculitis disease expert to review the completeness of the list and to add any missing studies.

A total of 20 references were identified with relevant information about disease remission rates in clinical trials in vasculitis.

10.5.3.1 Cyclophosphamide Studies

The studies in which cyclophosphamide was tested are summarized in Table 47. There have been 19 evaluable published studies of cyclophosphamide. In all these studies, cyclophosphamide was tested concomitantly with glucocorticoids. A total of 1516 patients were included in these studies. Patients with granulomatosis with polyangiitis (GPA or Wegener’s) constituted the majority of patients, 1029/1516 (68%), followed by microscopic polyangiitis (MPA; 369/1516 [24%]). Renal vasculitis, 49/1516 (3%), polyarteritis nodosa (PAN), 30/1516 (2%), and eosinophilic granulomatosis with polyangiitis (EGPA; 14/1516 [1%]) formed minority groups.

Disease remission was achieved in the majority of patients in most groups in these studies: in 16 of 21 groups of patients, disease remission was achieved in >60% of patients. The 5 studies with remission rates below 60% were examined to determine whether there was consistency in reasons for the lower remission rate. Reinhold-Keller et al. (1994) (remission rate of 30%) used a very strict definition of remission, including absence of clinical, serologic, and radiologic (including MRI) evidence of disease activity. Adu et al. (1997) (remission rate of 28%) required remission, defined by BVAS of 0, for at least 1 month, which is also stricter than most studies which requires only one time point in remission. Villa-Forte et al. (2007) (remission rate of 50%) required remission, defined by BVAS of 0, which is not unusual for ANCA-associated vasculitis studies. Hu et al. (2008) (remission rate of 44%) was very small (N=17 patients) and included only patients with MPA. Stone et al. (2010) (remission rate of 53%) was a relatively large study (N=197) with a typical remission definition of BVAS of 0 and successful glucocorticoid taper.

There were 4 studies with very high remission rates (>90%). The study by Fauci et al. (1983) (remission rate of 93%) did not include a remission definition based on BVAS and the time point of remission was also not specified. The study by Haubitz et al. (1998) (remission rate of 91%) included remission up to 12 months of treatment (longer than the 6 months used in other studies). The study by Jayne et al. (2003) (remission rate of 93%) used a definition of remission of absence of new or worse signs of disease activity and no more than 1 item indicating persistent disease, which is slightly different from other definitions. In the study by De Groot et al. (2005) (remission rate of 94%), remission was not defined in the paper.

A meta-analysis of the remission rate was done across all the cyclophosphamide studies. Results are presented in Table 50. The numerator, denominator and remission rates are presented for each study, as well as the variance, fixed effect weight, fixed effect estimates of the remission rate, Q-statistic for heterogeneity, weights pooled within and between study variance, and the DerSimonian-Laird estimate of the pooled rate. The method described by Henmi et al. (2010) was used to calculate the pooled rate and confidence intervals.

Based on these calculations, the average pooled remission rate is 74.6% for cyclophosphamide plus glucocorticoids. The lower limit of the 95% confidence interval of the remission rate is 67.5%.

Table 47: All Clinical Studies of Cyclophosphamide Plus Glucocorticoid Treatment in Patients with Vasculitis

Study	Type of Vasculitis	Age, yrs (mean)	Gender (male %)	Endpoint	Remission Rate	LL of CI[a]
(Fauci et al., 1983)	GPA[b]	41	56%	Remission (not defined) and time point not specified	79/85 (92.9%)	87.5%
(Hoffman et al., 1992)	GPA	41	50%	Remission (absence of evidence of active disease, complete resolution of pulmonary infiltrate or evidence of stable scarring without signs of active inflammation, absence of systemic inflammatory disease such as serositis and fever, and stabilization or improvement in renal function with no further evidence of active renal sediment)	119/158 (75.3%)	68.6%
(Reinhold-Keller et al., 1994)	GPA	47	47%	Complete remission (defined as absence of clinical, serologic, and radiologic [including MRI] evidence of disease activity), time point not specified	13/43 (30.2%)	16.5%
(Nachman et al., 1996)	MPA[c] (67%), NCGN [d] (33%)	58	55%	Remission (stabilization or improvement of renal function [as measured by serum creatinine], resolution of hematuria, and resolution of extrarenal manifestations of systemic vasculitis. Persistence of proteinuria was not considered indicative of persistence of disease activity.), time point not specified	61/72 (84.7%)	76.4%
(Adu et al., 1997)	GPA (54%), MPA (31%), PAN[e] (15%)	55	65%	Complete remission (BVAS of 0-1 for at least 1 month)	15/54 (27.8%)	15.8%
(Guillevin et al., 1997)	GPA	54	60%	Complete remission (patient's general condition improved, no new manifestations of GPA, ESR returned to normal. Stabilization or improvement [partial or total] in renal function and other parameters present initially was also necessary) within 6 months	31/50 (62.0%)	48.5%
(Haubitz et al., 1998)	GPA (47%), MPA (53%)	Not reported	Not reported	Complete remission (BVAS of 0 or 1) within up to 12 months of treatment	43/47 (91.5%)	83.3%

Study	Type of Vasculitis	Age, yrs (mean)	Gender (male %)	Endpoint	Remission Rate	LL of CI[a]
(Guillevin et al., 2003)	MPA (61%) and PAN (39%)	58	71%	Complete remission, not defined (time point not specified)	26/31 (83.9%)	70.9%
(Jayne et al., 2003)	GPA (61%), MPA (39%)	58	47%	BVAS Remission (absence of new or worse signs of disease activity and no more than 1 item indicating persistent disease) by 6 months	144/155 (92.9%)	88.9%
(De Groot et al., 2005)	GPA (93%), MPA (7%)	53	43%	BVAS remission (not defined) at 6 months	43/46 (93.5%)	86.3%
(Wegener's Granulomatosis Etanercept Trial Research Group, 2005)	GPA	50	60%	Sustained BVAS remission (BVAS of 0 for at least 6 months)	64/85 (75.3%)	66.1%
(Villa-Forte et al., 2007)	GPA	46	57%	Remission (BVAS of 0) at 6 months	41/82 (50.0%)	39.2%
(Hu et al., 2008)	MPA	48	35%	Remission (no clinical signs of vasculitis, improved or stable renal function, no active urine sediments and BVAS1 = 0, BVAS2 < 1) at 6 months	8/17 (47.1%)	23.3%
(Pagnoux et al., 2008)	GPA (76%), MPA (24%)	58	48%	Remission (BVAS of 0), time point not specified	126/159 (79.2%)	72.9%
(de Groot et al., 2009) (pulse CYC[f])	GPA (33%), MPA (50%), renal limited vasculitis (17%)	57	54%	BVAS Remission (absence of new or worse signs of disease activity and no more than 1 item indicating persistent disease)	67/76 (88.2%)	80.9%
(de Groot et al., 2009) (daily CYC)	GPA (42%), MPA (45%), renal limited vasculitis (12%)	58	64%	BVAS Remission (absence of new or worse signs of disease activity and no more than 1 item indicating persistent disease)	64/73 (87.7%)	80.1%
(Jones et al., 2010)	GPA (36%), MPA (36%), and renal limited vasculitis (27%)	67 (median)	55%	Sustained BVAS remission (BVAS of 0 for at least 6 months)	9/11 (81.8%)	59.0%
(Stone et al., 2010)	GPA (76%) and MPA (24%)	52	54%	BVAS remission at 6 months (BVAS of 0 and successful steroid taper)	52/98 (53.1%)	43.2%
(Jones, 2013) (submitted)	GPA (64%), rest not specified	60	49%	Remission (BVAS =0 on two occasions at least one month apart and adherence to prednisolone taper) at 6 months	52/70 (74.3%)	64.0%
(Pagnoux et al., 2015) (CYC plus C/S[g] for 26 months)	GPA (29%), MPA (45%), EGPA (12%), PAN (14%)	75	63%	Remission (BVAS of 0), time point not specified	44/51 (86.3%)	76.9%

Study	Type of Vasculitis	Age, yrs (mean)	Gender (male %)	Endpoint	Remission Rate	LL of CI[a]
(Pagnoux et al., 2015) (CYC plus C/S for 9 months)	GPA (40%), MPA (40%), EGPA (15%), PAN (5%)	75	51%	Remission (BVAS of 0), time point not specified	47/53 (88.7%)	80.1%

(a) Lower limit of the 95% confidence interval
(b) granulomatosis with polyangiitis
(c) microscopic polyangiitis
(d) necrotizing crescentic glomerulonephritis
(e) polyarteritis nodosa
(f) cyclophosphamide
(g) glucocorticoids

10.5.3.2 Rituximab Studies

The studies in which rituximab was tested are summarized in Table 48. There have been 3 evaluable published studies with of rituximab. In all these studies, rituximab was tested concomitantly with glucocorticoids. A total of 146 patients were included in these studies. Patients with granulomatosis with polyangiitis (GPA or Wegener's) constitute the majority of patients, 98/146 (67%), followed by microscopic polyangiitis (MPA; 44/146 [30%]). Renal vasculitis, 3/146 (2%) formed a minority group.

Disease remission was achieved in the majority of patients in these studies: in all three studies, disease remission was achieved in >60% of patients. The study by Shah et al, 2015 was a small (N=14) retrospective study in which the remission rate was 100%. The other two studies had remission rates of 64% and 76%, respectively.

A meta-analysis of the remission rate was done across all three studies. Results are presented in Table 51. Note that the Jones et al. (2010) and Shah et al. (2015) studies are combined in this table. The numerator, denominator and remission rates are presented for each study, as well as the variance, fixed effect weight, fixed effect estimates of the remission rate, Q-statistic for heterogeneity, weights pooled within and between study variance, and the DerSimonian-Laird estimate of the pooled rate.

Based on these calculations, the average pooled remission rate is 73.1% for rituximab plus glucocorticoids. The lower limit of the 95% confidence interval of the remission rate is 54.2%.

Table 48: All Clinical Studies of Rituximab Plus Glucocorticoid Treatment in Patients with Vasculitis

Study	Type of Vasculitis	Age, yrs (mean)	Gender (male %)	Endpoint	Remission Rate	LL of CI[a]
(Jones et al., 2010)	GPA[b] (55%), MPA[c] (36%), and renal limited vasculitis (9%)	68 (median)	52%	Sustained BVAS remission (BVAS of 0 for at least 6 months)	25/33 (76%)	61.4%
(Stone et al., 2010)	GPA (75%), MPA (24%), indeterminate (1%)	54	46%	BVAS remission at 6 months (BVAS of 0 and successful steroid taper)	63/99 (64.0%)	42.7%
(Shah et al., 2015) (retrospective)	GPA (43%), MPA (57%)	61 (median)	57%	Remission (not defined)	14/14 (100%)	80.7%

(a) lower limit of the 95% confidence interval

(b) granulomatosis with polyangiitis (Wegener's)

(c) microscopic polyangiitis

10.5.3.3 Glucocorticoid Studies

The studies in which glucocorticoids alone was tested are summarized in Table 49. There have been 3 evaluable published studies with of glucocorticoids. A total of 159 patients were included in these studies. There were 10/159 (6%) patients with GPA, 83/159 (52%) with MPA, 58/159 (36%) with PAN, and 8/159 (5%) with renal vasculitis.

Disease remission was achieved in >50% of patients in two of the three studies. The remission rate was 20% in one small group of 10 patients in the study by Hoffman et al. (1992).

A meta-analysis of the remission rate was done across all three studies. Results are presented in Table 52. The numerator, denominator and remission rates are presented for each study, as well as the variance, fixed effect weight, fixed effect estimates of the remission rate, Q-statistic for heterogeneity, weights pooled within and between study variance, and the DerSimonian-Laird estimate of the pooled rate.

Based on these calculations, the average pooled remission rate is 46% for glucocorticoids. The lower limit of the 95% confidence interval of the remission rate is 29%.

