CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214487Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	214487
Priority or Standard	Standard
Submit Date(s)	July 7, 2020
Received Date(s)	July 7, 2020
PDUFA Goal Date	October 7, 2021
Division/Office	Office of Immunology and Inflammation (OII) / Division of Rheumatology and Transplant Medicine (DRTM)
Review Completion Date	See electronic stamp date
Established/Proper Name	Avacopan
(Proposed) Trade Name	TAVNEOS
Pharmacologic Class	Complement 5a receptor antagonist
Applicant	ChemoCentryx, Inc.
Doseage form	10 mg capsules
Applicant proposed Dosing Regimen	30 mg twice daily with food
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA])
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adjunctive treatment of adult patients with severe active antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with standard therapy including glucocorticoids. TAVNEOS does not eliminate glucocorticoid use.
Recommended Dosing Regimen	30 mg twice daily with food

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Abbreviations: DRTM, Division of Rheumatology and Transplant Medicine; OCP, Office of Clinical Pharmacology; OB, Office of Bioequivalence.

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Glossary

AAV	ANCA-associated vasculitis
AC	adjudication committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse events of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
ANCA	anti-neutrophilic cytoplasmic antibody
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the curve
AZA	azathioprine
BID	twice daily
BMI	body mass index
BVAS	Birmingham Vasculitis Activity Score
C5aR	C5a receptor
CFR	Code of Federal Regulations
C_{max}	maximum serum concentration
CPK	creatinine phosphokinase
CMV	cytomegalovirus
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
CYC	cyclophosphamide
DAH	diffuse alveolar hemorrhage
DARRTS	Document Archiving Reporting and Regulatory Tracking System
DCN	Division of Cardiology and Nephrology
DCOA	Division of Clinical Outcome Assessment
DDI	drug-drug interaction
DHN	Division of Hepatology and Nutrition
DIIP	Division of Inflammation and Immune Pharmacology
DILI	drug-induced liver injury
DMC	data monitoring committee
DRTM	Division of Rheumatology and Transplant Medicine
ECG	electrocardiogram

eCRF	electronic case report form
EDC	Electronic Data Capture system
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
EGPA	eosinophilic granulomatosis with polyangiitis
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GC	glucocorticoids
GCP	good clinical practice
GTI	Glucocorticoid Toxicity Index
GN	glomerulonephritis
GPA	granulomatosis with polyangiitis
GTI-AIS	Glucocorticoid Toxicity Index-Aggregate Improvement Score
GTI-CWS	Glucocorticoid Toxicity Index-Cumulative Worsening Score
HBV	hepatitis B virus
hr-QoL	health-related quality of life
HTN	hypertension
IND	investigational new drug
IRB	Institutional Review Board
IRT	Interdisciplinary Review Team
ITT	intent to treat
LC-MS/MS	liquid chromatographic separation with tandem mass spectrometric
LLOQ	lower limit of quantification
MACE	major cardiac adverse events
MCP-1	monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MCS	Mental Component Score
MMF	mycophenolate mofetil
MMRM	mixed effects model for repeated measures
MPA	microscopic polyangiitis
MPO	myeloperoxidase
MTX	methotrexate
NCGN	necrotizing and crescentic glomerulonephritis
NDA	new drug application
NOAEL	no-observed-adverse-effect-level
OCP	Office of Clinical Pharmacology
OII	Office of Immunology and Inflammation
OND	Office of New Drugs
OSI	Office of Scientific Investigation

PBO	placebo
PCJ	*Pneumocystis jirovecii*
PCP	*Pneumocystis* pneumonia
PCS	Physical Component Score
PD	pharmacodynamics
PEXIVAS	Plasma Exchange and Glucocorticoids for Treatment of Anti-neutrophil Cytoplasm Antibody-associated Vasculitis
PK	pharmacokinetics
PP	per protocol
PR3	proteinase-3
PRO	patient reported outcome
PT	preferred term
QD	once daily
RAVE	Rituximab in AAV
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
RSV	respiratory syncytial virus
RTX	rituximab
SAE	serious adverse event
SAP	statistical analysis plan
SD	Sprague Dawley
SMQ	Standardized MedDRA Query
SOC	system organ class
TEAE	treatment emergent adverse event
TNF	tumor necrosis factor
UACR	urine albumin: creatinine ratio
ULN	upper limit of normal
UTI	urinary tract infection
VAS	Visual Analogue Scale
VDI	vasculitis damage index
WBC	white blood cell
WHO	World Health Organization

1. Executive Summary

1.1. Product Introduction

Avacopan is a small molecule antagonist of C5a receptor (C5aR). C5a, the cleaved fragment of C5, is a terminal component of the complement cascade and acts as a potent neutrophil chemoattractant and agonist. It has been proposed that C5a and C5aR may play a central role in the pathogenesis of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). One proposed mechanism involves the alternative complement pathway. Cytokines prime neutrophils to express ANCA antigens at the cell surface. Primed neutrophils adhere to the endothelium, and ANCAs interact with their antigens, resulting in further neutrophil activation. ANCA-activated neutrophils release factors that can directly damage the endothelium but can also activate the alternative complement pathway, which, in turn, generates C5a. C5a and C5aR on neutrophils then create an amplification loop for ANCA-mediated neutrophil activation, eventually culminating in severe necrotizing inflammation of the vessel wall (Kallenberg and Heeringa 2015). C5a may also directly activate vascular endothelial cells, promoting retraction and increased permeability leading to tissue edema. Plasma C5a levels have been found to be higher in patients with active ANCA vasculitis compared to patients in remission (Gou et al. 2013). In the anti-myeloperoxidase (MPO) murine model, mice with knocked-out C5aR were protected from development of ANCA-induced glomerulonephritis after administration of anti-MPO IgG. In a hC5aR knock-in mouse, blocking C5aR with avacopan 30 mg/kg decreased glomerular crescents, hematuria, proteinuria, and leukocyturia, and was dose dependent in the anti-MPO murine model (Xiao et al. 2014).

ChemoCentryx has proposed avacopan, a new molecular entity C5a receptor antagonist, for treatment of adult patients with ANCA-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]). The proposed dosing regimen is 30 mg twice daily orally.

1.2. Conclusions on the Substantial Evidence of Effectiveness

In new drug application (NDA) 214487, the results from a single phase 3 study, CL010_168, a multicenter, randomized, double-blind, active controlled study, and two phase 2 studies, CL002_168 and CL003_168, were submitted to provide the primary evidence for the effectiveness of avacopan in ANCA-associated vasculitis.

Study CL010_168

In Study CL010_168, 331 patients with AAV were randomized to receive avacopan 30 mg twice daily (BID) for 52 weeks or a protocol-specified 20-week prednisone taper. All patients received induction therapy with either cyclophosphamide (CYC) or rituximab (RTX). Patients who received CYC induction treatment received azathioprine as maintenance therapy, while patients who received RTX induction treatment did not receive any maintenance therapy.

Study CL010_168 met its primary endpoints, demonstrating superiority for sustained remission at Week 52 (avacopan vs. prednisone treatment difference 12.5% with 95% CI [2.6%, 22.3%]). Noninferiority, but not superiority was demonstrated for remission at Week 26 (avacopan vs. prednisone treatment difference 3.4% with 95% CI [-6.0%, 12.8%]). In the evaluation of the subgroups by background therapy, the treatment effect at Week 52 was observed in the RTX induction subgroup (treatment difference 15% with 95% CI [2.2%, 27.7%]) that did not receive maintenance standard of care, while no meaningful treatment effect was observed in the cyclophosphamide induction subgroup (treatment difference 3% with 95% CI [-14.8%, 21.4%]) that received maintenance treatment with azathioprine. We acknowledge that induction treatment was selected based on Investigator discretion, and that these subgroups were not randomized to background therapy; however, these findings suggest the possibility that avacopan may not be effective in patients receiving standard-of-care maintenance therapy. While subgroup analyses must be interpreted with caution as there is often low precision and considerable uncertainty around these estimates, this inconsistency raises concerns regarding the persuasiveness of the evidence of effectiveness and how avacopan may fit into the treatment armamentarium of AAV.

Assessment Differences

Additional differences between the assessments of Birmingham Vasculitis Activity Score (BVAS) remission performed by the Adjudication Committee, the specified primary analysis, and the Investigators, were most frequently attributed to persistent vasculitis which was not captured in the modified BVAS administered in the study. However, when the primary endpoint was analyzed based on the Investigators' assessment, the superiority of avacopan at Week 52 was no longer supported. Investigators were experienced in management of vasculitis, and their assessments may be more reflective of real-world use. These discrepancies in assessment between the Investigator and the Adjudication Committee were relatively balanced by treatment arm but underscore the lack of robustness of the superiority assessment.

Assessment for Noninferiority

As noted above, noninferiority but not superiority on remission was demonstrated at Week 26. Because both treatment arms received background therapy in the form of CYC or RTX and the

benefit of glucocorticoids on top of CYC or RTX is not well-understood, it is difficult to determine if similar remission rates at Week 26 observed on both arms can support a conclusion that avacopan is effective or if such similarities can be primarily attributed to both arms receiving induction with RTX or CYC. In addition, the Applicant did not provide adequate data or information that would isolate the effect of prednisone when added to RTX or CYC induction to inform the margin of the non-inferiority comparison in this study.

Interpretation of the non-inferiority comparison at Week 26 is further limited by the large number of patients (86%) who received glucocorticoids in the avacopan arm from Week 0 to 26. Therefore, the noninferiority assessment is not the intended comparison of avacopan vs. prednisone, but instead a comparison of avacopan plus lower dose glucocorticoids vs. higher dose glucocorticoids. Furthermore, based on the study design which specified the glucocorticoid use in the prednisone arm, it cannot be concluded that any differences in cumulative glucocorticoid use was due to a treatment effect of avacopan and not due to the specifications of the protocol. The use of glucocorticoids in AAV is evolving with more recent literature supporting that a lower dose steroid regimen may be sufficient for controlling disease activity compared to higher dose regimens (Walsh et al. 2020). In total, results of the efficacy analyses at Week 26 do not support the effectiveness of avacopan.

Assessment of Glucocorticoid Use

One of the objectives of the avacopan clinical program was to demonstrate that treatment avacopan could be steroid-sparing. Study CL010_168 was designed to compare avacopan to a standard protocol-specified dosing regimen of high dose prednisone (45-60 mg based on weight) tapered down over 20 weeks. Although the protocol specified that glucocorticoids above the protocol-specified taper should be discontinued by Week 4, 86% of patients in the avacopan arm received glucocorticoids from Week 0 to 26 (albeit at lower mean nominal doses compared to the prednisone arm). Further, glucocorticoid use from Week 26 to Week 52 was largely similar between the prednisone and avacopan groups. Therefore, the increased glucocorticoid use in the prednisone arm compared to the avacopan arm was limited to the period of the first 20 weeks of the study. The clinical relevance of the nominal differences in the glucocorticoid doses used from Week 0 to 26 between the prednisone and avacopan arms is uncertain, as it is an artifact of the study design rather than a reflection of avacopan's control of disease activity.