Table 49: All Clinical Studies of Glucocorticoid Treatment in Patients with Vasculitis

Study	Type of Vasculitis	Age, yrs (mean)	Gender (male %)	Endpoint	Remission Rate	LL of CI[a]
(Hoffman et al., 1992)	GPA[b]	Not reported	Not reported	Remission (absence of evidence of active disease, complete resolution of pulmonary infiltrate or evidence of stable scarring without signs of active inflammation, absence of systemic inflammatory disease such as serositis and fever, and stabilization or improvement in renal function with no further evidence of active renal sediment)	2/10 (20.0%)	2.5%
(Nachman et al., 1996)	MPA[c] (67%), NCGN[d] (33%) overall	58	55%	Remission (stabilization or improvement of renal function [as measured by serum creatinine], resolution of hematuria, and resolution of extrarenal manifestations of systemic vasculitis. Persistence of proteinuria was not considered indicative of persistence of disease activity.), time point not specified	14/25 (56%)	36.5%
(Ribi et al., 2010)	MPA (53%), PAN[e] (47%)	57	58%	Complete remission (defined as the absence of clinical and biologic manifestations of active vasculitis for ≥3 months), time point not specified	98/124 (79%) (MPA/PAN) 50/66 (76%) (MPA only)	71.8% 65.4%

(a) lower limit of the 95% confidence interval

(b) granulomatosis with polyangiitis (Wegener's)

(c) microscopic polyangiitis

(d) necrotizing crescentic glomerulonephritis

(e) polyarteritis nodosa

10.5.4 Determination of M1

There have been no true placebo-controlled studies in ANCA-associated vasculitis. This is likely because of the life-threatening nature of the disease. If left untreated, the disease invariably progresses, resulting in irreversible organ damage and death.

M1, according to FDA Guidance for Non-Inferiority Clinical Trials (Food and Drug Administration, 2016), is defined as the whole effect of the active control relative to placebo. Since the disease progresses in patients who are not treated, it can be safely assumed that the placebo remission rate will be 0%.

The remission rate with cyclophosphamide plus glucocorticoids is 74.6% (95% CI: 67.5%, 81.6%) based on the meta-analysis presented in Section 10.5.3.1. The remission rate with rituximab plus glucocorticoids is 73.1% (95% CI: 54.2%, 92.1%) based on the meta-analysis presented in Section 10.5.3.2. In our proposed Phase 3 clinical trial with avacopan, we plan to allow either cyclophosphamide or rituximab as background treatment. We estimate that 50% of patients will receive either cyclophosphamide or rituximab in the Phase 3 study. Therefore, the average of the remission rate with cyclophosphamide plus glucocorticoids and rituximab plus glucocorticoids is 73.9% (the average of 74.6% and 73.1%).

Based on the FDA Guidance for Non-Inferiority Clinical Trials, the lower bound of the 95% CI of the remission rate should be determined as a first approximation of M1. The lower bound of the 95% confidence interval for remission with cyclophosphamide plus glucocorticoid treatment is 67.5% based on the meta-analysis presented in Section 10.5.3.1 The lower bound of the 95% confidence interval for remission with rituximab plus glucocorticoid treatment is 54.2% based on the meta-analysis presented in Section 10.5.3.2. In our proposed Phase 3 clinical trial with avacopan, we plan to allow either cyclophosphamide or rituximab as background treatment. We estimate that 50% of patients will receive either cyclophosphamide or rituximab in the Phase 3 study. Therefore, the average of the lower limit of the 95% CI for remission with cyclophosphamide plus glucocorticoids and rituximab plus glucocorticoids is 60.9% (the average of 67.5% and 54.2%).

The next step is to estimate the contribution of glucocorticoids to the remission rate. The remission rate with glucocorticoids alone is 45.5% (95% CI: 28.7%, 62.3%) based on the meta-analysis presented in Section 10.5.3.3. Assuming that the contribution of glucocorticoids is additive, 45.5% is 62% of the cyclophosphamide/rituximab plus glucocorticoid remission rate (45.5% of 73.9% = 62%). Therefore, conservatively viewed, the contribution of glucocorticoids to the remission rate is at least half of the combined cyclophosphamide/rituximab plus glucocorticoid remission rate. Half of the lower limit of the 95% CI of the remission rate for cyclophosphamide/rituximab plus glucocorticoids is 30.5% (half of 60.9%). This is one method to estimate M1.

The second method to estimate M1 is to take the lower limit of the 95% CI of the remission rate with glucocorticoids only. This is 28.7% (Table 52).

The third way to estimate M1 is to ensure that by adding avacopan to cyclophosphamide or rituximab treatment, not any of the effect of cyclophosphamide or rituximab treatment effect is lost. The remission rate with glucocorticoids is 45.5% (Section 10.5.3.3) and the remission rate with glucocorticoids plus cyclophosphamide or rituximab is 73.9% (from Sections 10.5.3.1 and 10.5.3.2). Therefore, the glucocorticoid effect is 62% of the total treatment effect (45.5% of 73.9% = 62%). Therefore, if avacopan plus cyclophosphamide or rituximab is allowed to lose 38% (100% minus 62%) of the overall treatment effect (60.9%), it is no longer non-inferior to glucocorticoids plus cyclophosphamide or rituximab, but the effect of avacopan plus cyclophosphamide or rituximab is comparable to glucocorticoids alone. Using the lower limit of the 95% confidence interval means that M1 is 38% of 60.9%, which is 23.1%.

Based on these three methods, an M1 between 23% and 31% is considered reasonable.

10.5.5 Determination of M2

The FDA Guidance for Non-Inferiority Clinical Trials stipulates that M1 should be examined in the context of the quality of the studies used to estimate a treatment effect. The EMA Guideline on the Choice of the Non-Inferiority Margin (European Medicines Agency, 2005) points out that clinical judgment also needs to be considered in establishing the non-inferiority margin.

Factors to consider in establishing the non-inferiority margin are as follows:

1. There is a relatively large number of previous clinical studies in ANCA-associated vasculitis, especially with cyclophosphamide plus glucocorticoid, that provides precise guidance for determination of the non-inferiority margin;
2. Several of the previous clinical studies are relatively large, which increases confidence in the estimate of the remission rates;
3. There is some variability in the types of patients studied, the definition of remission used, as well as the time point of estimation of remission;
4. The three methods proposed to derive M1 include a conservative method (third method in Section 10.5.4) that ends with the glucocorticoid remission rate (not a placebo rate). This means that even if all the benefit from cyclophosphamide or rituximab is lost with the combination of avacopan plus cyclophosphamide or rituximab, efficacy similar to that achieved with glucocorticoids (without the glucocorticoid-associated side effects) will be retained.

In considering all these aspects, it is considered reasonable to propose a modest discounting of M1 to determine M2. Therefore, an M2 of 20% (a 13% to 35% discount) is considered appropriate for an avacopan Phase 3 non-inferiority study in ANCA-associated vasculitis.

10.5.6 Discussion and Conclusions

Avacopan showed evidence of efficacy in Phase 2 clinical trial CL002_168 in patients with ANCA-associated vasculitis. Based on results from this study, avacopan has the potential to replace the daily oral prednisone as part of the treatment regimen.

Several clinical trial designs were considered for the proposed Phase 3 study of avacopan in ANCA-associated vasculitis. A non-inferiority study design was considered the best of the options.

The FDA Guidance for Non-Inferiority Clinical Trials and the EMA Guideline on the Choice of the Non-Inferiority Margin were followed to determine an appropriate non-inferiority margin for the avacopan Phase 3 clinical trial.

Disease remission, based on the BVAS instrument, has been used to assess the efficacy of drugs in ANCA-associated vasculitis studies. Three groups of studies have been identified in the literature and with expert input: one of cyclophosphamide plus glucocorticoids, the second of rituximab plus glucocorticoids, and the third of glucocorticoids alone.

Based on results from 20 clinical trials, the lower limit of the 95% confidence interval of disease remission was determined to be 60.9% for a clinical trial of patients receiving cyclophosphamide plus glucocorticoids or rituximab plus glucocorticoids. Glucocorticoids contribute at least half of the efficacy signal. Therefore, a lower limit of the 95% confidence interval of disease remission of 30% for glucocorticoids alone is reasonable. Discounting this number by one-third yields 20%, which is considered reasonable for the non-inferiority margin for an avacopan Phase 3 clinical trial.

In the largest (N=197) recent study in ANCA-associated vasculitis with rituximab, a non-inferiority margin of 20% was utilized (Stone et al., 2010). This is the same as the non-inferiority margin proposed for our Phase 3 clinical trial with avacopan.

For the avacopan Phase 3 clinical trial, we are estimating that the BVAS remission rate at 6 months (26 weeks) will be approximately 60%. This is based on a blended BVAS remission rate from the cyclophosphamide plus glucocorticoids (53%) and rituximab plus glucocorticoids (64%) groups in the largest recent clinical trial in ANCA-associated vasculitis (Stone et al., 2010). With a non-inferiority margin of 20%, a sample size of 150 patients per treatment group (300 in total) would be required to demonstrate non-inferiority of the test group versus the control group (with power of at least 90%, alpha 0.05, and dropout rate of 10%).

In conclusion, a non-inferiority margin of 20% is considered reasonable for a clinical remission endpoint in a Phase 3 clinical trial testing avacopan plus cyclophosphamide or rituximab against prednisone plus cyclophosphamide or rituximab in ANCA-associated vasculitis.

Table 50: Calculation of Confidence Intervals of Previous Vasculitis Clinical Studies with Cyclophosphamide Plus Glucocorticoids

Study	Numerator	Denominator	Y_i (Rate)	σ_i^2 (variance)	w_i (fixed effect wt)	$\hat{\theta}_F$ (fixed effect estm of Rate)	Q (Q-stat for heterogeneity)	$\widehat{w_i}$ (wt pooled within and btw study variance)	$\hat{\theta}_R$ (contribution to the DerSimonian-Laird estm of Pooled Rate)
(Fauci et al., 1983)	79	85	93%	0.0008	1296	10%	15.07	40.2	4.8%
(Hoffman et al., 1992)	119	158	75%	0.0012	850	5%	3.97	39.6	3.8%
(Reinhold-Keller et al., 1994)	13	43	30%	0.0049	204	0%	54.96	34.5	1.3%
(Nachman et al., 1996)	61	72	85%	0.0018	556	4%	0.37	38.6	4.2%
(Adu et al., 1997)	15	54	28%	0.0037	269	1%	79.59	35.9	1.3%
(Guillevin et al., 1997)	31	50	62%	0.0047	212	1%	8.62	34.7	2.8%
(Haubitz et al., 1998)	43	47	91%	0.0017	604	4%	5.26	38.8	4.6%
(Guillevin et al., 2003)	26	31	84%	0.0044	229	2%	0.07	35.1	3.8%
(Jayne et al., 2003)	144	155	93%	0.0004	2351	18%	27.16	40.8	4.9%
(De Groot et al., 2005)	43	46	93%	0.0013	755	6%	9.67	39.3	4.7%
(Wegener's Granulomatosis Etanercept Trial Research Group, 2005)	64	85	75%	0.0022	457	3%	2.15	38.0	3.7%
(Villa-Forte et al., 2007)	41	82	50%	0.0030	328	1%	33.91	36.8	2.4%
(Hu et al., 2008)	8	17	47%	0.0147	68	0%	8.40	25.8	1.6%
(Pagnoux et al., 2008)	126	159	79%	0.0010	967	6%	0.82	39.8	4.1%
(de Groot et al., 2009)	67	76	88%	0.0014	728	5%	2.62	39.3	4.5%
(de Groot et al., 2009)	64	73	88%	0.0015	675	5%	2.06	39.1	4.4%
(Jones et al., 2010)	9	11	82%	0.0135	74	0%	0.00	26.6	2.8%
(Stone et al., 2010)	52	98	53%	0.0025	393	2%	33.31	37.5	2.6%
(Jones, 2013) (submitted)	52	70	74%	0.0027	366	2%	2.27	37.3	3.6%
(Pagnoux et al., 2015)	44	51	86%	0.0023	431	3%	0.73	37.8	4.2%
(Pagnoux et al., 2015)	47	53	89%	0.0019	528	4%	2.25	38.5	4.4%
			SUM=		12341	82%	293.27	774.0	$\hat{\theta}_R$ DerSimonian-Laird Estimate and 95% CI: **74.6% (67.5%, 81.6%)**

Table 51: Calculation of Confidence Intervals of Previous Vasculitis Clinical Studies with Rituximab Plus Glucocorticoids

Study	Numerator	Denominator	Y_i (Rate)	σ_i^2 (variance)	w_i (fixed effect wt)	$\hat{\theta}_F$ (fixed effect estm of Rate)	Q (Q-stat for heterogeneity)	$\widehat{w_i}$ (wt pooled within and btw study variance)	$\hat{\theta}_R$ (contribution to the DerSimonian-Laird estm of Pooled Rate)
(Jones et al., 2010) + (Shah et al., 2015)	39	47	83%	0.0030	333	36%	3.94	52.5	40.7%
(Stone et al., 2010)	63	99	64%	0.0023	428	36%	3.06	54.4	32.4%
			SUM=		761	0.72	7.00	106.9	$\hat{\theta}_R$ DerSimonian-Laird Estimate and 95% CI: **73.1% (54.2%, 92.1%)**

Table 52: Calculation of Confidence Intervals of Previous Vasculitis Clinical Studies with Glucocorticoids Only

Study	Numerator	Denominator	Y_i (Rate)	σ_i^2 (variance)	w_i (fixed effect wt)	$\hat{\theta}_F$ (fixed effect estm of Rate)	Q (Q-stat for heterogeneity)	$\widehat{w_i}$ (wt pooled within and btw study variance)	$\hat{\theta}_R$ (contribution to the DerSimonian-Laird estm of Pooled Rate)
(Hoffman et al., 1992)	2	10	20%	0.0160	62.5	1%	2.50	62.5000	9.3%
(Nachman et al., 1996)	14	25	56%	0.0099	101.5	6%	2.74	30.4464	12.7%
(Ribi et al., 2010)	50	66	76%	0.0028	359.4	52%	3.95	41.4336	23.1%
			SUM=		523.3	65%	7.33	135.9764	$\hat{\theta}_R$ DerSimonian-Laird Estimate and 95% CI: **45.5% (28.7%, 62.3%)**

10.6 Pre-Specified Sensitivity Analyses for the Primary Endpoints in Phase 3 Study CL010_168

The pre-specified sensitivity analyses for the two primary endpoints of the Phase 3 study are discussed in the following sections.

10.6.1 Per Protocol Population Analyses

The Per Protocol (PP) population included all of the patients in the ITT population who were compliant with taking avacopan/placebo and who did not have major protocol deviations that might significantly affect the interpretation of the study results.

The following aspects were relevant for consideration of patients to be excluded from the PP analysis or imputed as non-responders for the PP analysis:

- Patients with significant protocol deviations regarding inclusion and exclusion criteria that may impact evaluation of the primary endpoints.
- Patients with significant lack of compliance of study medication administration (avacopan/placebo) defined as:
    - For the Week 26 primary endpoint: All patients who were <75% compliant with taking avacopan/placebo from Day 1 through Week 26 based on study medication accountability records;
    - For the Week 52 primary endpoint: All patients who were <75% compliant with taking avacopan/placebo from Day 1 through Week 52 based on study medication accountability records.
- Patients administered non-allowed medications defined as:
    - For the Week 26 primary endpoint: All patients who had received rituximab or cyclophosphamide, or a clinically significant dose of mycophenolate (except if used instead of azathioprine per protocol), methotrexate, anti-TNF treatment, abatacept, alemtuzumab, belimumab, tocilizumab, eculizumab, or other experimental or immunosuppressive drugs other than protocol-specified use between Day 1 and Week 26;
    - For the Week 52 primary endpoint: In addition to those for the Week 26 primary endpoint, all patients who had rituximab or cyclophosphamide, or a clinically significant dose of mycophenolate (except if used instead of azathioprine per protocol), methotrexate, anti-TNF treatment, abatacept, alemtuzumab, belimumab, tocilizumab, eculizumab, or other experimental or immunosuppressive drugs between Week 26 and 52 that was not associated with a relapse event.
- Patients with missing BVAS data:
    - For the Week 26 primary endpoint: All patients with missing Week 26 BVAS data due to BVAS not being assessed or early withdrawal from the study;

- For the Week 52 primary endpoint: All patients with missing Week 26 or Week 52 BVAS data due to BVAS not being assessed or early withdrawal from the study.

Patients who had minor deviations in per protocol use of rituximab or cyclophosphamide, e.g., IV infusion rates, dose withholding due to infections (which is recommended in the prescribing information for these drugs), rituximab dosing without glucocorticoid pre-medication, or dosing not on the exact day of the protocol-specified schedule were considered for inclusion in the PP population. However, patients with rituximab or cyclophosphamide use at times not specified per protocol were taken into account for the PP population, e.g., dosing of rituximab or cyclophosphamide during the last 26 weeks of the treatment period.

Patients who needed to be taken into account for the PP population were identified and documented prior to the database freeze and prior to unblinding of the database for the analysis of the primary endpoints.

For the analysis of the primary efficacy endpoints in the PP population, patients with important deviations regarding inclusion criteria, e.g., no clear evidence of anti-PR3 or anti-MPO ANCA-associated vasculitis at study entry, and patients with missing Week 26 data were excluded as a whole from the PP population. For lack of compliance and for non-allowed medications, non-responder imputation were applied, i.e., not achieving remission at Week 26 and/or not achieving sustained remission at Week 52.

Patients who received glucocorticoids at doses higher than those provided in the protocol guidance were assessed through sensitivity analyses in the ITT population (see section 10.6.3).

10.6.2 Unstratified Analyses

Sensitivity analyses were based on the unstratified analysis comparing the remission rates for the two primary efficacy endpoints for the ITT population. The same hypothesis tests described for the primary analysis were applied to the sensitivity analyses.

10.6.3 Sensitivity Analyses for High Non-Study Supplied Glucocorticoid Use

Sensitivity analyses (stratified) were also performed to assess the impact of glucocorticoid use other than study prednisone. Analyses were based on adjudicated BVAS and relapse data.

1. For the BVAS remission at Week 26 endpoint:
    a. Patients who used more than 1460 mg prednisone equivalent within the first 26 weeks of the study were considered not to have achieved the BVAS remission at Week 26 endpoint (Remission was ‘No’ for these patients and denominator was the ITT population);
    b. Patients who used more than 1460 mg prednisone equivalent within the first 26 weeks of the study were excluded from the analysis (denominator was the ITT population minus patients excluded from the analysis).

The rationale for selection of a 1460-mg threshold was as follows: Up to 900 mg prednisone equivalent could be used within the first 4 weeks of the study. Pre-medication with glucocorticoids for IV rituximab use to avoid hypersensitivity reactions is common. The glucocorticoid dose typically used for this purpose is 100 mg methylprednisolone IV (i.e., 125 mg prednisone equivalent) for each of 4 IV rituximab doses given within the first 4 weeks of the study. This is the prednisone equivalent of 500 mg, i.e., 125 mg x 4. The protocol also allowed for tapering of oral glucocorticoids from ≤20 mg on Day 1 to zero by the end of 4 weeks. This equates to up to 400 mg prednisone equivalent dose over the first 4 weeks. Therefore, the total prednisone equivalent dose over the first 4 weeks could be up to 900 mg, i.e., 500 mg for rituximab pre-medication plus 400 mg for oral glucocorticoid tapering over the first 4 weeks.

The protocol also allows for short bursts of low dose glucocorticoids to treat non-major manifestations of ANCA-associated vasculitis (doses up to 20 mg for up to 14 days). Two such short bursts equate to 560 mg prednisone equivalent, i.e., 20 mg x 14 days x 2 bursts. Therefore, the total prednisone equivalent dose over the first 26 weeks could be up to 1460 mg in patients who do not have major manifestations of ANCA-associated vasculitis over the first 26 weeks of the study, i.e., 900 mg over the first 4 weeks plus 560 mg for two short bursts of glucocorticoids.

2. For the BVAS sustained remission at Week 52 endpoint:
    a. Patients who used more than 560 mg prednisone equivalent from Week 26 through Week 52 were considered not to have achieved the BVAS sustained remission at Week 52 endpoint (Sustained Remission was 'No' for these patients and denominator was the ITT population);
    b. Patients who used more than 560 mg prednisone equivalent from Week 26 through Week 52 were excluded from the analysis (denominator was the ITT population minus patients excluded from the analysis).

    The rationale for selection of a 560-mg threshold is as follows: As mentioned in (1) above, the protocol allowed for short bursts of low dose glucocorticoids to treat non-major manifestations of ANCA-associated vasculitis (doses up to 20 mg for not more than 14 days). Two such short bursts equate to 560 mg prednisone equivalent, i.e., 20 mg x 14 days x 2 bursts.

10.6.4 Alternative Endpoints

The following preplanned analyses based on BVAS=0 were done:

1. Proportion of patients achieving BVAS=0 at Week 26, independent of non-study supplied glucocorticoid use, were compared across treatment groups in the ITT population.
2. The proportion of patients achieving BVAS=0 at Week 26 and Week 52, independent of non-study supplied glucocorticoid use, and with no relapse between Week 26 and 52 were compared across treatment groups in the ITT population.

Analyses for the alternative endpoints were based on adjudicated BVAS data.

10.6.5 Adjudicated vs Non-Adjudicated Results

The primary endpoint analyses were based on the adjudicated BVAS remission at Week 26, and adjudicated BVAS sustained remission at Week 52 results.

Sensitivity analyses were conducted on the Investigator-assessed BVAS data (non-adjudicated results) for the two primary endpoints, BVAS remission at Week 26 and BVAS sustained remission at Week 52.

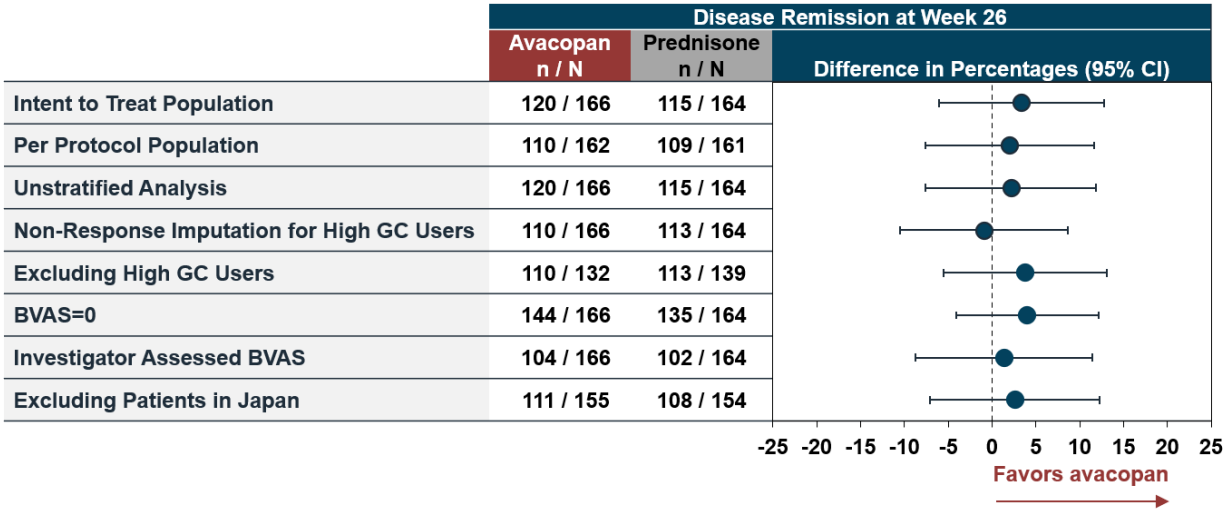
10.6.6 Analysis Excluding Japan

When the clinical trial was launched, Japan was not included. Japan was added later to the trial and therefore Japanese patients were enrolled towards the end of the enrollment period. In order to evaluate the efficacy of the regions included at study initiation, a sensitivity analysis were conducted for the two primary endpoints, excluding patients enrolled in Japan.