To further support the assessment of steroid-sparing effect of avacopan, the Applicant assessed a novel instrument, Glucocorticoid Toxicity Index (GTI), as a secondary endpoint. The GTI, a quantitative measure intended to capture glucocorticoid toxicity and the glucocorticoid-sparing ability of therapies, showed a greater improvement from baseline in the avacopan arm on GTI-Cumulative Worsening Scale (GTI-CWS) and GTI-Aggregate Improvement Score (GTI-AIS) at Weeks 13 and 26. However, the study design specified the prednisone doses to be used in the

control group, and the differences in GTI between the treatment groups may be more reflective of the study design, rather than of the effect of avacopan. Therefore, the observed differences are to be expected based on the study design. The GTI was not assessed at later time points to assess the effects of glucocorticoids after completion of the pre-specified prednisone taper, and to further assess any potential long-term glucocorticoid toxicities at later time points in the study. Therefore, in Study CL010_168, where differences in glucocorticoid use were pre-specified in the protocol, the GTI does not provide information beyond that of the cumulative glucocorticoid doses to further inform the effect of avacopan. In addition, Division of Clinical Outcome Assessment (DCOA) reviewed the GTI instrument and concluded that the GTI is not fit-for-purpose to measure glucocorticoid-related toxicities or glucocorticoid-sparing effects for the context of use of this drug development program, based on the following: the measure is not comprehensive of the intended claim, limitations of the score interpretability, insufficient evidence to support clinically meaningful within-patient change, the study design which systematically assessed toxicity for glucocorticoids (GCs) without a comparable measure of potential toxicity profile for the avacopan arm (e.g., hepatotoxicity), and the lack of adjustment for multiplicity.

Secondary Endpoints

Other secondary endpoints do not support a clinically meaningful treatment benefit of avacopan. Further, the secondary endpoints were not adjusted for multiplicity; therefore, these endpoints are considered exploratory.

- **Disease relapse:** More relapses were observed in the prednisone arm compared to the avacopan arm through the study duration (20.1% in the prednisone arm compared to 9.6% in the avacopan arm); however, other assessments of increased disease activity, including persistent vasculitis, maintenance of remission, and worsening vasculitis, were similar between treatment groups. In addition, the study was not designed to assess time to relapse or proportion of relapses. The analyses were not based on the randomized population in remission at baseline, and, thus, the treatment arms may not be reliably comparable for establishing an effect on relapse.
- **Vasculitis Damage Index:** No clinically meaningful differences in change in Vasculitis Damage Index, an instrument intended to assess cumulative organ damage as a result of AAV, were observed between treatment groups from baseline to Week 52.
- **Renal assessments:** Multiple renal endpoints were assessed as secondary endpoints. Mean improvement in estimated glomerular filtration rate (eGFR) from baseline to Week 52 for patients meeting BVAS criteria for renal disease at baseline was greater in the avacopan group compared to the prednisone group; however, the difference between groups was small at 3.3 mL/min/1.73 m^2 (95% CI: [-0.4, 6.9]) and was not sustained by 8 weeks post-treatment. Percent change in urine albumin: creatinine ratio

improved in both arms and improved more quickly in the avacopan arm by Week 4; however, improvement was similar between treatment arms after this early time point. Need for dialysis, a clinically meaningful consequence of disease activity, was also similar between groups and does not support a meaningful effect of avacopan on renal outcomes in this study.

- **Health related-Quality of Life (hr-QoL):** Favorable trends towards improvement were observed in quality of life, based on the SF-36 and EQ-5D-5L, in the avacopan group compared to the prednisone group; however, there was large variability around the point estimates. Importantly, the DCOA review team determined that there is insufficient evidence of content validity to ensure adequate interpretation of hr-QoL in the AAV population. Given the complexity of hr-QoL, (b) (4) (b) (4) for this drug development program, a robust outcome on the primary endpoint, a clear estimand, and an *a priori* endpoint model with appropriate control for multiplicity are necessary considerations for regulatory decision-making.

Studies CL002_168 and CL003_168

Two additional randomized, double-blind, placebo-controlled phase 2 studies were submitted by the Applicant. Neither of these studies provide supportive efficacy data. These studies were small and evaluated a BVAS 50% response, defined as a BVAS percent reduction from baseline of at least 50% plus no worsening in any body system component, as the primary endpoints at Week 12. The Agency had previously raised concerns about the clinical meaningfulness of a 50% response as well as the early time point of assessment, at which point patients were still receiving glucocorticoids, to assess the treatment effect. In Study CL002_168, 67 patients with AAV were randomized to avacopan, avacopan plus low dose prednisone, or standard-of-care prednisone. All patients received background treatment with CYC or RTX. Based upon a BVAS 50% response, the greatest treatment response was observed in the avacopan plus low dose prednisone group. However, the greatest response on BVAS remission, a more clinically relevant endpoint and more similar to the primary endpoint used in the phase 3 study CL010_168, was observed in the standard-of-care prednisone arm. In Study CL003_168, 32 patients with AAV were randomized to receive avacopan 10 mg, avacopan 30 mg, or placebo. All patients received a standard-of-care prednisone taper and background treatment with CYC or RTX. The greatest treatment responses based on BVAS 50% response and BVAS remission at Week 12 were observed in the avacopan 10 mg group. No dose dependent effect was demonstrated. A numerically greater proportion of patients in the standard-of-care prednisone arm had a BVAS 50% response and BVAS remission at Week 12, although differences between all the treatment groups for both endpoints were based on single patients. In summary, the phase 2 studies do not provide evidence to support the treatment benefit of avacopan compared to standard-of-care prednisone.

Considerations on Substantial Evidence of Effectiveness Based on a Single Study

There are situations where the U.S. Food and Drug Administration (FDA) may rely on a single study to provide substantial evidence of effectiveness, such as if FDA determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence are sufficient to establish effectiveness. In this submission, the Applicant has provided a single adequate and well-controlled multicenter trial. As discussed in the FDA Draft Guidance Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, "reliance on a single large multicenter trial to establish effectiveness should generally be limited to situations in which the trial has demonstrated a clinically meaningful and statistically very persuasive effect on mortality, severe or irreversible morbidity, or prevention of a disease with potentially serious outcome… and confirmation of the result in a second trial would be impracticable or unethical. (December 2019)."

- **Strength of the treatment effect:** Study CL010_168 demonstrated a statistically significant effect on a clinically meaningful endpoint of sustained remission at Week 52. The primary endpoint results appear to be robust to alternative missing data assumptions. However, while subgroup analyses must be interpreted with caution, the results of these pre-specified analyses suggest a treatment benefit may be limited to the group that did not receive standard-of-care maintenance therapy. At Week 26, a timepoint at which use of maintenance therapy would not be expected to impact the results, superiority was not demonstrated. As previously noted, the noninferiority results in Study CL010_168 cannot support a conclusion that avacopan is effective. Discrepancies between the Investigator and the Adjudication Committee BVAS assessments, such that analysis based on Investigator assessment no longer supports the superiority of avacopan at Week 52, also underscores the lack of robustness of the superiority assessment. In addition, the secondary endpoints and phase 2 studies do not provide confirmatory evidence of a treatment effect of avacopan.

  Overall, the review team does not consider the findings of Study CL010_168 to be statistically very persuasive. Further, the clinical meaningfulness of the superiority results observed in the subgroup that did not receive standard-of-care maintenance therapy leaves uncertainties about how labeling can inform how avacopan should be used in clinical practice. For example, it is unclear whether avacopan should be used instead of standard-of-care maintenance treatments, as part of induction treatment, as part of maintenance treatment, or more broadly. While the review team acknowledges that superiority was demonstrated on a clinically meaningful endpoint at Week 52, given the remaining uncertainties, we do not consider the findings of Study CL010_168 to be clinically meaningful in the absence of additional information to inform its use.

- **Previous approvals for closely related indications**: Avacopan was approved in Japan for treatment of GPA and MPA on September 27, 2021.
- **Pharmacologic class**: Avacopan, a C5a receptor inhibitor, is a new molecular entity and does not have an established pharmacologic class, and so comparison of the proposed mechanism cannot be compared to similar drugs or to similar indications. There are two FDA-approved complement inhibitors of C5, ravulizumab and eculizumab; neither product is approved in AAV or related indications.
- **Mechanistic support:** Plasma C5a levels, as well as C5b-9 and C3a levels, have been found to be higher in patients with active AAV compared to patients in remission (Gou et al. 2013), and C5a levels have been increased in plasma and urine in patients with AAV. While plasma C5a levels were higher in patients with active AAV than in patients in remission, patients with lupus nephritis (LN), and normal controls, urinary C5a levels were similar between patients with AAV and LN (Yuan et al. 2012). In murine models of anti-MPO mediated glomerulonephritis (necrotizing and crescentic glomerulonephritis [NCGN]), treatment with a monoclonal antibody that inhibits C5 activation prevented disease in pretreated mice and decreased crescentic glomeruli and albuminuria in animals after onset of disease (Huugen et al. 2007). As C5 inhibition inhibits C5a activity as well as the formation of C5b-9, the authors note that the therapeutic effect may be due to either or both mechanisms. Another study suggested that C6 and the membrane attack complex are not important for the pathogenesis of anti-MPO NCGN, as C6 knock-out and wildtype mice both developed similar glomerular crescents (Xiao et al. 2014). However, mice with knocked-out C5aR were protected from development of NCGN after administration of anti-MPO IgG. In a hC5aR knock-in mouse, blocking C5aR with avacopan 30 mg/kg decreased glomerular crescents, hematuria, proteinuria, and leukocyturia, and was dose dependent in the anti-MPO murine model (Xiao et al. 2014). No data were provided to support the inhibition of C5aR in GPA renal vasculitis or on the overall population of MPA and GPA, the proposed patient population. In addition, the relevance of the findings in murine models at doses of avacopan 30 mg/kg to the proposed human dose of 30 mg twice daily is unknown. Overall, these data may provide limited support to the relevance of the mechanism of action in anti-MPO ANCA-mediated renal vasculitis, but do not provide compelling mechanistic evidence to support the proposed population.
- **Natural history of the disease:** The Applicant has provided limited literature on sustained remission and relapse in AAV. In the Rituximab in AAV (RAVE) study (Specks et al. 2013), remission at 6 months and sustained remission at 12 months were notably lower in both treatment groups (64% and 48% in the RTX arm vs. 53% and 39% in the CYC/ azathioprine (AZA) group, respectively), as compared to the control arm of Study CL010_168 (70% and 55%), suggesting that there may be differences in patient populations, concomitant therapies, or study designs that limit comparisons. In a more

recent study comparing repeat RTX to AZA maintenance therapy, relapse was observed in 13% of the RTX group vs. 38% of the AZA group (Smith et al. 2019). As discussed with the Applicant during development, Study CL010_168 was not adequately designed to evaluate relapse. The Applicant also identifies an unmet need for effective treatment of AAV-associated renal disease, stating that 42% of patients with AAV develop end-stage renal disease or die at 2 years (Jayne 2000). It is important to note that the follow-up period in Study CL010_168 is limited to 1 year. However, the mortality and dialysis rates in both arms of Study CL010_168 are substantially lower than cited in the literature reference, suggesting that the population enrolled in Study CL010_168 may not be comparable to the populations described in the literature.

- **Considerations on clinical circumstances where additional flexibility may be warranted:** AAV is a rare and serious disease associated with high morbidity and mortality. AAV can be life-threatening, and, prior to the introduction of GC, CYC, and RTX treatment, mortality rates were very high. With more recent therapeutic regimens, rates of remission have improved substantially. While relapse continues to be a concern, more recent studies have shown relapse rates of 5-13% over approximately 2 years (Smith et al. 2019). The responses in the control arm of the ADVOCATE study support the effectiveness of currently available therapies with remission achieved in 95% of subjects, and relapse in 21% of subjects who received maintenance treatment in the control arm. While currently available therapies are effective at achieving remission and preventing relapse, there remains an unmet need for additional therapeutic options for those who do not respond to currently available therapies, as well as a need for alternatives with fewer toxicities.

  - The review team believes that additional studies are ethical, feasible, and necessary to better inform the context of use for avacopan. A new study design could be informed by the completed phase 3 study in which exploratory subgroup analyses showed trends for increased response in patients with MPA and patients with relapsing disease. The study should be designed to better inform how avacopan should be used in the treatment of AAV, including the patient population (relapsing/refractory vs. the broader population), use for maintenance treatment vs. induction treatment vs. both, and a clearer evaluation of the treatment benefit of avacopan over the background therapies. If the Applicant wishes to pursue an assessment of avacopan to reduce use of glucocorticoids in addition to the efficacy in treatment of AAV, a study could be appropriately designed to evaluate this with glucocorticoid use based on Investigator discretion while blinded to treatment assignment, rather than specified glucocorticoid use in one arm.