10.6.7 Results from the Pre-Specified Sensitivity Analyses

A Forest plot of the sensitivity analyses for the first primary endpoint, remission at Week 26, is shown in Figure 20.

Figure 20: Sensitivity Analyses for Remission at Week 26 in Phase 3 Study CL010_168

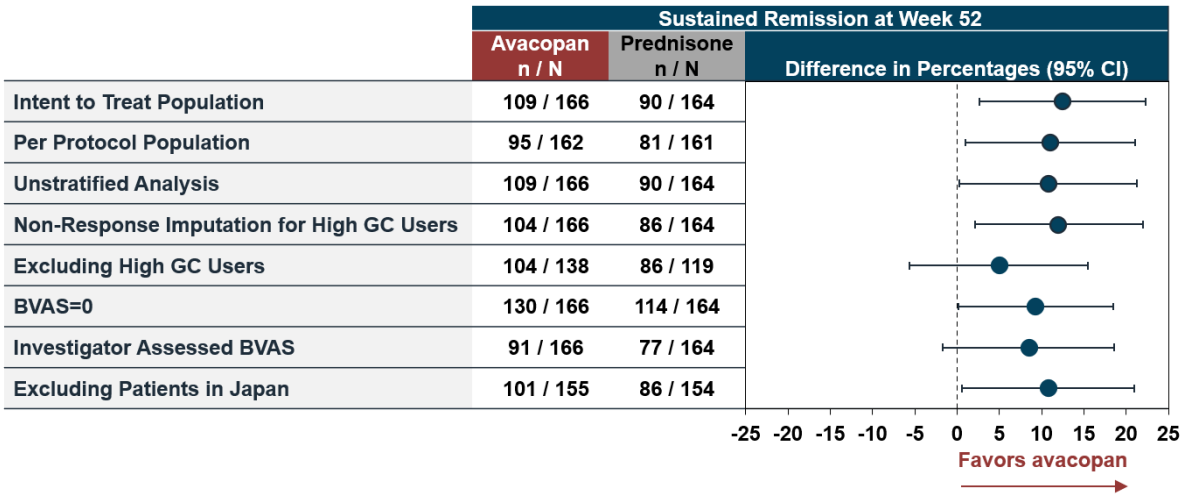


BVAS=Birmingham Vasculitis Activity Score; CI=confidence interval; GC=glucocorticoid.

Results from the sensitivity analyses showed that the avacopan group was consistently non-inferior to the prednisone group across all pre-specified sensitivity analyses. This includes the Per Protocol population analysis, high glucocorticoid use non-responder imputation analysis, exclusion of high glucocorticoid user analysis, BVAS=0 irrespective of glucocorticoid use analysis, Investigator assessment analysis, and the Japan exclusion analysis. The non-inferiority P-values were <0.0001 for all these sensitivity analyses.

A Forest plot of the sensitivity analyses for sustained remission at Week 52 is shown in Figure 21.

Figure 21: Sensitivity Analyses for Sustained Remission at Week 52 in Phase 3 Study CL010_168



BVAS=Birmingham Vasculitis Activity Score; CI=confidence interval; GC=glucocorticoid.

The results from the pre-specified sensitivity analyses of the second primary endpoint are consistent with the results for the ITT analysis. This includes the high glucocorticoid use non-responder imputation analysis, exclusion of high glucocorticoid user analysis, BVAS=0 irrespective of glucocorticoid use analysis, Investigator assessment analysis, and the Japan exclusion analysis.

The non-inferiority P-values were <0.0001 for all these sensitivity analyses. The superiority P-values were <0.025 for all these analyses except for the exclusion of high glucocorticoid user analysis and the Investigator assessment analysis. Regarding the former, the incidence of high glucocorticoid use was higher in the prednisone group (45 of 164 patients [27.4%]) compared to the avacopan group (28 of 166 patients [16.9%]). The majority of these patients who were high glucocorticoid users, i.e., 41 of 45 patients in the prednisone group and 23 of 28 patients in the avacopan group did not fare well during the study and did not achieve sustained remission at Week 52. Therefore, exclusion of these patients from the analysis inflated the incidence of sustained remission at Week 52 disproportionately in the prednisone group compared to the avacopan group, and introduced a bias in favor of the prednisone group. A more relevant sensitivity analysis is the analysis where the high glucocorticoid users in both treatment groups were imputed as non-sustained remitters. This analysis showed that the avacopan group was superior to the prednisone group for sustained remission at Week 52 (P=0.0087).

Regarding sustained remission as assessed by the Investigators, 77 of 164 patients (47.0%) in the prednisone group and 91 of 166 patients (54.8%) in the avacopan group achieved this endpoint (P=0.0513). The difference between Investigator-assessed and the AC-assessed sustained remission is not surprising, because many Investigators are not as experienced in assessing

BVAS as the expert adjudicators. Following is a summary of the notes from the Adjudication Committee that assessed the BVAS data blinded:

Most differences between Investigator and Adjudicator-assessed BVAS relate to either: (1) differentiation between activity (scored on BVAS), and damage (scored on VDI), or (2) attribution to active vasculitis as opposed to another cause.

The purpose of adjudication was to have a consistent approach to the scoring or not scoring of items on BVAS with a focus on assessment at Weeks 26 and 52. The Adjudication Committee made all assessments blinded to treatment group. Such adjudicating practices are consistent with FDA guidance for central assessment of primary endpoint data.

Specific organ system comments from the Adjudication Committee:

Constitutional

- These clinical features tend to have a low specificity for active vasculitis and when occurring as sole items, typically have other explanations.

Ear, Nose, and Throat (ENT)

- Most patients with ANCA-associated vasculitis and ENT involvement have chronic symptomatology, initially as a result of disease activity (scored on BVAS), and subsequently as a result of damage (scored on VDI). Unless there is supportive evidence that the physician thinks the disease is worsening, evidenced by an increase in therapy, items should not be repeatedly scored in BVAS.
- Hearing loss is only scored on BVAS if worse.

Renal

- Many patients have persisting hematuria and proteinuria after an episode of nephritis. If the glomerular filtration rate is stable or improving, persisting and not worsening hematuria or proteinuria are not scored on BVAS. Isolated proteinuria without hematuria does not reflect activity and is not scored on BVAS.
- Hypertension is very rarely caused by active ANCA-associated vasculitis and is usually a consequence of renal injury or medication. In the absence of features of renal activity, it is not scored.

The pre-specified primary analyses were based on the adjudicated results (conducted in a blinded manner) which showed superiority of the avacopan group compared to the prednisone group for sustained remission at Week 52 (P=0.0066).

10.7 Tipping Point Analyses for the Primary Endpoints

To evaluate the potential influence of missing data on the two primary endpoints of the Phase 3 study, tipping point analyses were conducted.

The missing data rates in the Phase 3 study were low and balanced between the 2 treatment groups:

- 10/164 (6.1%) and 10/166 (6.0%) patients at Week 26 in prednisone and avacopan groups, respectively.
- 12/164 (7.3%) and 15/166 (9.0%) patients at Week 52 in prednisone and avacopan groups, respectively.

Table 53 shows the results for the tipping point analyses for Week 26 remission. The tipping point sensitivity analyses results are presented as the lower bound of the 95% confidence interval for the difference in the proportion of responders for each pair of shift parameters. The tipping point analyses are two-dimensional: avacopan and prednisone. As the total numbers of patients with missing data are relatively small in both primary efficacy endpoints, all possible scenarios of shift parameter combinations were considered. All observed data are included as non-missing, regardless of adherence to treatment or use of prohibited medications. Fifty imputed datasets were randomly generated for each pair of shift parameters. The common difference (avacopan minus prednisone) adjusted for randomization strata (newly diagnosed or relapsed ANCA-associated vasculitis, anti-PR3 or anti-MPO ANCA, and IV rituximab or cyclophosphamide [IV or oral] standard of care treatment) using the stratified Summary score test as in the primary efficacy analysis was calculated from each imputed dataset. Each cell is the lower bound of 95% confidence intervals from common difference using Rubin's formula. Note: For the cases of zero missing non-responders imputed to responders, and the case of all missing non-responders imputed to responders in both treatment groups, there is no randomness. The displayed lower bound of 95% confidence intervals is based on 1 imputed dataset instead of 50. The horizontal axis is the number of non-responders imputed to responders in the missing in the avacopan group. The vertical axis is the number of non-responders imputed to responders in the missing in the prednisone group.

The cells shaded in green in Table 53 indicate where the lower limit of the 95% confidence interval of the difference between the avacopan and prednisone groups is above -20 percentage points, the pre-specified noninferiority margin. All cells are shaded green, indicating that missing data at Week 26 did not influence the outcome of the Week 26 remission results.

Table 53: Tipping Point Analysis for Week 26 Remission

Prednisone + Standard of Care (N=164)	10	-11.2	-10.7	-10.2	-9.6	-9.0	-8.3	-7.5	-6.8	-6.1	-5.5	-4.9
	9	-10.7	-10.2	-9.7	-9.1	-8.4	-7.7	-7.0	-6.3	-5.6	-5.0	-4.4
	8	-10.2	-9.6	-9.1	-8.6	-7.9	-7.3	-6.5	-5.8	-5.1	-4.4	-3.9
	7	-9.7	-9.1	-8.6	-8.1	-7.3	-6.7	-6.0	-5.3	-4.6	-3.9	-3.4
	6	-9.1	-8.6	-8.1	-7.6	-6.8	-6.2	-5.5	-4.8	-4.1	-3.4	-2.9
	5	-8.6	-8.1	-7.6	-7.0	-6.3	-5.7	-5.0	-4.2	-3.6	-2.9	-2.3
	4	-8.1	-7.5	-7.0	-6.5	-5.8	-5.1	-4.4	-3.7	-3.1	-2.4	-1.8
	3	-7.6	-7.0	-6.5	-6.0	-5.3	-4.6	-3.9	-3.2	-2.6	-1.9	-1.3
	2	-7.0	-6.5	-6.0	-5.4	-4.8	-4.1	-3.4	-2.7	-2.0	-1.4	-0.8
	1	-6.5	-5.9	-5.4	-4.9	-4.3	-3.5	-2.8	-2.2	-1.5	-0.9	-0.3
	0	-6.0	-5.4	-4.9	-4.4	-3.7	-3.1	-2.3	-1.7	-1.0	-0.4	0.2
		0	1	2	3	4	5	6	7	8	9	10
		Avacopan + Standard of Care (N=166)										

Table 54 shows the results for the tipping point analyses for Week 52 sustained remission. The cells shaded in green indicate where the lower limit of the 95% confidence interval of the difference between the avacopan and prednisone groups is above 0, the superiority margin. All cells are above -20 percentage points, the pre-specified noninferiority margin. Also, the lower limit of 95% confidence interval of the difference between avacopan and prednisone groups was above 0 (the superiority margin) for 81% of all cases. A total of more than 5 patients in the prednisone group with missing Week 52 data had to be flipped from non-remission to remission, and none in the avacopan group before the tipping point would be reached. Therefore, the outcome of the Week 52 sustained remission analysis was not materially influenced by missing data.