Conclusions

In summary, although Study CL010_168 demonstrated superiority of avacopan on sustained remission at Week 52 and non-inferiority on remission at Week 26, the review team finds that the Applicant has not provided confirmatory evidence to support the reliance on a single study to provide substantial evidence of effectiveness. Given the limitations of the noninferiority comparison discussed above, the efficacy of avacopan in AAV is based on a single endpoint at a single timepoint of assessment, sustained remission at Week 52, without confirmatory evidence.

The Applicant has also asserted that avacopan reduces the need for glucocorticoid treatment in AAV. The Agency acknowledges that reducing GC use is an important goal in treatment of patients with AAV, if it occurs in the context of a treatment that effectively controls disease activity. Reduction in steroid use has typically been used as supportive evidence of efficacy but not as the primary evidence of efficacy, as there is no universal definition of "steroid-sparing" effect or the magnitude of such effect on clinically meaningful outcomes. Importantly, reducing the use of GC refers to reducing the toxicity of chronic non-physiologic/higher dose GC treatment, i.e., implied safety benefit rather than efficacy. The use of glucocorticoids in both treatment arms in Study CL010_168, as well as the use of protocol-specified glucocorticoids in the prednisone arm, rather than glucocorticoid use guided by disease activity, preclude a determination that differences in glucocorticoid use are due to a treatment effect of avacopan, rather than the design of the study. Study CL010_168 was also not designed for a reliable safety comparison (b) (4) that avacopan is less toxic than GCs, as discussed with the Applicant throughout development.

The clinical and statistical review teams do not believe that the current data meet the Agency's usual evidentiary standard for effectiveness. Further, the current data do not inform the use of avacopan in the treatment approach to AAV, that is, how avacopan should be used (induction, maintenance, adjunct to steroids and/or background treatment) to support labeling. We acknowledge that the single phase 3 study has met the primary endpoint and that the use of regulatory flexibility for this rare disorder may be considered by other members of the review team.

The Division Director finds that the threshold for substantial evidence of effectiveness has been met and that the benefit-risk of avacopan in adults with severe active AAV is favorable; thus, the Division Director recommends Approval. The Division Director acknowledges the several areas of concern identified by the clinical and statistical review teams detailed above, which have determined their overall recommendation, because these concerns created lack of clarity regarding the treatment effect size of avacopan, whether the substantial evidence threshold has been met, and, therefore, what the true benefit-risk of avacopan is. These concerns and

the Division Director perspective on them are addressed by topic in the Division Director Comments Section.

To briefly summarize, the Division Director finds that the threshold for substantial evidence of effectiveness has been met, despite reliance on a single adequate and well-controlled study, for the following reasons:

- Study CL010_168 was a large, global, multicenter trial, with procedures in place to ensure trial quality. Such trials are generally less vulnerable to certain biases, such as selection or measurement bias.
- Despite limitations of the design of this study that make it more difficult to interpret what the size of the treatment effect of avacopan is, the study met both its pre-specified primary endpoints: non-inferiority in remission rate at Week 26 to a high-dose prednisone taper and superiority in sustained remission rate at Week 52 to a control arm that included patients who received either cyclophosphamide induction on azathioprine maintenance or rituximab induction with no maintenance. Neither the Week 26 comparison nor the Week 52 comparison necessarily captured a realistic therapeutic scenario, which makes it difficult to characterize what the treatment benefit might be if it were used in clinical practice in patients receiving concomitant standard-of-care therapy. However, study results, along with the pattern of extra glucocorticoid use during these time periods, did demonstrate a favorable treatment effect of avacopan.
- Additionally, both the Week 26 and Week 52 endpoints were based on BVAS remission, an established and clinically meaningful endpoint with respect to the severe and life-threatening manifestations of ANCA-associated vasculitis.
- Secondary endpoints in Study CL010_168, while not adjusted for multiplicity, included assessments, such as rates of relapse, which are clinically relevant because another important objective of the management of AAV, after induction of remission, is to prevent relapses which could be severe, organ- or life-threatening and require additional immunosuppression. Based on the review team's analyses, the proportion of patients who never achieved remission or achieved remission but had a relapse was larger in the prednisone group (24.4% in the prednisone group vs 14.5% in the avacopan group, difference: -9.9% with 95% CI: [-18.4%, -1.5%]). Notwithstanding the exploratory nature of these analyses, the Division Director concluded that these results clearly support the clinical activity of avacopan in addition to that demonstrated by the primary endpoint analyses and support a conclusion of substantial evidence of effectiveness.
- Finally, the Division Director also considered the mechanistic data submitted to be relevant and supportive evidence regarding the plausibility of the therapeutic benefit with avacopan.

The Division Director also acknowledges that the optimal use of avacopan has not been well characterized based on the avacopan clinical program. However, these uncertainties do not preclude conclusions of the effectiveness of avacopan in the studied population and further characterization of the risks and benefits of avacopan can be addressed in a postmarketing setting.

The submitted safety database is relatively small, limited to 52 weeks of exposure, and has identified potential safety risks of hepatotoxicity and hypersensitivity, which are risks also seen with other drugs in the therapeutic armamentarium. While these risks can potentially be managed through labeling, a postmarketing required study with longer controlled comparisons is warranted to further characterize these safety risks.

The Division Director also considered the clinical circumstances where additional flexibility may be warranted with respect to the acceptability of uncertainties such as those identified in the avacopan clinical program. AAV is a rare and serious disease associated with high morbidity and mortality. There is also a limited armamentarium of currently available therapies that are effective at achieving remission and preventing relapse, and there remains an unmet need for additional therapeutic options for those who do not respond to currently available therapies, as well as a need for alternatives with fewer toxicities. The avacopan program studied AAV patients with active severe, and life-threatening spectrum of the disease for whom avacopan has the potential to address some of this unmet need.

Thus, the Division Director recommends Approval with a revised and limited indication, a postmarketing requirement for safety, and a postmarketing commitment for additional clinical efficacy data to support a specific context of use. The Office Director concurs with the recommendation of the Division Director for approval of avacopan (see Office Director Comments section).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a form of systemic vasculitis affecting small to medium-size vessels, associated with the presence of ANCA, and includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). These vasculitides are chronic, relapsing, multisystem autoimmune diseases, with pulmonary, renal, neurologic, and other organ manifestations. Severe disease includes life- or organ-threatening manifestations, such as rapidly progressive glomerulonephritis, diffuse alveolar hemorrhage (DAH), mesenteric ischemia, scleritis, and nervous system involvement. C5a is a terminal component of the complement cascade that acts as a potent neutrophil chemoattractant and agonist and has been proposed to play a role in the pathogenesis of AAV. Current treatment guidelines recommend remission induction treatment in organ-threatening or life-threatening AAV with a combination of glucocorticoids (GC) and either cyclophosphamide (CYC) or rituximab (RTX), followed by remission maintenance with a combination of GCs and either azathioprine (AZA), RTX, methotrexate, or mycophenolate mofetil. Despite high remission rates with treatment, patients with AAV are at risk of relapse. Rates of relapse vary across studies and range from 10 to 60 percent (Nachman et al. 1996; Hogan et al. 2005; Smith et al. 2019). Although there are available effective therapies, there remains an unmet need for therapies for patients who do not respond or who subsequently relapse and alternative therapeutic options with fewer toxicities.

ChemoCentryx has submitted a new drug application (NDA) for avacopan, a new molecular entity C5a receptor antagonist, for treatment of adult patients with ANCA-associated vasculitis (GPA and MPA). The proposed dosing regimen is 30 mg twice daily orally. To support the application, the Applicant submitted a single phase 3 study, CL010_168, and two phase 2 studies, CL002_168 and CL003_168. Study CL010_168 was a randomized, double-blind, active controlled study to evaluate the safety and efficacy of avacopan compared to a protocol-specified 20-week prednisone taper in 331 patients with newly diagnosed or relapsed ANCA-associated vasculitis. All patients received induction treatment with cyclophosphamide or rituximab. Patients who received cyclophosphamide received maintenance therapy with azathioprine, while patients who received rituximab induction did not receive maintenance treatment. The primary endpoints of Study CL010_168 were remission at Week 26 and sustained remission at Week 52, each evaluated for both non-inferiority and superiority. Based on the multiple testing procedure in Study CL010_168, which included null hypotheses associated with the two primary endpoints, avacopan demonstrated superiority for sustained remission at Week 52 (avacopan vs. prednisone treatment difference 12.5% with 95% CI [2.6%, 22.3%]). However, in the evaluation of the

subgroups by background therapy, the treatment effect was observed in the RTX induction subgroup (treatment difference 15% with 95% CI [2.2%, 27.7%]) that did not receive maintenance standard of care, while no meaningful treatment effect was observed in the cyclophosphamide induction subgroup (treatment difference 3% with 95% CI [-14.8%, 21.4%]) that received maintenance treatment with AZA. While subgroup analyses must be interpreted with caution as there is often low precision, and considerable uncertainty around these estimates, this inconsistency raises concerns regarding the persuasiveness of the evidence of effectiveness and how avacopan may fit into the treatment armamentarium of ANCA-associated vasculitis. In addition, analysis based on the Investigator Birmingham Vasculitis Activity Score (BVAS) Assessment did not support superiority. Differences between the Investigator Assessment and the pre-specified analysis based on the Adjudication Committee were due to differences in attribution of persistent vasculitis. These discrepancies between the Investigator and the Adjudication Committee were relatively balanced by treatment arm but underscore the lack of robustness of the superiority assessment. Noninferiority but not superiority was demonstrated for remission at Week 26 (avacopan vs. prednisone treatment difference 3.4% with 95% CI [-6.0%, 12.8%]). However, because both treatment arms received background therapy in the form of cyclophosphamide or rituximab and the benefit of glucocorticoids on top of cyclophosphamide or rituximab is not well-understood, it is difficult to determine if similar remission rates observed on both arms can support a conclusion that avacopan is effective or if similarities can be primarily attributed to both arms receiving rituximab or cyclophosphamide. Further, while only the prednisone group was intended to receive the protocol-specified prednisone taper, 87% of patients in the avacopan treatment group also received glucocorticoids during the study for vasculitis and other clinical conditions. Thus, the assessment of non-inferiority is a comparison of avacopan and lower dose glucocorticoids versus higher dose glucocorticoids. Finally, the increased glucocorticoid use in the prednisone arm compared to the avacopan arm was limited to the period of the first 20 weeks of the study. Differences in the glucocorticoid doses used from Week 0 to 26 between the prednisone and avacopan arms may therefore be an artifact of the study design rather than a reflection of better control of disease activity in the avacopan arm.

Secondary endpoints were not adjusted for multiplicity, and therefore, the results are considered exploratory. While decreases in relapses were observed in the avacopan group, other measures of increased disease activity were similar between the avacopan and prednisone treatment groups. Urine albumin: creatinine ratio improved in both arms and more quickly in the avacopan arm by Week 4; however, improvement from baseline was similar between treatment arms after this early time point. Differences in estimated glomerular filtration rate (eGFR) were small, not sustained, and of unclear clinical relevance. There were no differences in renal outcomes, such as dialysis. There were no differences in Vasculitis Damage Index. Overall, the secondary endpoints provide limited support of a clinically meaningful benefit of avacopan treatment. In addition, the phase 2 studies, which included different doses of avacopan and varying concomitant prednisone tapers, shorter treatment

duration, small patient populations, and different efficacy assessments, do not provide additional support for the treatment benefit of avacopan when administered without GCs, as proposed.

The overall safety database is relatively small (n=239), including 166 patients exposed to avacopan for up to 52 weeks in CL010_168. The differences in study designs and treatment arms in the phase 2 studies preclude pooling with the safety data of CL010_168. In the pivotal study, a greater proportion of avacopan-treated patients had hepatobiliary adverse events (AEs) and serious adverse events (SAEs), AEs related to liver enzyme elevations, and hepatobiliary AEs leading to discontinuation. There were 4 cases of probable or highly likely drug-induced liver injury due to avacopan. In addition, there was one liver enzyme-related SAE attributed to avacopan in the phase 2 study CL002_168. Imbalances in angioedema and creatinine phosphokinase (CPK) elevations were also observed. Other events including deaths, SAEs, AEs leading to discontinuation, treatment emergent adverse events (TEAEs), infections, and serious infections generally occurred in similar or fewer numbers of patients in the avacopan arm compared to the prednisone arm. Given the small safety database, conclusions regarding rare and latent toxicities, which are more relevant for chronic immunosuppressants like avacopan, are limited; however, imbalances in hepatotoxicity, liver enzyme elevations, and angioedema were observed despite the small sample size.

In summary, although Study CL010_168 demonstrated superiority of avacopan on sustained remission at Week 52 and non-inferiority on remission at Week 26, the Applicant has not provided confirmatory evidence to support the reliance on a single study to provide substantial evidence of effectiveness. In addition, while the Applicant has asserted that avacopan spares or reduces the need for glucocorticoid treatment in AAV, the use of glucocorticoids in both treatment arms, as well as the use of protocol-specified glucocorticoids in the prednisone arm, preclude a determination that differences in glucocorticoid use are due to a treatment effect of avacopan, rather than the design of the study. In addition, there are safety concerns related to hepatotoxicity and angioedema that have not been fully characterized in the small available safety database. Given these concerns, the context of use is uncertain and the benefit-risk of avacopan in AAV cannot be determined. Therefore, the review team recommends a Complete Response for NDA 214487 for avacopan for adult patients with ANCA-associated vasculitis (GPA and MPA), based on the currently available data. Conduct of a second study could provide additional evidence for the effectiveness of avacopan, better define the population in which the benefit-risk is favorable and provide additional safety data to characterize the risks of hepatotoxicity and angioedema.

The Division Director acknowledges the several areas of concern identified by the clinical and statistical review teams and their recommendation. The Division Director's recommendation of approval takes into consideration these recommendations and concerns, but

believes additional considerations ameliorate and outweigh those concerns. Study CL010_168 was a large, global, multicenter trial, that showed non-inferiority in remission rate at Week 26 to a prednisone taper and superiority in sustained remission rate at Week 52 compared to a control arm that included patients who received either cyclophosphamide induction on azathioprine maintenance or rituximab induction with no maintenance. These endpoints were based on BVAS remission, an established and clinically meaningful endpoint with respect to the severe and life-threatening manifestations of ANCA-associated vasculitis. While not adjusted for multiplicity, Study CL010_168, included relevant clinical assessments, such as rates of relapse, the analyses of which support the clinical activity of avacopan and support a conclusion of substantial evidence of effectiveness. The Division Director also acknowledges that the optimal use of avacopan has not been well characterized. However, these uncertainties do not preclude conclusions of the effectiveness of avacopan in the studied population. The submitted safety database is relatively small, limited to 52 weeks of exposure, and has identified potential safety risks of hepatotoxicity and hypersensitivity, which are risks also seen with other drugs in the therapeutic armamentarium. While these risks can potentially be managed through labeling, a postmarketing required study with longer controlled comparisons is warranted to further characterize these safety risks. The Division Director also considered the clinical circumstances where additional flexibility may be warranted with respect to the acceptability of uncertainties such as those identified in the avacopan clinical program. AAV is a rare and serious disease associated with high morbidity and mortality for which an unmet medical need remains. The avacopan program studied AAV patients with active largely severe, and life-threatening spectrum of the disease for whom avacopan has the potential to address some of this unmet need. Despite the uncertainties in the avacopan clinical program, the benefit-risk profile is favorable for avacopan as an adjunctive treatment of adult patients with severe active AAV, who are also receiving standard therapy. However, avacopan does not eliminate the need for use of systemic glucocorticoids in this patient population. The Office Director concurs with the Division Director's recommendation for approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ANCA-associated vasculitis is a chronic, relapsing, multisystem autoimmune disease, with pulmonary, renal, neurologic, and other organ manifestations. • Severe disease includes life- or organ-threatening manifestations, such as rapidly progressive glomerulonephritis, DAH, mesenteric ischemia, scleritis, and nervous system involvement. • The prevalence of AAV is 200-400 cases per million people. GPA is more common in patients of European ancestry while MPA is more common in patients from Eastern Asia (Almaani et al. 2021). It occurs more frequently in males, between the ages of 60 to 70 years, and in White and Asian populations (Geetha and Jefferson 2020). • If left untreated, AAV can be fatal with a mean survival time of <1 year. • Despite high remission rates with treatment, patients with AAV may relapse. Rates of relapse vary across studies, ranging from 10 to 60 percent (Nachman et al. 1996; Hogan et al. 2005; Smith et al. 2019). Factors associated with higher risk of relapse include younger age; proteinase 3 (PR3)-antibody; persistence of ANCA or increase in titers; GPA; prior relapse; lung, upper respiratory tract, or cardiac involvement; discontinuation of immunosuppression or prednisone; B-cell reconstitution after rituximab; chronic nasal carriage of S. Aureus; and HLA-DP1*04 alleles. • In the first year after diagnosis of AAV, the most frequent causes of death are therapy related (59%) and active vasculitis (14%) (Little et al. 2010).	AAV is a rare and serious medical condition. Patients with AAV are at increased risk for pulmonary failure, renal failure, and death.
Current Treatment	• The treatment paradigm for AAV is comprised of two phases: induction and maintenance treatment. Induction treatment typically lasts 3-6 months with	Although many patients with AAV may respond to initial treatment with the current treatment options, there remain

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Options	the goal of establishing remission. Then, maintenance therapy is initiated to prevent relapse. • The choice of therapy for induction and maintenance is tailored based on the severity of disease. • Rituximab is the only FDA-approved treatment for AAV; it is approved for GPA and MPA in adult and pediatric patients 2 years of age and older in combination with GC. • Current treatment guidelines recommend remission induction treatment in organ-threatening or life-threatening AAV with a combination of GC and either CYC or RTX. Recommended remission maintenance includes a combination of GCs and either azathioprine, RTX, methotrexate, or mycophenolate mofetil. Maintenance therapy for AAV should be continued for at least 24 months following induction of sustained remission (Yates et al. 2016). • Therapy-related toxicities include infection, myelosuppression, infertility, and malignancy.	patients who fail to achieve remission or who relapse after remission. In addition, there are significant toxicities associated with current treatments. There is an unmet need for additional therapeutic options for this population.
Benefit	• The Applicant submitted a single phase 3 study, CL010_168, and two phase 2 studies, CL002_168 and CL003_168, to support the application. Due to differences in study designs including treatment doses and use of concomitant GCs, Study CL010_168 provides the primary data to support the efficacy of avacopan in AAV. • The primary endpoints of Study CL010_168 were remission at Week 26 and sustained remission at Week 52. The assessments were analyzed based on a	The primary data to support the efficacy of avacopan in AAV comes from the single phase 3 study, CL010_168. Superiority was demonstrated for sustained remission at Week 52. The treatment effect was observed in the RTX induction subgroup that did not receive maintenance standard of care, while no meaningful treatment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	sequential multiple testing procedure, testing first for noninferiority and then for superiority. • Superiority and noninferiority were demonstrated for sustained remission at Week 52 (avacopan vs. prednisone treatment difference 12.5%), while only noninferiority (avacopan vs. prednisone treatment difference 3.4%) was demonstrated for remission at Week 26. - At Week 52, the treatment effect in the RTX induction subgroup that did not receive maintenance therapy was 15%. The treatment effect in the CYC induction subgroup that received maintenance therapy with azathioprine was 3%. - Analysis of sustained remission based on Investigator assessment rather than the pre-specified analysis using the Adjudication Committee assessment did not support superiority. Differences between Investigator and Adjudication Committee assessments were most frequently related to attribution of persistent vasculitis. - Throughout the development program, FDA advised the Applicant that a non-inferiority comparison would not be sufficient to show that avacopan can replace GCs, as it would be difficult to establish whether avacopan is effective or whether an effect was due to the rituximab or cyclophosphamide administered to both treatment arms. - The Applicant has not provided adequate data or information to isolate the effect of prednisone when added to RTX or CYC induction to inform the margin of the non-inferiority comparison.	effect was observed in the cyclophosphamide induction subgroup that received maintenance treatment with AZA. While subgroup analyses must be interpreted with caution, this inconsistency raises concerns regarding the persuasiveness of the evidence of effectiveness and how avacopan may fit into the treatment armamentarium for ANCA-associated vasculitis. In addition, analysis based on the Investigator BVAS Assessment did not support superiority. Differences between the Investigator Assessment and the pre-specified analysis based on the Adjudication Committee were due to differences in attribution of persistent vasculitis. These discrepancies between the Investigator and the Adjudication Committee were relatively balanced by treatment arm but underscore the lack of robustness of the superiority assessment. Noninferiority but not superiority was demonstrated for remission at Week 26.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Non-study supplied GC were used by 87% of patients in the avacopan arm, including 86% of patients up to Week 26, for reasons including for treatment of vasculitis, making the non-inferiority comparison at Week 26 a comparison of avacopan plus lower dose GC versus higher dose GC. • Mean cumulative GC use at Week 26 was 1072.9 mg in the avacopan arm and 3192.5 mg in the prednisone; differences between group are likely reflective of the specified use of steroids in the prednisone arm. From Weeks 27 to 52, the mean cumulative dose of GC was similar between arms. • Secondary endpoints were not controlled for multiplicity and are considered exploratory. - Greater improvement from baseline was observed in the Glucocorticoid Toxicity Index (GTI) Cumulative Worsening Score and GTI Aggregate Improvement Score at Weeks 13 and 26, reflecting the differences in GC use from Weeks 0 to 26, as specified by the protocol. GTI was not assessed at later time points. - There were fewer relapses in the avacopan group; however, other assessments of increased disease activity, including persistent vasculitis, maintenance of remission, and worsening vasculitis, were similar between groups. In addition, analyses of relapse are not based on the randomized population in remission at baseline, and, therefore, the treatment arms may not be comparable for assessing relapse. - There were no clinically meaningful differences in the Vasculitis Damage Index.	However, as discussed in pre-submission communications, because both arms received background therapies and the effect of prednisone on top of these therapies is not well understood, the similar remission rates of avacopan compared to the control arm may be attributed to the background therapies, and such a comparison cannot support a conclusion that avacopan is effective. In addition, the Agency does not find that the non-inferiority margin to be adequately justified. One of the objectives of the program was to demonstrate that avacopan spared or reduced the use of glucocorticoids. However, GC were used by patients in both treatment arms. Differences in glucocorticoid use observed from Week 0 to 26, likely reflect the design of the study which specified the GC use in the control arm rather than dosing GC based on the need to control disease activity. In addition, in the second half of the study, after completion of the specified prednisone