Table 54: Tipping Point Analysis for Week 52 Sustained Remission

Prednisone + Standard of Care (N=164)	12	-4.3	-3.7	-3.2	-2.6	-2.1	-1.4	-0.6	0.3	1.3	2.1	2.8	3.4	4.2	4.5	5.2	5.9
	11	-3.8	-3.1	-2.6	-2.0	-1.5	-0.8	0.0	0.9	1.9	2.7	3.3	4.0	4.8	5.1	5.8	6.4
	10	-3.2	-2.5	-2.0	-1.4	-0.9	-0.2	0.6	1.4	2.4	3.2	3.9	4.6	5.2	5.7	6.3	7.0
	9	-2.6	-1.9	-1.4	-0.8	-0.4	0.3	1.1	2.0	2.9	3.8	4.4	5.1	5.8	6.3	6.9	7.6
	8	-2.0	-1.3	-0.9	-0.2	0.2	0.9	1.7	2.5	3.4	4.3	5.0	5.7	6.4	6.9	7.5	8.1
	7	-1.4	-0.7	-0.3	0.3	0.9	1.5	2.2	3.1	4.0	4.9	5.6	6.3	7.0	7.5	8.1	8.7
	6	-0.9	-0.2	0.3	0.9	1.4	2.1	2.8	3.7	4.5	5.5	6.1	6.9	7.6	8.1	8.7	9.3
	5	-0.3	0.4	0.9	1.5	2.0	2.7	3.3	4.3	5.0	6.1	6.7	7.5	8.1	8.7	9.3	9.9
	4	0.3	0.9	1.5	2.0	2.6	3.3	4.0	4.9	5.6	6.7	7.4	8.0	8.7	9.3	9.9	10.5
	3	0.9	1.5	2.0	2.6	3.2	3.8	4.6	5.5	6.3	7.3	8.0	8.6	9.2	10.0	10.4	11.1
	2	1.4	2.1	2.6	3.2	3.7	4.4	5.2	6.0	6.9	7.8	8.4	9.1	9.8	10.5	10.9	11.6
	1	2.0	2.7	3.2	3.7	4.3	5.0	5.7	6.6	7.5	8.4	9.0	9.6	10.3	11.1	11.5	12.2
	0	2.6	3.3	3.8	4.3	4.9	5.5	6.4	7.1	8.1	8.9	9.6	10.2	10.9	11.7	12.1	12.8
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
		Avacopan + Standard of Care (N=166)															

10.8 Criteria for Pausing or Stopping Study Medication in Study CL010_168

Safety laboratory tests were performed frequently over the course of the study. Laboratory reports with abnormal findings were reviewed by the Investigator and the Medical Monitor. The Investigator may have been advised to take appropriate steps, such as increasing the frequency of monitoring, or potentially discontinuing study medication, in case the abnormalities persist.

If a patient developed Grade 3 or greater increased hepatic transaminases (> 5 times the upper limit of normal), or if a patient developed Grade 2 or greater increased transaminases (> 3 times the upper limit of normal) with elevation of bilirubin to > 2 times the upper limit of normal, dosing with study drug (avacopan/placebo) had to be paused in this patient, and evaluation for possible drug-induced liver injury had to be undertaken.

Study medication (avacopan or placebo) had to be permanently discontinued if any of the following occurred that could not be attributed to a reversible etiology unrelated to study medication (e.g., cholelithiasis):

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN and Total Bilirubin >2xULN or INR >1.5
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

If drug induced hepatic toxicity was ruled out following complete evaluation and if all laboratory values had returned to normal, then resumption of study drug might be considered after discussion with and the agreement of the Medical Monitor. If study drug was resumed, hepatic transaminases and bilirubin were to be monitored closely.

If a patient developed Grade 3 or greater leukopenia (WBC count < 2 x 10^9/L) or neutropenia (< 1 x 10^9/L), or grade 4 lymphopenia (< 0.2 x 10^9/L), then study drug had to be paused in this patient. In addition, if a patient developed Grade 2 leukopenia (WBC count <3 x 10^9/L, but ≥2 x 10^9), the patient had to be followed closely for infection and for further significant reduction (reduction by an additional 0.5 x 10^9/L, or to < 2 x 10^9/L) in WBC; if either occurs, then study drug had to be paused in this patient. Study drug might be resumed only if the abnormal value returned to normal and the Investigator deemed resumption to be appropriate.

If a patient developed grade 3 or worse CPK increase (>5 times the upper limit of normal), dosing with study drug had to be paused in this patient. Study drug might be resumed only if the CPK returned to normal levels.

10.9 Prednisone Exposure in Phase 2 Studies CL002_168 and CL003_168

In a drug-drug-interaction study (CL008_168), avacopan increased the plasma concentration of the sensitive CYP3A4 probe substrate, midazolam by less than 2-fold (1.81-fold). The major clearance pathway for prednisone is the 11beta-hydroxysteroid dehydrogenase enzyme (HSD) which converts (reduces) prednisone into prednisolone (the active drug). Avacopan was shown not inhibit 11beta-HSD in vitro. While prednisone is a substrate of CYP3A4, its major metabolic pathway is not through CYP3A4 and therefore CYP3A4 inhibitors are not expected to interact with prednisone significantly. In fact, potent CYP3A4 inhibitors such as that grape fruit juice does not affect prednisone or prednisolone plasma concentrations (Hollander et al., 1995).

Nevertheless, since prednisone is a CYP3A4 substrate, the prednisone plasma concentrations were measured in Phase 2 studies CL002_168 and CL003_168, to evaluate whether there was any significant effect of avacopan co-administration on plasma prednisone concentrations.

The prednisone plasma concentrations on the first day of dosing in Phase 2 study CL002_168 are shown in Figure 22. The placebo + full dose prednisone group received 60 mg prednisone, the CCX168 (avacopan) + low dose prednisone received 20 mg prednisone, and the CCX168 (avacopan) + no prednisone received no prednisone. As anticipated, the full dose prednisone group had the highest prednisone plasma concentrations, followed by the low dose prednisone group, and then the no prednisone group.

The prednisone plasma concentrations on the first day of dosing in Phase 2 study CL003_168, where all subjects in all three groups received 60 mg prednisone on Day 1, are shown in Figure 23. All three treatment groups had a similar plasma prednisone profile indicating no material effect of avacopan on plasma prednisone concentrations.

Single sample prednisone plasma concentrations on Days 8 through 85 of the Phase 2 studies are shown in Figure 24 and Figure 25, respectively, for study CL002_168 and CL003_168. As anticipated, these plasma concentrations are highly variable across study days, since the plasma samples were not collected at a consistent time following dosing with prednisone. No material effect of avacopan on plasma prednisone concentrations were evident.

In summary, evaluation of the plasma prednisone concentrations in the two Phase 2 studies did not show a material effect of avacopan co-administration on plasma prednisone concentrations.

Figure 22: Phase 2 Study CL002_168: Plasma Prednisone Concentrations on Day 1 of Dosing

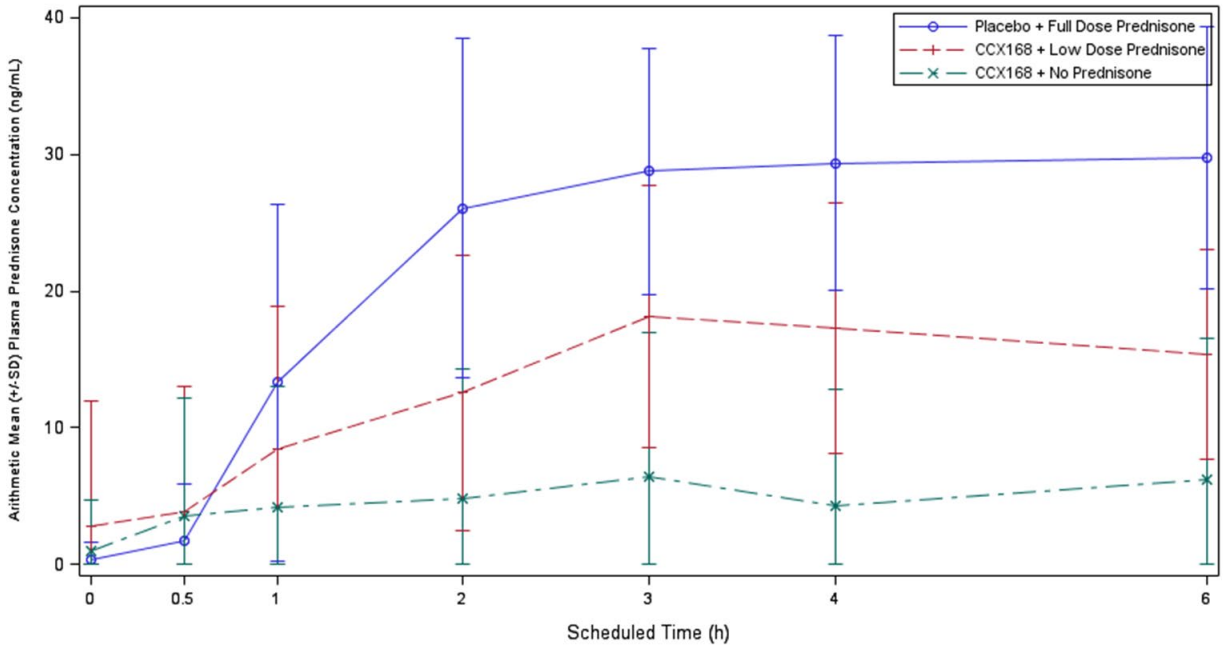


Figure 23. Phase 2 Study CL003_168: Plasma Prednisone Concentrations on Day 1 of Dosing

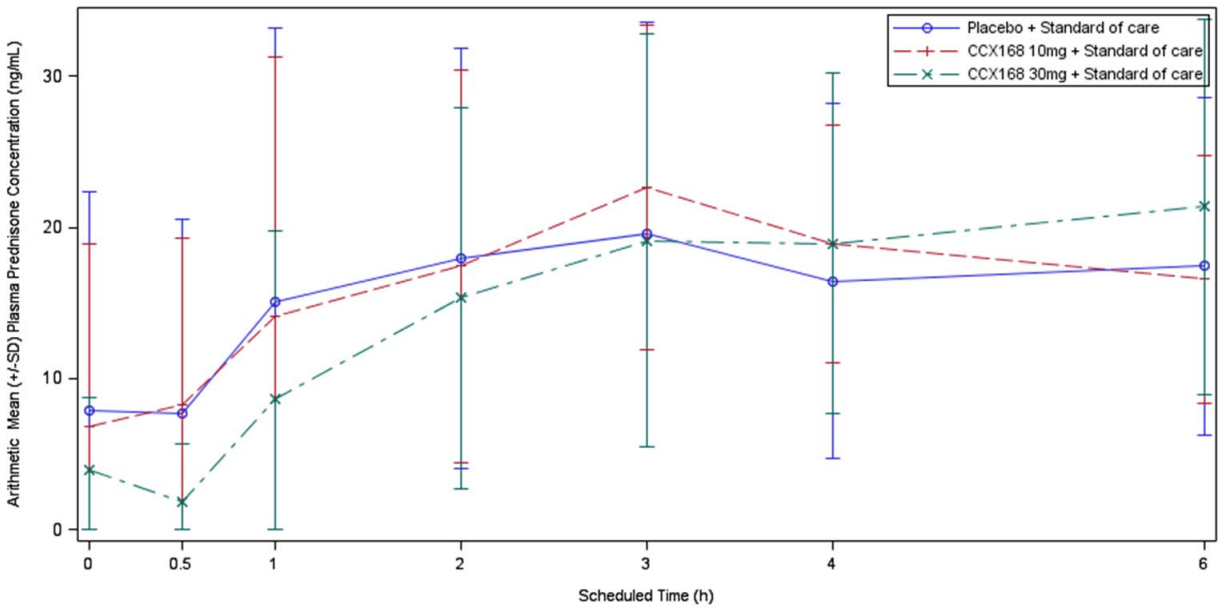


Figure 24: Phase 2 Study CL002_168: Plasma Prednisone Concentrations on Days 8 through 85 of the Dosing Period