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Renal endpoints were assessed in patients with renal disease at baseline as determined based on BVAS renal criteria. However, these criteria may not have adequately selected for patients with active renal vasculitis. Differences in changes in GFR were small (mean difference between treatment arms of 3.3 mL/min/1.7 m^2 at Week 52) and was not sustained; the mean difference decreased to 0.6 by Week 60, eight weeks post-treatment. Urine albumin: creatinine ratio improved in both arms and improved more quickly in the avacopan arm by Week 4; however, improvement was similar between treatment arms after this early time point. There were no differences between arms in patients requiring dialysis. - There were favorable trends in quality-of-life measures, SF-36 and EQ-5D-5L; however, there was large variability around the point estimates and these instruments have not been established for use for regulatory purposes in AAV. • The phase 2 studies do not demonstrate that avacopan 30 mg twice daily (BID) without concomitant prednisone (i.e., the proposed dose) had the greatest treatment response over standard of care. - In Study CL002_168, avacopan with low dose prednisone had a greater BVAS 50% response compared to avacopan without prednisone or standard-of-care prednisone taper without avacopan.	taper in the prednisone arm, the mean cumulative dose of GCs was similar between treatment arms. Therefore, the clinical meaningfulness of the differences in GC use is unclear. Secondary endpoints were not adjusted for multiplicity, and, therefore, the results are considered exploratory. While decreases in relapses were observed in the avacopan group, other measures of increased disease activity were similar between treatment groups. Differences in renal endpoints, such as eGFR and urine albumin:creatinine ratio, were small, not sustained, and of unclear clinical relevance. There were no differences in renal outcomes, such as dialysis. There were no differences in Vasculitis Damage Index. Overall, the secondary endpoints provide limited support of a clinically meaningful benefit of avacopan treatment. The phase 2 studies do not provide additional support for the treatment benefit

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- In Study CL003_168, avacopan 10 mg BID had a greater BVAS 50% response compared to avacopan 30 mg BID or placebo, when all arms received a prednisone taper.	of avacopan when administered without GCs, as proposed.
Risk and Risk Management	• Studies CL010_168, CL003_168, and CL002_168 provide the data for the safety assessment. The overall safety database is relatively small (n=239), including 166 patients exposed to avacopan for up to 52 weeks in CL010_168. The differences in study designs and treatment arms in the phase 2 studies preclude pooling of the safety data. • In the pivotal study, generally similar or fewer numbers of patients in the avacopan arm compared to the prednisone arm experienced deaths (2 vs. 4 patients), SAEs (42% vs. 45%), AEs leading to discontinuation (16% vs. 17%), and TEAEs (99% vs. 98%). Differences were due to differences in small numbers of patients between arms. • Adverse events of special interest (AESI) included infections, AEs due to hepatic abnormalities (including hepatobiliary AEs and liver enzyme elevation) neutropenia and lymphopenia, and hypersensitivity/angioedema. • The proportions of patients with serious infections and serious opportunistic infections were low and generally similar across treatment arms (avacopan 13.3% and 3.6%; prednisone 15.2% and 6.7%, respectively). There were no cases of *N. meningitides* in the avacopan arm. • A greater proportion of avacopan-treated patients compared to prednisone treated patients had hepatobiliary AEs (6% vs. 1.8%), SAEs (3.6% vs. 0.6%), and AEs leading to drug discontinuation (3.0% vs. 0).	The size of the safety database for avacopan in AAV is relatively small (n=239). Given the small safety database, conclusions regarding rare and latent toxicities, which are more relevant for chronic immunosuppressants like avacopan, are limited; however, imbalances in hepatotoxicity, liver enzyme elevations, CPK elevations, and angioedema are observed despite the small sample size.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Liver enzyme-related AEs were similar across treatment arms. • There were seven patients who discontinued study treatment due to AEs associated with hepatic abnormalities (including AEs in the Hepatobiliary disorders system organ class [SOC] and Investigations SOC) in the avacopan arm, compared to two in the prednisone arm. • There were nine SAEs associated with hepatic abnormalities in the avacopan arm, compared to 6 SAEs in the prednisone arm. Four of the cases were considered probable or highly likely drug-induced liver injury due to avacopan. In addition, there was one liver enzyme-related SAE related to avacopan in the phase 2 study CL002_168. • There were two patients with angioedema, one serious, in the avacopan arm compared to no patients with angioedema in the prednisone arm. There was an additional case of rash and fever in the avacopan arm that resolved after discontinuation of avacopan. • AEs of increased CPK levels were more frequently reported by avacopan-treated patients (3.6%) compared to prednisone-treated patients (0.6%). None of the events were SAEs or associated with rhabdomyolysis; one avacopan-treated patient discontinued avacopan due to Grade 3 elevated CPK levels.	

1.4. Patient Experience Data

Patient Experience Data Relevant to This Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Section 8.1.1.1
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Section 8.1.1.1
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

Vasculitis is an autoimmune disease caused by inflammation and necrosis of blood vessels and can be categorized based on the size of the vessels involved (Jennette et al. 2013). ANCA-associated vasculitis is a group of vasculitides affecting small and medium arteries and include MPA, GPA, and eosinophilic granulomatosis with polyangiitis (EGPA). These vasculitides are associated with antineutrophil cytoplasmic antibodies that target proteinase 3 (PR3) or MPO. The incidence of AAV is about 20 per million per year in Europe and North America, and the prevalence is 200 to 400 cases per million people (Almaani et al. 2021). It occurs more frequently in males, between the ages of 60 to 70 years, and in White and Asian populations (Geetha and Jefferson 2020).

The presentation and natural history of AAV can be highly variable. The spectrum of disease may range from relatively mild and localized to the upper respiratory tract to life-threatening involvement of multiple organ systems (upper and lower respiratory tract, kidneys, etc.) (Malyak 2002). AAV is thus categorized into the localized or generalized disease, and then generalized disease can be further broken down into limited or severe disease. Localized disease refers to patients with symptoms restricted to the upper and/or lower airways without constitutional symptoms or systemic vasculitis (Bosch et al. 2007). Limited disease encompasses all non-life- or organ-threatening manifestations, including mild renal or pulmonary disease. Severe disease, on the other hand, can be defined as life- or organ-threatening manifestations, including rapidly progressive GN, diffuse alveolar hemorrhage (DAH), mesenteric ischemia, scleritis, and nervous system involvement (Lally and Spiera 2015). Avacopan was developed for severe generalized AAV (GPA and MPA).

If left untreated, AAV is a uniformly fatal disorder with a mean survival time of <1 year (Malyak 2002). Patients frequently die from respiratory failure and renal failure. Availability of therapies, starting with glucocorticoids in 1948 and cyclophosphamide in the 1960s, has had a profound impact on the mortality. With currently available treatments, more recent remissions rates are as high as 90%, and mortality has decreased to 20% at 5 years (Emejuaiwe 2019). In general, in the first year after diagnosis of AAV, the most frequent causes of death are therapy-related toxicities (59%) and active vasculitis (14%) (Little et al. 2010). Therapy-related toxicities include infection, myelosuppression, infertility, and malignancy (Emejuaiwe 2019). Despite high remission rates and improved mortality, relapse rates range from 10 to 60%, particularly in the 12-18 months after immunosuppression is discontinued (Nachman et al. 1996; Hogan et al. 2005; Smith et al. 2019). Several factors have been identified as leading to a higher risk for relapse. These include the following (Geetha and Jefferson 2020):

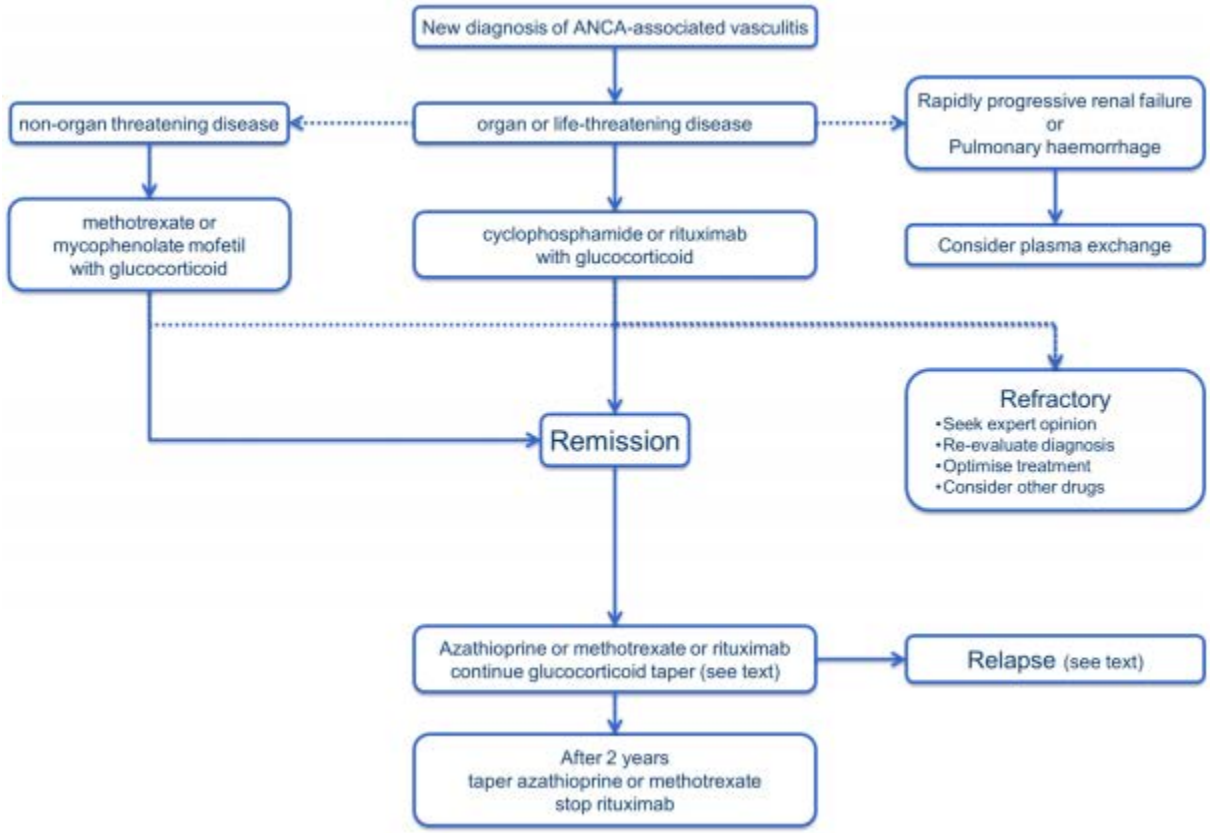
- Demographics: younger patients
- ANCA: PR3-antibody, persistence of ANCA after induction, increase in ANCA titers (more predictive of renal relapse)
- Clinical phenotype: GPA; lung, upper respiratory tract, or cardiac involvement; preserved renal function; prior relapse
- Therapy: discontinuation of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

2.2. Analysis of Current Treatment Options

The treatment strategy for patients with AAV involves several fundamental principles. First, the treatment paradigm is comprised of 2 phases: induction and maintenance treatment. This paradigm arose from the desire to minimize exposure of potent immunosuppressants (namely, cyclophosphamide) (Emejuaiwe 2019). Induction treatment typically lasts 3-6 months with the goal of establishing remission. Then, maintenance therapy is initiated to prevent relapse. The optimal duration of maintenance is unknown. The choice of therapy for induction and maintenance is tailored based on the severity of disease.

The 2015 update to the 2009 recommendations provided by the European League Against Rheumatism (EULAR) along with the European Renal Association – European Dialysis and Transplant Association, as shown in Figure 1, reflects standard-of-care therapy (Yates et al. 2016). For severe AAV, induction therapy involves a combination of glucocorticoids and either cyclophosphamide or rituximab. Induction therapy should be continued until remission is achieved, typically 3-6 months. Because relapse is so common in patients with AAV, maintenance therapy is utilized to prevent relapse and disease- and treatment-related morbidity and mortality (Geetha and Jefferson 2020). For remission maintenance, the treatment guidelines recommend low-dose glucocorticoids and either AZA, RTX, methotrexate (MTX), or mycophenolate mofetil (MMF) (Yates et al. 2016). As previously mentioned, the optimal duration of maintenance therapy is an area of debate, but there is a general sense that longer maintenance therapy will better prevent relapse as relapse rates tends to increase after discontinuation of immunosuppression (Geetha and Jefferson 2020). The EULAR guidelines recommend at least 24 months of maintenance therapy after induction of remission (Yates et al. 2016). Of the current treatment paradigm, there are limited FDA-approved treatment options. Rituximab is FDA-approved for the treatment of GPA and MPA in combination with glucocorticoids, while there are specific glucocorticoids approved for the broader indication of vasculitis.

Figure 1. Management of ANCA-Associated Vasculitis



Source: (Yates et al. 2016)

Evolving Landscape of AAV Treatment

Rituximab

RTX is a chimeric/human monoclonal antibody directed against the CD20 antigen. It was approved for treatment of GPA and MPA in combination with glucocorticoids on April 19, 2011, and the approval was based on data from the RAVE trial. RAVE was a randomized, double-blind, active-controlled non-inferiority trial in 197 patients with GPA or MPA. All patients received a glucocorticoid taper and were randomized to either oral CYC 2 mg/kg daily for 3 to 6 months followed by AZA for 12 to 15 months or RTX (375 mg/m^2 body surface area administered once a week for 4 weeks) followed by placebo. Glucocorticoids were tapered over 20 weeks in both treatment arms. The primary endpoint in RAVE was achievement of complete remission at six

months defined as a BVAS/WG[1] of zero and successful completion of the glucocorticoid taper six months after randomization. Patients discontinued glucocorticoids for one month prior to assessment of the primary endpoint. The data supported that RTX was not inferior to daily CYC for induction of remission in AAV (Stone et al. 2010). A long-term assessment of efficacy at 12 and 18 months in RAVE showed no significant difference in complete remission at 12 and 18 months in these 2 treatment arms, suggesting that a single course of RTX may be as effective as CYC and azathioprine for 18 months (Specks et al. 2013). However, these were tertiary endpoints in the RAVE trial, and rate of relapse remained high in both arms. Rituximab for maintenance therapy was formally evaluated in Maintenance of Remission using rituximab in Systemic ANCA-associated Vasculitis (MAINRITSAN), a randomized controlled trial in 115 patients with AAV who achieved remission with CYC and then were randomized to maintenance treatment with either RTX (500 mg on Days 0 and 14 and then at a fixed dose interval at Months 6, 12, and 18) or AZA (2 mg/kg daily for 12 months, then 1.5 mg/kg daily for 6 months, then 1 mg/kg for 4 months) (Guillevin et al. 2014). Prednisone was continued for at least 18 months. More patients had sustained remission, defined as a BVAS of 0, at Month 28 in the RTX arm. Major relapse occurred in 5% of patients in the rituximab group and 29% in the azathioprine group. Based on the results of this trial, on October 18, 2018, rituximab prescribing information was updated to include the use for follow-up treatment in patients with GPA and MPA who have achieved disease control with induction treatment.

Since MAINRITSAN, two other studies from the same investigator group evaluated the use of rituximab for maintenance therapy. MAINRITSAN2 was an open-label, randomized, controlled trial evaluating 2 rituximab infusion strategies for the maintenance of remission (N=162). Patients in the individually tailored treatment group received rituximab 500 mg on Day 0 after randomization and then received additional infusions only if CD19+ lymphocytes or ANCA reappeared. The other treatment arm received a fixed infusion of RTX on Days 0 and then every 6 months (Months 6, 12, and 18). The primary endpoint was the number of relapses (i.e., new, or reappearing symptoms or worsening disease with BVAS >0) at Month 28. The investigators reported that there was no difference in relapse rates between the 2 treatment regimens, but the individually tailored arm received fewer infusions (Charles et al. 2018). Patients who completed MAINRITSAN2 and were in complete remission could be rerandomized into MAINRITSAN3. MAINRITSAN3 was a multicenter, double-blind, randomized controlled trial comparing prolonged maintenance with IV rituximab 500 mg given every 6 months over 18 months with placebo (N=97). The primary endpoint was relapse-free survival at Month 28.

[1] BVAS/WG is a modification of the original BVAS comprised of 34 separate disease items categorized into 9 groups and an "other" section. Fifteen items are considered major. Items are classified as persistent, new/worse, or none. BVAS/WG score ranges from 0 to 64 (Stone et al. 2001).

Significantly more patients in the RTX group (96%) achieved the primary endpoint compared to the placebo group (74%). The investigators concluded that all 3 MAINRITSAN trials supported that (1) rituximab should become the new gold standard to maintain remission, (2) rituximab 500 mg per infusion is an adequate dose, (3) treatment should be prolonged, and (4) an individually tailored regimen may be prescribed. In fact, the authors proposed that rituximab should be given over a prolonged period (specifically, 36 months after achieving remission) for any patients at high risk for relapse, namely, those with PR3 ANCAs and those who previously experienced a relapse (Charles et al. 2020).

RITAZAREM was a randomized, controlled trial designed to assess whether rituximab is superior to azathioprine for the maintenance of remission following induction of remission with rituximab and glucocorticoids in patients with relapsing AAV. There were three phases to the trial: induction phase, maintenance phase, and follow-up phase. Data from the induction phase were published in 2020 and showed that 90% (i.e., 171 out of 188 patients) with relapsing disease achieved BVAS remission (Smith et al. 2020). Patients in RITAZAREM had evidence of disease relapse at the time of enrollment (defined as one major or three minor disease activity items on the BVAS/WG) after previously achieving remission following at least three months of induction therapy. Induction therapy including RTX (375 mg/m^2/week for 4 weeks) and 2 glucocorticoid regimens (high dose starting at 60 mg daily and low dose starting at 30 mg daily, both tapered to 10 mg daily by month 4). BVAS remission was defined as BVAS/WG ≤1 with prednisone ≤10 mg by 4 months. One hundred seventy patients were then randomized to RTX or AZA for maintenance. Results from the maintenance phase showed that, 20 months after randomization, 11/85 (13%) patients in the RTX arm had experienced a relapse compared to 32/85 (38%) patients in the AZA arm (Smith et al. 2019). The data from this trial appear to further support the role of RTX for induction and maintenance in patients with relapsing disease.

Role of Glucocorticoids in AAV Treatment

Glucocorticoids have been a mainstay of therapy in the treatment of AAV. As previously noted, glucocorticoid treatment led to a significant decrease in mortality in AAV when it was first introduced in the 1940s. Also, early glucocorticoid withdrawal appeared to be a strong predictor of relapse. However, “there is no consensus on the best tapering regimen or duration of glucocorticoid therapy for AAV” (Geetha and Jefferson 2020). In addition, there is concern that glucocorticoids may be responsible for much of the morbidity and mortality in AAV, such as infection and cardiovascular disease (Miloslavsky et al. 2018). Various cohort studies seemed to show benefit with lower doses of glucocorticoids such as reduced duration of glucocorticoid therapy after RTX induction (Miloslavsky et al. 2018) and after a combined RTX and CYC induction (Pepper et al. 2019). However, this issue has recently been further highlighted because of the results of the Plasma Exchange and Glucocorticoids for Treatment of Anti-neutrophil Cytoplasm Antibody-associated Vasculitis (PEXIVAS) trial. The PEXIVAS was a

randomized, controlled trial involving patients with severe, active AAV (Walsh et al. 2020). The trial was a 2-by-2 factorial design which allowed separate evaluations of initial treatment with plasma exchange as compared with no plasma exchange (with either cyclophosphamide or rituximab background therapy) and of 2 different regimens of oral glucocorticoids. Focusing on the glucocorticoid part of this trial, all patients were treated with daily IV methylprednisolone for 1 to 3 days for a maximum cumulative dose of 1 to 3 g. Then, patients received either a standard-dose regimen (based on regimens used in "a contemporary international trial") or a reduced-dose regimen (identical first week of treatment with dose reduction beginning in Week 2 and with 60% less cumulative glucocorticoids by Month 6) (Walsh et al. 2020). (See Table 131 in the Appendix for details of the prednisone taper in PEXIVAS, as compared to RAVE and CLEAR [CL002_168, one of the phase 2 avacopan studies].) The investigators concluded that the reduced dose regimen was noninferior to the standard dose regimen in terms of the primary outcome of composite death from any cause or end-stage kidney disease. Therefore, current standard of care treatment with glucocorticoids (specifically, the dose and duration of therapy) may exceed what is necessary for treatment of patients with AAV, and the optimal glucocorticoid treatment regimen remains an area for further consideration.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Avacopan is a new molecular entity that is not currently marketed in the U.S. Avacopan was approved in Japan for treatment of GPA and MPA on September 27, 2021.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Agency had several regulatory interactions with the Applicant regarding the development of avacopan for the treatment of AAV. Key discussion points are summarized below:

Table 1. Summary of Presubmission/Submission Regulatory Activity

Meeting/ Date	Summary
Pre-IND meeting April 21, 2014	Study CL002_168 was a randomized, double-blind, placebo-controlled phase 2 study. It was conducted in 3 phases in Europe. At the time of the pre-IND meeting, ChemoCentryx was proposing to expand the study to its 3rd phase which would include a treatment arm without glucocorticoids. The original target population was ANCA-associated renal vasculitis. The Agency had several concerns regarding the proposed study: • Lack of dose-ranging • Recommended primary endpoint of BVAS remission or change in BVAS • Clinical meaningfulness of BVAS 50% response unclear • Timing of endpoint (Week 12) too short to document successful treatment of renal vasculitis or assess impact on glucocorticoid requirement • Avacopan should be administered as an adjunct to standard of care, including a standard glucocorticoid regimen, until there is adequate data to support that modified regimens would not lead to irreversible harm • Did not agree with non-inferiority trial design If ChemoCentryx pursued renal vasculitis, the Agency recommended the following: • Renal biopsy for inclusion • Renal remission endpoints Consider broadening the patient population to generalized AAV
May 19, 2014	Avacopan received orphan drug designation for the treatment of AAV.
IND 120784 opened July 2014	ChemoCentryx proposed to open the IND with Study CL003_168, a randomized, double-blind, placebo-controlled, dose assessment phase 2 study to evaluate avacopan in patients with AAV. Two doses of avacopan were evaluated in this study. All patients received standard of care therapy including CYC or RTX plus a 6-month prednisone taper. ChemoCentryx conducted the third part of Study CL002_168 in Europe. The Applicant broadened the patient population to AAV but proceeded with a no prednisone arm.
October 24, 2014 May 24, 2016	ChemoCentryx submitted requests for fast track designation and breakthrough therapy designation on 2 occasions (before and after completion of study CL002_168). Requests were denied both times. The Agency determined that the rationale and non-clinical data were not robust enough to support the designations in the absence of accompanying supportive clinical data. The results from Study CL002_168 were of unclear clinical relevance and did not demonstrate substantial improvement over existing therapies in one or more clinically significant endpoints. In addition, concerns were raised about greater numbers of SAEs of vasculitis activity in the avacopan arms, suggesting ongoing vasculitis activity.
End-of-phase 2 (EOP2) meeting July 14, 2016	The Agency had multiple concerns with the data from Study CL002_168 and limited data available from Study CL003_168, including the clinical meaningfulness of the endpoint and early time point of assessment, observed SAEs suggestive of active vasculitis in CL002_168, and difficulty determining effect of avacopan from glucocorticoids and background therapy in CL003_168. Concerns with proposed pivotal study, CL010_168, a randomized, double-blind, placebo-controlled study evaluating 2 treatment arms (b) (4) (b) (4) (b) (4) were discussed. Removing glucocorticoids (standard of care) and replacing it