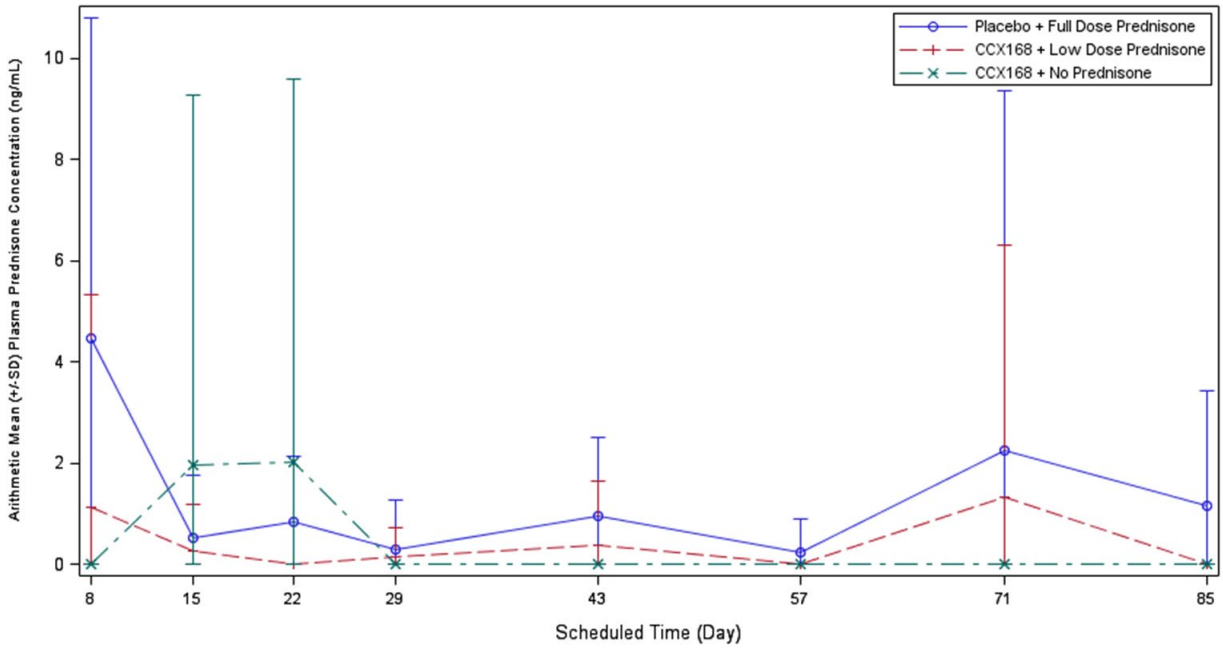
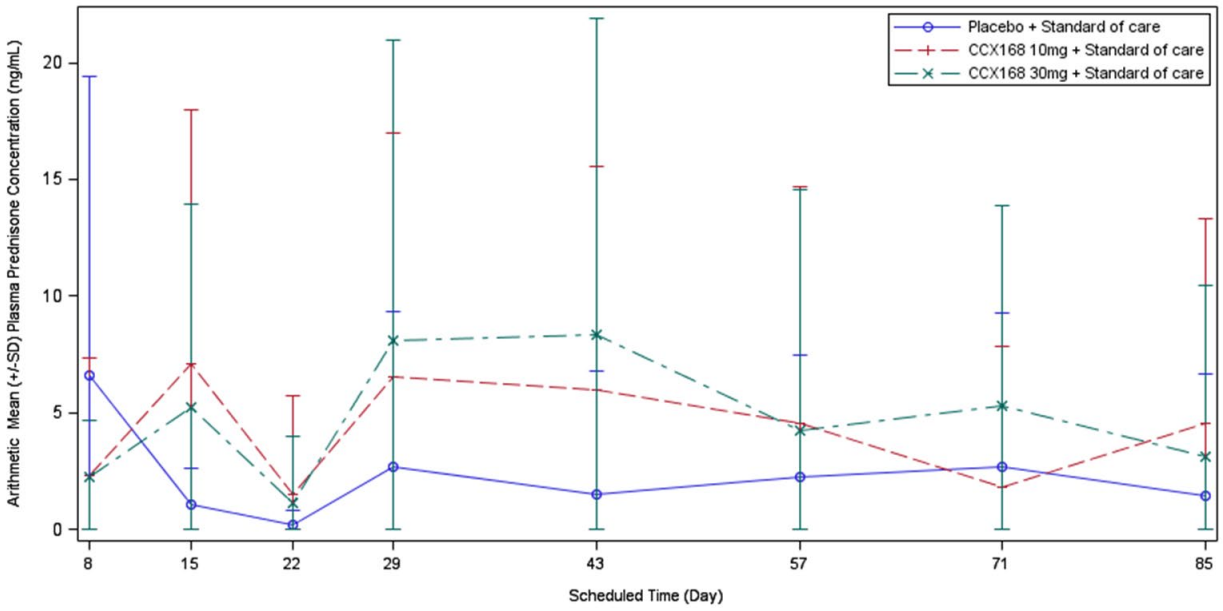


Figure 25: Phase 2 Study CL003_168: Plasma Prednisone Concentrations on Days 8 through 85 of the Dosing Period



10.10 Supportive Phase 2 Study CL002_168: Explanation of Study Design

The supportive Phase 2 Study CL002_168 was conducted in a step-wise manner, comprising 3 steps, as described below and illustrated in Figure 26.

In Step 1, 12 patients were randomized, 8 and 4 patients, respectively, to receive either:

- 30 mg avacopan twice daily orally plus a reduced starting dose of prednisone (20 mg once daily) plus cyclophosphamide, or
- Avacopan-matching placebo plus a full starting dose of prednisone (60 mg once daily) plus cyclophosphamide (control group).

If Step 1 were successful, i.e., there was not more than one suspected unexpected serious adverse reaction (SUSAR) and not an excess of glucocorticoid rescue events in patients in the avacopan group, Step 2 would be launched.

Step 1 was completed successfully. Therefore, Step 2 was launched.

In Step 2, 14 patients were randomized, 8 and 6 patients, respectively, to receive either:

- 30 mg avacopan twice daily orally plus prednisone-matching placebo plus cyclophosphamide, or
- Avacopan-matching placebo plus a full starting dose of prednisone (60 mg once daily) plus cyclophosphamide (control group).

Per Protocol, if Step 2 were successful, i.e., there was not more than one SUSAR and not an excess of glucocorticoid rescue events in patients in the avacopan group, Step 3 would be launched.

Step 2 was also completed successfully. Therefore, Step 3 of the trial was launched.

Step 3 was an expansion of the size of the trial.

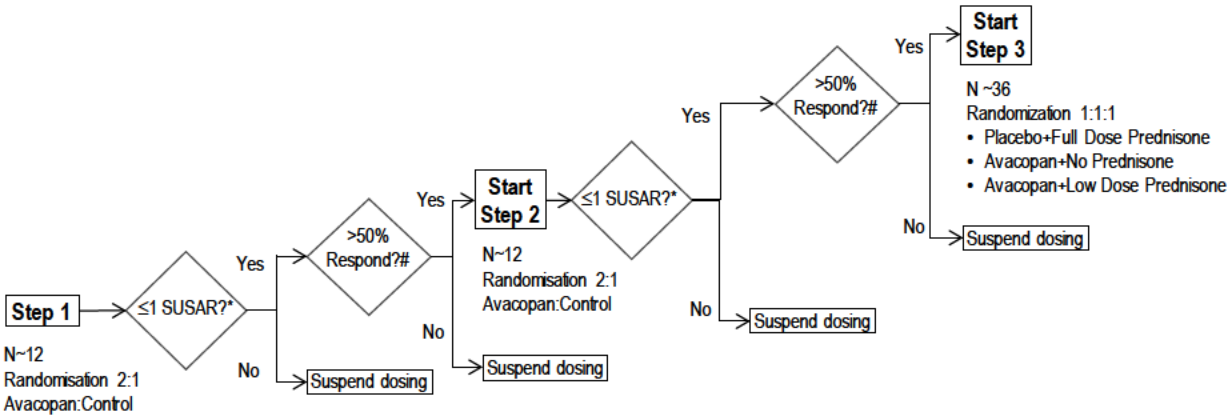
In Step 3, 41 patients were randomized, 13, 14, and 14 patients, respectively, to one of three treatment groups:

- Avacopan-matching placebo plus a full starting dose of prednisone (60 mg once daily) plus cyclophosphamide or rituximab (control group), or
- 30 mg avacopan twice daily orally plus a reduced starting dose of prednisone (20 mg once daily) plus cyclophosphamide or rituximab, or
- 30 mg avacopan twice daily orally plus prednisone-matching placebo plus cyclophosphamide or rituximab.

The treatment period of the trial was 12 weeks, with a 12-week follow-up period.

All patients, irrespective of treatment group, received standard of care cyclophosphamide 15 mg/kg (up to 1.2 g) IV every 2 to 4 weeks (in all three steps) or rituximab 375 mg/m^2 IV once weekly for 4 weeks (in Step 3).

Figure 26: Schema for Study CL002_168



Step 1 = Partial glucocorticoid elimination (67% reduced oral dose) (N~12 subjects)
Step 2 = Complete glucocorticoid elimination (100% reduced oral dose) (N~12 subjects)
Step 3 = Include both partial glucocorticoid elimination (67% reduced oral dose), and complete glucocorticoid elimination (100% reduced oral dose) (N ~ 36 subjects)
* Not more than one suspected unexpected serious adverse reaction (SUSAR) most likely related to avacopan, observed in subjects receiving avacopan.
# >50% of subjects maintained on avacopan without need for rescue IV glucocorticoids

IV=intravenous

10.11 Supportive Phase 2 Study CL002_168: Eligibility Criteria

Inclusion Criteria

Patients who met all of the following criteria were eligible to participate in the study:

1. Clinical diagnosis of granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) or renal limited vasculitis, consistent with Chapel-Hill consensus definitions (Jennette et al., 2013);
2. Male and postmenopausal (lack of menses for at least 2 years without an alternative explanation) or surgically sterile female patients, aged at least 18 years, with new (within 4 weeks prior to Screening) or relapsed ANCA-associated vasculitis where treatment with cyclophosphamide or rituximab would be required. If female under 50 years, the postmenopausal status was to be confirmed by the relevant hormonal test. Male patients with partners of childbearing potential could participate in the study if they had a vasectomy at least 6 months prior to randomization, or if adequate contraception was used during, and for at least 3 months after study completion. Adequate contraception was defined as resulting in a failure rate of less than 1% per year. Acceptable methods for patients included combined estrogen and progestogen (oral, intravaginal, or transdermal), or progestogen-only hormonal contraception (oral, injectable, or implantable), intra-uterine device, intrauterine hormone releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence;
3. Positive indirect immunofluorescence (IIF) test for perinuclear-ANCA (P-ANCA) or cytoplasmic ANCA (C-ANCA), or positive enzyme-linked immunosorbent assay (ELISA) test for anti-PR3 or anti-MPO at Screening. If only the IIF assay was positive at Screening, and none of the ELISA tests, there must have been documentation in the study records of a positive ELISA assay in the past;
4. Had at least 1 “major” item, or at least 3 non-major items, or at least 2 renal items on the BVAS version 3;
5. Estimated glomerular filtration rate ≥ 20 mL per minute (per Modification of Diet in Renal Disease Study [MDRD] equation);
6. Willing and able to give written informed consent and to comply with the requirements of the study protocol; and
7. Judged to be otherwise healthy by the Investigator, based on medical history, physical examination (including electrocardiogram [ECG]), and clinical laboratory assessments. Patients with clinical laboratory values that were outside of normal limits (other than those specified in the Exclusion Criteria) and/or with other abnormal clinical findings that were judged by the Investigator not to be of clinical significance, could have been entered into the study.