Meeting/ Date	Summary
	with avacopan complicates the study design and subsequent interpretation of data. Additional discussion focused on: • Uneven comparison of prednisone treatment for 26 weeks to avacopan treatment for 52 weeks • Clarification of how ChemoCentryx envisions the use of avacopan in clinical practice (induction vs. induction and maintenance) Non-inferiority study design would not be sufficient to show that avacopan can replace glucocorticoids. There are no historical placebo-controlled trials evaluating the efficacy of glucocorticoids as an add-on therapy to CYC or RTX. Agency noted that ChemoCentryx's determination of the extent of the contribution of glucocorticoids to historical remission rates is based on key, implausible, and unverifiable assumptions. Agency suggested multiple alternative study designs for pivotal trial: • Design a superiority trial to show benefit of avacopan vs. glucocorticoids. • Change the timing of efficacy assessment from Week 26 to Week 52 after patients have been off glucocorticoids for a more extended amount of time. • Change just one variable in the treatment arms, thus, 3 treatment arms. One arm evaluates avacopan + CYC or RTX. One arm evaluates PBO + CYC or RTX. One arm evaluates standard of care (glucocorticoids + CYC or RTX). This study design would inform the benefit of avacopan and assess the contribution of glucocorticoids. • Utilize the same treatment arms as suggested by ChemoCentryx but assess superiority on a direct assessment of benefit such as ESRD or death. ChemoCentryx subsequently suggested alternative study designs and assessments. • (b) (4) Agency expressed reservation about the clinical meaningfulness of this assessment, as the goal is long-term benefit in this disease. • (b) (4) Agency continued to have concerns and stated that non-inferiority would not be sufficient to show that avacopan can replace glucocorticoids. • Agency was amenable to looking at remission based on BVAS 0 at Week 26 and sustained remission based on BVAS 0 at Week 52. Agency requested further justification for enrollment of children into pivotal trial, particularly with ongoing concerns with proposed study design. Agency reiterated concerns with the non-inferiority study design and offered alternate development programs as post-meeting comments: • Superiority study with 2 treatment arms (avacopan + CYC/RTX vs. prednisone + CYC/RTX) with primary endpoint of time to event for BVAS remission (up to 26 weeks). Supportive secondary endpoints showing superiority in remission (Week 52) or sustained remission (Week 26 to 52). • Superiority study comparing avacopan + CYC/RTX vs. CYC/RTX + rapid glucocorticoid taper) with primary endpoint of BVAS remission at Week 26 and/or 52. Additional treatment arm with CYC/RTX + standard-of-care glucocorticoid arm as a benchmark reference. • Superiority study comparing avacopan + CYC/RTX + rapid glucocorticoid taper vs. CYC/RTX + rapid glucocorticoid taper with primary endpoint of BVAS remission at Week 26 and/or 52. Additional treatment arm with CYC/RTX + standard of care glucocorticoid arm as a benchmark reference.

Meeting/ Date	Summary
Type C meeting (post-EOP2) November 1, 2016	ChemoCentryx proposed a new study design for CL010_168, evaluating the same 2 treatment arms (b) (4) with co-primary endpoints of BVAS remission at Week 26 and sustained remission (Weeks 26 to 52). The primary endpoints will be analyzed for non-inferiority and superiority. The Agency continued to express concerns with this new study design. Specifically, the Agency reiterated that a non-inferiority study would not be sufficient to show that avacopan can replace glucocorticoids. It would be difficult to tease out whether avacopan or RTX/CYC was driving the efficacy results. The proposed study would not be adequate to support a safety comparison that avacopan is less toxic than standard-of-care glucocorticoids. If ChemoCentryx proceeded with this study design, the Agency agreed that superiority would be essential to demonstrate efficacy and that non-inferiority would not be sufficient. Agency continued to recommend a third standard-of-care arm with CYC/RTX + rapid taper glucocorticoids or no glucocorticoids. Agency did not agree (b) (4) All patients should be considered as having a flare, regardless of whether remission is achieved. An analysis solely of relapse after remission would be considered explorator (b) (4) The GTI includes several biomarkers whose validity for serving as surrogate markers is unclear. Thus, it will not be utilized to support regulatory or labeling decisions. Concerns with inclusion of SF-36 and EQ-5D-5L as secondary endpoints, as these are not validated measures in vasculitis. Concerns with measures of renal function, e.g., UACR and % change in urinary MCP-1:creatinine ratio.
Pre-NDA meeting March 19, 2020	The Agency reiterated that the study design of the pivotal trial, CL010_168, will make the data difficult to interpret and to determine the clinically meaningful benefit of avacopan. The Agency advised the Applicant to justify the clinical relevance of the results and to address how they intend for avacopan to be used in clinical practice. The Agency explained again that the clinical meaningfulness of GTI as a novel instrument that captures biomarkers and other assessments without including direct patient input has not been characterized. There are limited long-term safety data of avacopan treatment. The completed study was not designed to assess whether replacing potential toxicity of treatment with glucocorticoids with potential toxicities with avacopan represents a clinical benefit to patients. The Agency noted that external input may be required in the interpretation of the clinical benefits of the avacopan program.

Source: Clinical Reviewer
Abbreviations: AAV, ANCA-associated vasculitis; ANCA, anti-neutrophilic cytoplasmic antibody; AZA, azathioprine; BID, twice daily; BVAS, Birmingham Vasculitis Activity Score; CYC, cyclophosphamide; ESRD, end stage renal disease; GTI, Glucocorticoid Toxicity Index; IND, Investigational New Drug; NDA, New Drug Application; MCP-1, monocyte chemoattractant protein-1; PBO, placebo; RTX, rituximab; SAE, serious adverse event; UACR, urine albumin: creatinine ratio.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

The Division of Clinical Compliance from the Office of Scientific Investigations (OSI) was consulted to conduct clinical site inspections of the following facilities:

- Dr. John Niles: Site #102; Boston, MA
- Dr. Peter Merkel: Site #101; Philadelphia, PA

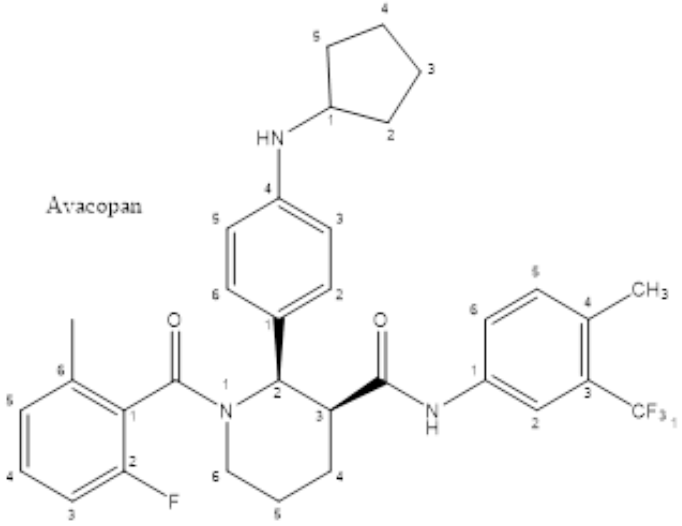
The clinical sites were selected using risk ranking from the clinical site selection tool for the phase 3 study based on high enrollment, high response rate (b) (4) (b) (4)

Upon completion of study site inspections, OSI Investigations concluded that the data generated by these clinical investigators' sites submitted by the Applicant appear acceptable and in support of this NDA. For complete details, refer to the review by OSI Medical Officer, Tina Chang, MD, dated January 4, 2021.

4.2. Product Quality

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

Figure 2. Chemical Name and Structure of Avacopan



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

Source: CMC Reviewer

Avacopan is a white to pale yellow crystalline solid that is practically insoluble in water. Avacopan is formulated as a 10 mg capsule (size 0) for oral administration with the following inactive ingredients: polyethylene glycol 4000, polyoxyl-40 hydrogenated castor oil. The hard gelatin capsules are light orange and yellow opaque bicolor with a clear gelatin sealing band. The top half of the capsule is printed with "CCX168" in black ink. The capsule shell contains gelatin, red iron oxide, yellow iron oxide, and titanium dioxide, and the capsule sealing band contains gelatin and polysorbate 80. The avacopan drug product is supplied in bottles of 30 and 180 capsules with child-resistant heat induction seal closures which are to be stored at controlled room temperature.

The Quality Assessment Team has determined that the drug substance and drug product information is adequate. The drug substance manufacturing process has been demonstrated to be satisfactory. The Applicant's specification for the drug substance meets the International Conference on Harmonisation Q6A, Q3C and Q3D guidelines. The drug substance as well as the specified and potential impurities in it have the (b) (4) structural alert for mutagenicity, however, the impurity limits were determined to be acceptable. A bulk storage shelf life of (b) (4) months (b) (4) is supported. Based on the stability data submitted to date, the expiry dating period for (avacopan) capsules shall be 36 months when stored at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F).

Testing facilities were approved based on inspectional coverage and compliance history and based on information in the Field Accomplishment and Compliance Tracking System (FACTS), Compliance Management Services (CMS) and Online Search and Retrieval (OSAR) databases.

The Applicant provided development studies to support the proposed parameter ranges for the commercial scale equipment, and a detailed explanation of the control strategy; minor issues have been resolved during the review.

The Biopharmaceutics review focused on the evaluation of dissolution method and acceptance criterion, which were found to be acceptable.

The Product Quality team recommends approval of this application from the product quality perspective. For complete details, refer to the Integrated Quality Review dated March 22, 2021.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

No device or companion diagnostic issues are submitted for review in support of this supplement.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Avacopan (CCX168) is a small molecule antagonist of complement component 5a receptor (C5aR), that is being developed as an oral treatment for adult patients with ANCA-associated vasculitis. This review evaluates the nonclinical pharmacology and toxicology program to support the safety of avacopan for marketing approval.

Primary Pharmacology

Specific leukocytes, including neutrophils and monocytes, express C5aR, which mediates chemotactic activity and activation of these cells by the anaphylatoxin, C5a. Pharmacology studies demonstrated that CCX168 is an antagonist of complement component 5a receptor (C5aR). C5aR amino acid sequence alignment identified a key tryptophan residue located within the 5th transmembrane region (TM-5) for human, cynomolgus monkeys, and hamster, while other species have variable amino acid residues at this location.

In Vitro Pharmacology

In an in vitro competitive ligand binding assay, CCX168 was evaluated for its ability to displace ^{125}I-human C5a from the C5a receptor on human U937 cells. In this assay CCX168 displaced ^{125}I-human C5a from the C5a receptor with an average IC_{50} of 0.45 nM.

Calcium mobilization assays were conducted in human neutrophils and U937 cells. CCX168 was added to the cells and hC5a was added either 25 seconds (neutrophils) or 1-2 minutes later (U937 cells). In the calcium mobilization assay in U937 cells, the A2 value (a 2- shift in the dose-response curve) was 0.1 nM. CCX168 inhibited C5aR-mediated calcium mobilization with an IC_{50} value of 0.2 nM for human neutrophils and 0.4 nM for human monocytes. No calcium mobilization was detected in neutrophils or monocytes in the time window (1 to 2 minutes) between the addition of CCX168 and prior to the addition of C5a.

In nonclinical and clinical studies, CCX168-M1, a methyl hydroxylation metabolite, was found to be the major metabolite of CCX168. In clinical studies in patients with ANCA-associated vasculitis, CCX168-M1 was found to constitute approximately 30-50% of the total systemic exposure at steady state. In vitro assays demonstrated that the M1 metabolite possessed pharmacologic activity similar to CCX168. Pretreatment with the M1 metabolite (C0335273) was demonstrated to have activity against human C5aR in multiple chemotaxis assays using either the human U937 cell line or human peripheral blood leukocytes (in whole blood) when stimulated with h5Ca, resulting in A2 values of 0.3 nM and 3 nM, respectively. In addition,

CCX168-M1 demonstrated inhibition of upregulation of the neutrophil surface CD11b adhesion molecule in response to stimulation with hC5a. Therefore, metabolite CCX168-M1 could contribute to potential systemic pharmacodynamic activity of avacopan.