Exclusion Criteria

Patients who met any of the following criteria were excluded from participation in the study:

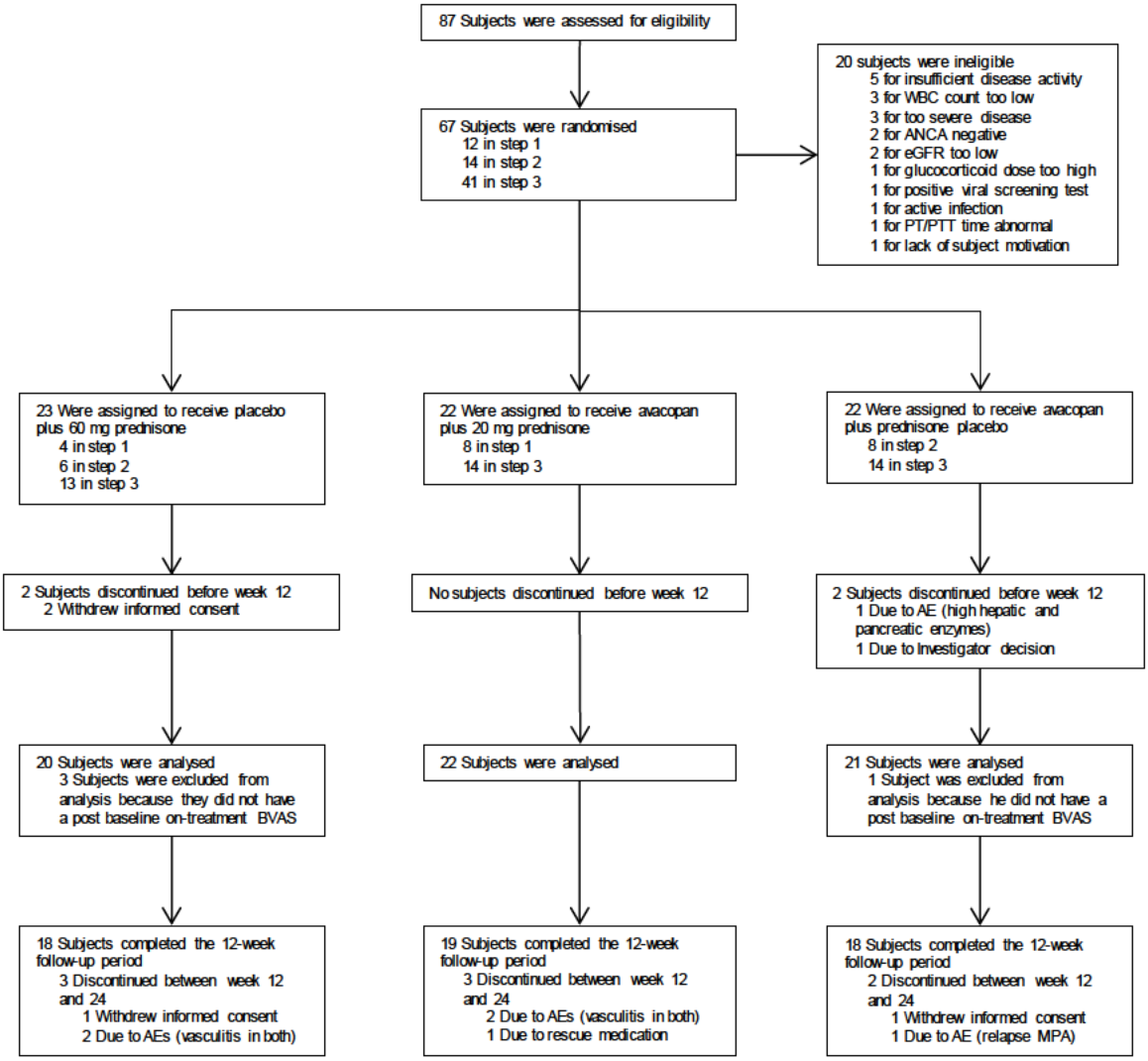
1. Severe disease as determined by rapidly progressive glomerulonephritis such that commencement of renal replacement therapy could have been anticipated within 7 days, alveolar hemorrhage leading to Grade 3 or higher hypoxia (i.e., decreased oxygen saturation at rest, e.g., pulse oximeter < 88% or partial pressure of arterial oxygen ≤ 55 mmHg), hemoptysis, rapid-onset mononeuritis multiplex (Grade 3 or higher, leading to severe symptoms that limit self-care activities of daily living or requiring an assistive device), or central nervous system involvement;
2. Any other multi-system autoimmune disease including eosinophilic granulomatosis with polyangiitis (Churg Strauss), systemic lupus erythematosus, immunoglobulin (Ig)A vasculitis (Henoch Schönlein purpura), rheumatoid vasculitis, Sjögren's disease, anti-glomerular basement membrane disease, or cryoglobulinemia;
3. Medical history of coagulopathy or bleeding disorder;
4. Received cyclophosphamide within 12 weeks prior to Screening; if on azathioprine, mycophenolate mofetil, or methotrexate at the time of Screening, these drugs must have been withdrawn prior to receiving the cyclophosphamide dose on Day 1;
5. Received IV corticosteroids, > 3000 mg methylprednisolone equivalent, within 12 weeks prior to Screening;
6. Had been taking an oral daily dose of a corticosteroid of more than 10 mg prednisone equivalent for more than 6 weeks continuously prior to the Screening visit. If on an oral corticosteroid at a daily dose of more than 10 mg prednisone equivalent at the time of Screening, the oral dose needed to be reduced to a daily dose not exceeding 10 mg prednisone equivalent prior to Day 1;
7. Received rituximab or other B-cell antibody within 52 weeks of Screening or 26 weeks provided B-cell reconstitution had occurred (i.e., CD19 count > 0.01 x 10^9/L); received anti-tumor necrosis factor treatment, abatacept, alemtuzumab, IV Ig, belimumab, tocilizumab, or plasma exchange within 12 weeks prior to Screening;
8. Symptomatic congestive heart failure requiring prescription medication, clinically evident peripheral edema of cardiac origin, poorly-controlled hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg), history of unstable angina, myocardial infarction, or stroke within 6 months prior to Screening;
9. History or presence of any form of cancer within the 5 years prior to Screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or cervical carcinoma in situ or breast carcinoma in situ that had been excised or resected completely and was without evidence of local recurrence or metastasis;
10. Presence of tuberculosis based on chest X-rays performed during Screening as part of the BVAS assessment;

11. Positive hepatitis B virus, hepatitis C virus, or human immunodeficiency virus (HIV) viral Screening test;
12. Any infection requiring antibiotic treatment within 4 weeks prior to Screening (except for prophylactic treatment for *Pneumocystis carinii* pneumonia [PCP] or treatment for suspected infection that instead turned out to be a consequence of ANCA vasculitis, e.g., pneumonitis);
13. Received a live vaccine within 4 weeks prior to Screening;
14. White blood cell (WBC) count < 4000/μL, or neutrophil count < 2000/μL, or lymphocyte count < 1000/μL;
15. Hemoglobin < 9 g/dL (or 5.56 mmol/L) at Screening;
16. Evidence of hepatic disease; aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, or bilirubin > 3 x the upper limit of normal;
17. Prothrombin time or partial thromboplastin time above the normal reference limit;
18. Clinically significant abnormal ECG during Screening, e.g., QTcF > 450 msec;
19. Participated in any clinical study of an investigational product within 30 days prior to Screening or within 5 half-lives after taking the last dose; or
20. History or presence of any medical condition or disease which, in the opinion of the Investigator, may have placed the patient at unacceptable risk for study participation.

10.12 Supportive Phase 2 Study CL002_168: Consort Diagram of Patient Flow

A Consort diagram of patient flow through the study is shown in Figure 27.

Figure 27: Consort Diagram of Patient Flow Through Study CL002_168



AE=adverse event; ANCA=anti-neutrophil cytoplasmic autoantibody; BVAS=Birmingham Vasculitis Activity Score; eGFR=estimated glomerular filtration rate; MPA=microscopic polyangiitis; PT=prothrombin time; PTT=partial thromboplastin time; AE=adverse event; WBC=white blood cell

10.13 Supportive Phase 2 Study CL002_168: Statistical Analysis Plan

10.13.1Statistical Methods for Study CL002_168

For the purposes of data analysis, the ITT Population included all patients who were randomized, had received at least 1 dose of study medication, and had at least 1 post-baseline on treatment BVAS assessment. Data for patients from Steps 1, 2, and 3 treated with placebo were combined for summary and analysis purposes.

The primary analysis was performed across all 3 steps. The proportion of patients achieving disease response during the 84-day treatment period was calculated to compare each avacopan group against the placebo (standard of care) group. If the Day 85 result was missing, the last post-randomization, on-treatment BVAS result was used, unless the patient had worsening of ANCA-associated vasculitis and required rescue treatment. In the latter case, the patient was considered a non-responder.

If the lower bound of the 1-sided 95% confidence interval (CI) for the difference (avacopan minus control group) was greater than -0.20 (20%), the respective avacopan group was considered not inferior to the placebo group. If the lower bound was greater than 0.0, the respective avacopan group was considered superior to the placebo group in achieving the disease response. For the purpose of data presentation, the 2-sided 90% CIs were displayed since the lower bound of the 1-sided 95% CI was identical to the lower bound of the 2-sided 90% CI. The p-values from the hypothesis tests of non-inferiority (H1: $p1-p2 > -0.2$) and superiority (H1: $p1-p2 > 0$) were also displayed. The primary analysis included all patients in all 3 steps.

Similar analyses were performed to compare the all avacopan group to the placebo group. In addition, the analyses were repeated for all patients in Step 3, for patients in Steps 1 + 2 combined, and for Steps 1 and 2 separately. For these analyses, CIs and p-values were not displayed for Steps 1 and 2 due to the small sample sizes.

10.13.2Sample Size for Study CL002_168

Steps 1 and 2 were designed to provide an initial evaluation of the safety and feasibility of using avacopan as a glucocorticoid sparing or replacement therapy during induction of remission. The study progressed to Step 3 if ANCA-associated vasculitis disease activity in the majority of patients on avacopan (> 50%) was maintained without the need for rescue glucocorticoid therapy. A sample size of 12 patients (8 patients who received active study treatment and 4 patients who received placebo) per step for the first 2 steps of the study was based on feasibility.

A sample size of 36 patients in Step 3 (12 in each of the avacopan groups and 12 in the placebo group) provided a total of approximately 60 patients across all 3 steps, and approximately 20 patients in each of the treatment groups. Assuming a control group BVAS response of 44% at Day 85 and avacopan group response of 86%, a sample size of 20 in each group provided approximately 90% power for the primary efficacy analysis.

10.14 Supportive Phase 2 Study CL003_168: Eligibility Criteria

The complete eligibility criteria for participating in Study CL003_168 are listed below.

Inclusion Criteria

Patients must have met all of the following inclusion criteria to enter the study:

1. Clinical diagnosis of granulomatosis with polyangiitis (Wegener's) (GPA), microscopic polyangiitis (MPA) or renal limited vasculitis, consistent with Chapel Hill consensus definitions (Jennette et al., 2013);
2. Male and female patients aged at least 18 years, with new (typically within 4 weeks prior to screening) or relapsed ANCA-associated vasculitis where treatment with cyclophosphamide or rituximab would be required. Female patients of childbearing potential could have participated if adequate contraception was used during the study, and for at least 6 months after the last cyclophosphamide dose (if receiving cyclophosphamide) and at least 12 months after the last rituximab dose (if receiving rituximab). Male patients with partners of childbearing potential could have participated in the study if they had a vasectomy at least 6 months prior to randomization or if adequate contraception was used during the study, and for at least 6 months after the last cyclophosphamide dose (if receiving cyclophosphamide) and at least 12 months after the last rituximab dose (if receiving rituximab). Adequate contraception was defined as 1 highly effective method plus 1 effective method; highly effective methods included hormonal contraceptives, e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants; intrauterine device or intrauterine system; vasectomy and tubal ligation; effective methods included barrier methods of contraception, e.g., male condom, female condom, cervical cap, diaphragm, or contraceptive sponge plus a spermicide;
3. Positive indirect immunofluorescence test for P-ANCA or C-ANCA, or positive ELISA test for anti-PR3 or anti-MPO at screening; if only the indirect immunofluorescence assay was positive at screening, and none of the ELISA tests, there must have been documentation in the study records of a positive ELISA assay in the past;
4. Have at least 1 "major" item, or at least 3 non-major items, or at least 2 renal items on the BVAS version 3;
5. Estimated glomerular filtration rate (eGFR) $\geq$ 20 mL per minute per 1.73 m^2 (per Modification of Diet in Renal Disease Study equation);
6. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol; and
7. Judged to be otherwise healthy by the Investigator, based on medical history, physical examination (including ECG), and clinical laboratory assessments. Patients with clinical laboratory values that were outside of normal limits (other than those specified in the Exclusion Criteria) and/or with other abnormal clinical findings that were judged by the Investigator not to be of clinical significance, may have been entered into the study.

Exclusion Criteria

Patients should have been excluded from the study if they met any of the following criteria:

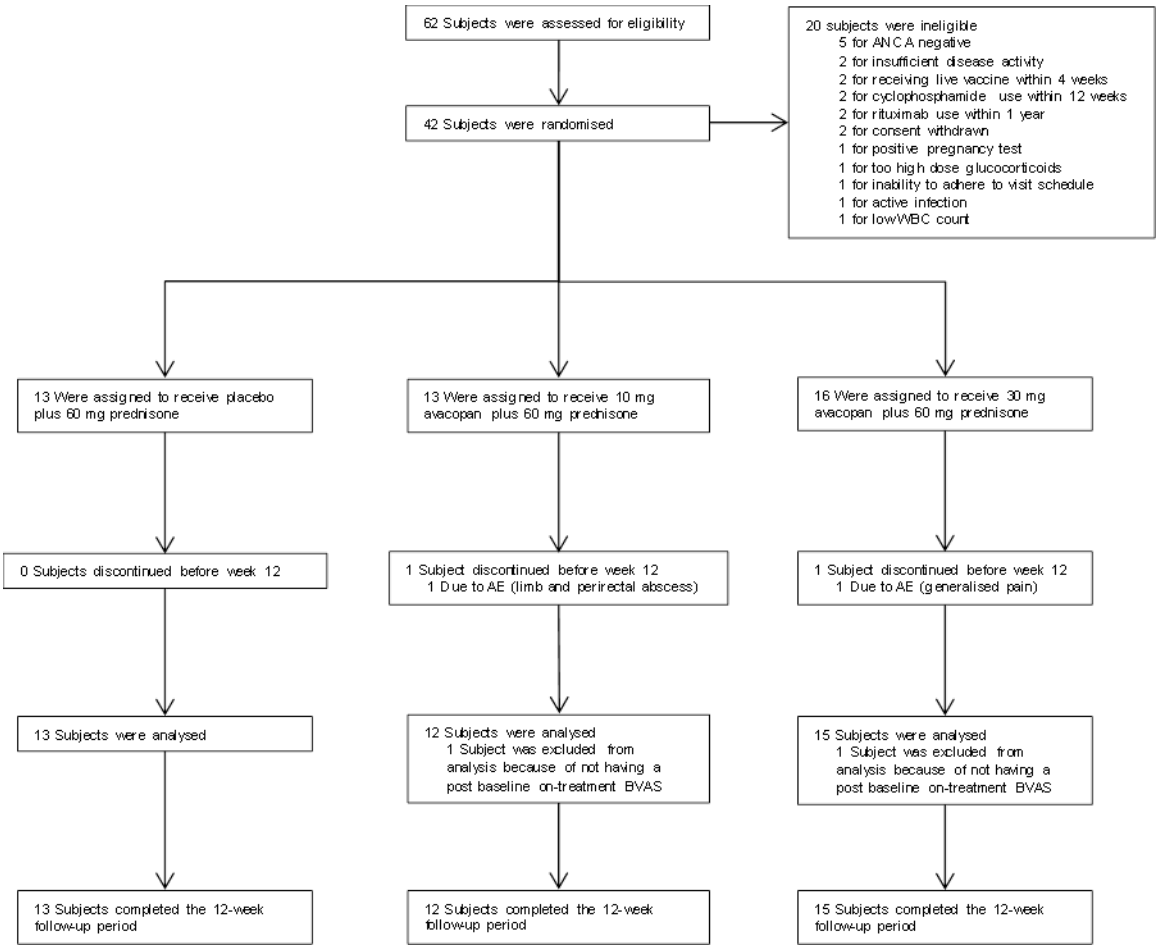
1. Severe disease as determined by rapidly progressive glomerulonephritis such that commencement of renal replacement therapy could be anticipated within 7 days, or alveolar hemorrhage leading to Grade 3 or higher hypoxia (i.e., decreased oxygen saturation at rest [e.g., pulse oximeter < 88% or partial pressure of arterial oxygen ≤ 55 mmHg]);
2. Women who were pregnant (positive pregnancy test) or breastfeeding at study entry; women should not have breastfed during the study, and if receiving rituximab, until drug levels were no longer detectable after study completion;
3. Any other multi-system autoimmune disease including eosinophilic granulomatosis with polyangiitis (Churg Strauss), systemic lupus erythematosus, immunoglobulin (Ig)A vasculitis (Henoch-Schönlein purpura), rheumatoid vasculitis, Sjögren's disease, anti-glomerular basement membrane disease, or cryoglobulinemia;
4. Medical history of coagulopathy or bleeding disorder;
5. Received cyclophosphamide within 12 weeks prior to screening; if patient was on azathioprine, mycophenolate mofetil, or methotrexate at the time of screening, these drugs must have been withdrawn prior to the patient receiving the cyclophosphamide or rituximab dose on Day 1;
6. Received IV corticosteroids, > 3000 mg methylprednisolone equivalent, within 12 weeks prior to screening;
7. Had been taking an oral daily dose of a corticosteroid of more than 10 mg prednisone-equivalent for more than 6 weeks continuously prior to the screening visit. If on corticosteroids at the time of screening, the non-study supplied corticosteroids were stopped when the patient started taking the study supplied 60 mg prednisone dose on Day 1;
8. Received rituximab or other B-cell antibody within 52 weeks of screening or 26 weeks provided B-cell reconstitution had occurred (i.e., CD19 count > 0.01 x 10^9/L); received anti-tumor necrosis factor treatment, abatacept, alemtuzumab, IV immunoglobulin (IVIg), belimumab, tocilizumab, or plasma exchange within 12 weeks prior to screening;
9. Symptomatic congestive heart failure requiring prescription medication, clinically evident peripheral edema of cardiac origin, poorly-controlled hypertension (systolic blood pressure > 160 or diastolic blood pressure > 100), history of unstable angina, myocardial infarction or stroke within 6 months prior to screening;
10. History or presence of any form of cancer within the 5 years prior to screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or cervical carcinoma in situ or breast carcinoma in situ that had been excised or resected completely and was without evidence of local recurrence or metastasis;

11. Evidence of tuberculosis based on chest x-rays performed during screening as part of the BVAS assessment;
12. Positive hepatitis B virus, hepatitis C virus, or human immunodeficiency virus (HIV) viral screening test;
13. Any infection requiring antibiotic treatment within 4 weeks prior to screening (except for prophylactic treatment for Pneumocystis carinii pneumonia [PCP] or treatment for suspected infection that instead turned out to be a consequence of ANCA vasculitis, e.g., pneumonitis);
14. Received a live vaccine within 4 weeks prior to screening;
15. White blood cell (WBC) count < 4000/µL, or neutrophil count < 2000/µL, or lymphocyte count < 1000/µL;
16. Hemoglobin < 9 g/dL (or 5.56 mmol/L) at screening;
17. Evidence of hepatic disease; aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, or bilirubin > 3 x the upper limit of normal;
18. Prothrombin time or partial thromboplastin time > normal reference limit;
19. Clinically significant abnormal ECG during screening, e.g., QTcF > 450 msec;
20. Participated in any clinical study of an investigational product within 30 days prior to screening or within 5 half-lives after taking the last dose;
21. Known hypersensitivity to avacopan or inactive ingredients of the avacopan capsules (including gelatin, polyethylene glycol, or Cremophor), cyclophosphamide or its metabolites (for patients scheduled to receive cyclophosphamide), or known Type I hypersensitivity or anaphylactic reactions to murine proteins, Chinese Hamster Ovary cell proteins, or to any component of rituximab (for patients scheduled to receive rituximab);
22. Urinary outflow obstruction, active infection (especially varicella zoster infection), or platelet count < 50,000/µL (for patients scheduled to receive cyclophosphamide treatment); or
23. History or presence of any medical condition or disease which, in the opinion of the Investigator, may have placed the patient at unacceptable risk for study participation.

10.15 Supportive Phase 2 Study CL003_168: Consort Diagram of Patient Flow

A Consort diagram of patient flow through the study is shown in Figure 28.

Figure 28: Consort Diagram of Patient Flow Through Study CL003_168



AE=adverse event; ANCA=anti-neutrophil cytoplasmic autoantibody; BVAS=Birmingham Vasculitis Activity Score; WBC=white blood cell

10.16 Supportive Phase 2 Study CL003_168: Statistical Analysis Plan

In Study CL003_168, the ITT Population comprised all patients who were randomized, received at least 1 dose of study medication and had at least 1 post-baseline, on-treatment BVAS assessment. The main efficacy analysis was in the ITT Population. If deemed appropriate, sensitivity analyses also could have been performed on all randomized patients and a per protocol population, excluding patients with major protocol deviations. Data were summarized descriptively by treatment group and overall. For continuous variables, summary statistics included the sample size, mean, median, standard deviation, standard error of the mean, minimum, and maximum. Continuous variables with skewed distributions were log-transformed for analysis including UACR, urinary RBC count, urinary MCP-1:creatinine ratio, and hsCRP. Frequency counts and percentages were presented for categorical variables. All data are displayed in data listings.

The primary efficacy endpoint was the proportion of patients achieving disease response at Day 85 defined as BVAS reduction from baseline of at least 50% plus no worsening in any body system component. Because of the relatively small sample size of the study, no inferential statistical analysis was performed on the primary endpoint.

The proportion of patients achieving disease response during the 84-day treatment period was calculated and used to compare each avacopan group against the placebo (standard of care) group. Similar comparisons were made between the pooled group of all patients randomized to avacopan treatment and the placebo group. If the Day 85 result was missing, the last post-randomization result was used, unless the patient had worsening of ANCA-associated vasculitis and required rescue treatment. In the latter case, the patient was considered a non-responder. Of the 42 randomized patients, 2 patients had no post-randomization assessment, so the ITT Population comprised 40 patients.

For the purpose of data presentation, the 2-sided 90% confidence intervals (CIs) were displayed since the lower bound of the 1-sided 95% CI was identical to the lower bound of the 2-sided 90% CI. These disease response analyses were repeated for the 168-day study period. For this analysis, if the Day 169 result was missing, the last result after Day 85 was used, unless the patient had worsening of ANCA-associated vasculitis and required rescue treatment. In the latter case, the patient was considered a non-responder. Of the 40 patients with Day 85 results, 3 additional patients had no Day 169 assessment, so their Day 113 assessment was carried forward for the analysis. Subgroup analyses were performed for the following subgroups: patients with renal disease at baseline (defined as patients with BVAS items scored in the renal organ system), patients without renal disease at baseline (defined as patients with no BVAS items scored in the renal organ system), patients receiving cyclophosphamide background treatment, patients receiving rituximab background treatment, patients with newly diagnosed disease, patients with relapsed disease, patients with MPO+ disease, patients with PR3+ disease, patients with GPA, and patients with MPA.

The sample size was based on practical rather than statistical considerations.