In chemotaxis assays using peripheral blood leukocytes (human, cynomolgus, hamster, rabbit) or thioglycollate-elicited peritoneal lavage leukocytes, a mixture of neutrophils and macrophages (rat and mouse), pretreatment with CCX168 inhibited C5a-mediated chemotaxis of leukocytes in human, cynomolgus monkey, and hamster whole blood at A2 of 1.7, 18, 14 nM respectively. Similarly, CCX168-M1 inhibited C5a-mediated chemotaxis of leukocytes with comparable activity to CCX168 in human, cynomolgus monkey, and hamster whole blood at A2 values of 3 nM, 2.6 nM, and 10 nM, respectively. Therefore, the cynomolgus monkey and hamster were considered pharmacologically relevant species. Based on the lack of affinity of CCX168 and CCX168-M1 for the rat, mouse, and rabbit C5aRs (A2>1,000 nM) these nonclinical species were not considered pharmacologically relevant species.

In Vivo Pharmacology

In a C5a-induced neutropenia challenge study in cynomolgus monkeys, pretreatment with CCX168 reduced hC5a-induced neutropenia. Cynomolgus monkeys were first pretreated with CCX168 at 3 mg/kg or 30 mg/kg. Subsequently the monkeys were administered C5a at doses ranging from 2, 10, or 50 µg/kg to induce neutropenia. In a previous proof of concept neutropenia challenge study, 10 µg/kg hC5a was shown to induce neutropenia challenge adhesion causing neutrophils to adhere to blood vessel walls, thereby reducing the neutrophil concentration in blood. Pretreatment with CCX168 at 3 mg/kg and 30 mg/kg resulted in 50% and 100% inhibition of C5a-induced neutropenia, respectively.

Because of that lack of affinity of CCX168 for the mouse and rat C5a receptor, mice and rats were considered not pharmacologically relevant species for CCX168. Therefore, a human C5a receptor knock in (hC5aR KI) transgenic mouse strain was generated, where the murine C5aR gene was replaced by the human C5aR gene. In an in vitro proof of concept assay, neutrophils from these hC5aR knock-in mice were activated by C5a in a functional assay conducted in whole blood. Pretreatment with CCX168 at 38 nM in blood inhibited this effect by 10-fold (A10 value of 38 nM). In a murine ANCA disease model, ten-week-old female hC5aR KI mice were injected in the tail vein with 50 mg/kg anti-myeloperoxidase antibody, mimicking autoantibodies against neutrophil cytoplasm-expressed proteins, which cause lysis of neutrophils, releasing granule components which kill nearby endothelial cells, thereby activating the alternative complement pathway. In turn, more neutrophils are recruited, and they are primed for respiratory burst. The mice were dosed orally with CCX168 at doses of 0.1, 1 or 37.5 mg/kg once daily or vehicle control once daily, or 5 mg/kg CCX168 twice daily for 7 days. Mice were euthanized on day 7. Blood and urine samples were collected, and the kidneys were harvested and then analyzed for glomerular necrosis and crescent formation. Administration of CCX168 at 5 mg/kg BID and

37.5 mg/kg once daily (QD) resulted in significant reduction in the incidence of glomerular crescent formation and necrosis, relative to vehicle treated mice. Analysis of blood and urine samples indicated CCX168 treatment resulted in dose-dependent decreases in urinary leukocytes and erythrocytes. Treatment-related reduction in total urinary protein was also noted, although the relationship to the dose was not clear.

CCX168 was tested ex vivo for the ability to inhibit C5a-mediated CD11b upregulation of leukocytes using hC5aR KI mice. hC5aR-KI mice were treated with CCX168 at doses from 0.1 up to 5 mg/kg, or vehicle. Blood was collected 1-hour post CCX168 treatment and recombinant hC5a was added to whole blood to stimulate neutrophils. The samples were analyzed by flow cytometry for upregulation of CD11b. A dose response for a CCX168-dependent shift in the EC_{50} of hC5a-mediated CD11b upregulation on neutrophils relative to vehicle treated mice was noted. A CCX168 plasma concentration of 4.75 nM was required to shift the EC_{50} value 2-fold and a plasma concentration of 38 nM was required to shift the EC_{50} value 10-fold. These data were suggestive that treatment with CCX168 reduced the potency of exogenous hC5a to upregulate the adhesion molecule CD11b on blood neutrophils in hC5aR mice.

From the totality of the Applicant's in vitro and in vivo pharmacology studies, it was concluded that CCX168 and its metabolite, CCX168-M1, were potent antagonists of the human C5a receptor. CCX168 and CCX168-M1 did not appear to have agonist activity at C5aR on neutrophils or monocytes.

Secondary Pharmacology

The off-target selectivity of CCX168 was evaluated at 10 µM against a panel of 55 receptors and membrane associated proteins and the glucocorticoid receptor. CCX168 at 10 µM did not achieve 50% inhibition against any receptors or membrane associated protein in the screening panel. There was greater than 1000-fold selectivity for hC5aR relative to off-target activities identified in this study.

The M1 metabolite was tested for off-target activity at 10 µM against a panel of 17 chemotactic receptors and a panel of 56 unrelated receptors and membrane-associate proteins. The M1 metabolite exhibited weak activity at the human CB1 receptor (53% inhibition), sodium channel (site 2) (65% inhibition), and the GABAA receptor (51% inhibition) at 10 µM.

CCX168 was evaluated in a human glucocorticoid radioligand binding assay using human Hela 53 cells with 3 nM [^{3}H] Dexamethasone. No significant effects were noted at the screening concentration of 10 µM.

Safety Pharmacology

CCX168 was evaluated in a standard battery of safety pharmacology studies. In vitro, CCX168 did not inhibit hERG channel current in HEK293 cells, stably expressing hERG, at concentrations up to 6.9 µM. CCX168-M1 inhibited hERG channel currents by 38% at 3 µM. CCX168-M1 at concentrations of 10 and 15.8 µM resulted in a similar degree of inhibition. In cardiovascular safety pharmacology studies in telemetered male cynomolgus monkeys (single oral doses of 0, 5, 15, 50 mg/kg CCX168), systolic, diastolic, and arterial blood pressure values were decreased by approximately 7 to 10% at the 50 mg/kg dose level relative to controls during the time period from 15 mins to 225 mins after dosing. No treatment related effects were observed on QTc interval. In a respiratory safety pharmacology in rats (single oral doses of 0, 3.5, 19, 73 mg/kg CCX168), no treatment related effects were observed at any dose tested. No treatment related findings were observed in central nervous system (CNS) or renal safety pharmacology studies in rats at doses up to 100 mg/kg. In totality, single high doses of avacopan did not have any significant adverse effects on the cardiovascular, CNS, respiratory, and renal parameters that were evaluated.

Pharmacokinetics

Absorption

Oral bioavailability of CCX168 ranged from 55-104% in Sprague Dawley (SD) rats when dosed at 30 and 100 mg/kg.

When SD rats were administered oral doses of CCX168 of 100 or 300 mg/kg QD, and at 50, 100 or 300 mg/kg twice daily for 7 days, exposures (AUC_{0-24}) and C_{max} of CCX168 and CCX168-M1 were higher at 100 mg/kg than 300 mg/kg QD and BID. These data suggest saturation of exposure occurred at ≥100 mg/kg QD or BID.

Distribution

CCX168 and CCX168-M1 were highly protein bound (>99%) in plasma from SD rats, hamsters, cynomolgus monkey, and humans and >96.7% bound in plasma from CD-1 mice, rabbits, and dogs.

Metabolism

CCX168 was extensively metabolized in liver microsomes from human and nonclinical species. There were no metabolites unique to humans. CCX168-M1 was the major metabolite in human, monkey, rabbit, and rat (17.7%, 10.6%, 17.1%, and 20.4%, respectively) in liver microsome incubations. The unchanged parent compound accounted for the largest proportion of all metabolites detected. Characterization of the human metabolic pathways of CCX168 suggested that CYP3A4/5 was the primary isozyme involved in the in vitro metabolism of CCX168 and M1.

Excretion

In cynomolgus monkey, metabolism, rather than direct renal and biliary elimination of the intact drug, was the dominant route of CCX168 elimination. The primary route of elimination of the metabolites was through biliary excretion into feces.

General Toxicology

Several good laboratory practice-compliant pivotal repeat-dose toxicology studies were conducted with CCX168 for up to 13 weeks in hamster, 26 weeks in rats, and 44 weeks in monkey. The hamster and monkey were determined to be pharmacologically relevant species. The rat was not a pharmacologically relevant species, although metabolism of CCX168 was similar to that observed in humans. The hamster and monkey could assess on- and off-target toxicity while the rat could only assess off-target toxicity.

In the 13-week oral toxicity study in hamster, animals received 0 (vehicle), 10, 30, 100 and 1000 (500 BID) mg/kg/day CCX168. It is noted that the hamster is a pharmacologically relevant species for CCX168. No CCX168-related adverse findings were identified during the dosing or recovery period. Administration of CCX168 at doses up to 1000 mg/kg/day for 13-weeks was well tolerated. CCX168 exposure was saturated at doses ≥100 mg/kg/day. Based upon the observed saturation, the no-observed-adverse-effect-level (NOAEL) was 100 mg/kg/day, the lowest dose where the saturation was first observed, and the highest drug exposure was achieved. Exposure values for CCX168 at the 100 mg/kg/day were C_{max} =4,410 ng/mL, and AUC_{0-24}=39,900 ng*hr/mL for combined sexes on day 91 of dose administration.

In the pivotal 6-month chronic oral toxicity study in rats, animals received 0 (vehicle), 5, 15, 100 and 200 (100 mg/kg BID) mg/kg/day CCX168. There were no treatment-related toxicities at any of the doses tested. It is noted that the rat is not a pharmacologically relevant species for CCX168. CCX168 exposure was saturated at doses ≥100 mg/kg/day. Based upon the observed saturation, the NOAEL was 100 mg/kg/day, the lowest dose where the saturation was first observed, and the highest drug exposure was achieved.

In the pivotal 44-week chronic toxicity study in monkeys, monkeys received either 0 (vehicle control article), 5, 15 mg/kg QD, or 30 (15 BID) mg/kg/day of CCX168 over the first 25 weeks of the study (Groups 1-5). At the beginning of the study, CCX168 and the vehicle were administered by nasogastric intubation (Weeks 1-5). Starting at Week 6, the route of administration was switched to oral gavage (Weeks 6-44). After Week 25, to increase CCX168 exposure, the doses were increased to 0 (vehicle control article), 7.25, 22.5 mg/kg QD, or 22.5 mg/kg BID (45 mg/kg/day) of CCX168 for Groups 1-5, respectively, from Weeks 26-44. No CCX168-related mortalities occurred during the treatment or recovery period. No CCX168 treatment related findings were observed. The NOAEL was considered as the high dose (30 mg/kg/day (Weeks 1- 25) and 45 mg/kg/day (Weeks 26-44)).

Genetic Toxicology

Avacopan was negative for genotoxicity in a standard battery of genetic toxicology tests (in vitro Ames bacterial reverse mutation test, in vitro mouse lymphoma assay, and in vivo rat micronucleus assay). Metabolite CCX168-M1 was judged negative for mutagenicity in the Ames test for bacterial gene mutation based on confirmation that CCX168-M1 was formed upon incubation of CCX168 with S9.

Carcinogenicity

No treatment-related tumors were identified in 2-year oral studies with SD rats (0 [vehicle-control], 0 [water-control], 10, 30, and 100 mg/kg/day) and hamsters ((0 [vehicle-control], 0 [water-control], 10, 30, and 100 mg/kg/day) that were conducted to assess the carcinogenic potential of CCX168.

Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

In a hamster fertility study, male and female hamsters were treated before being paired for mating (28 days for males and 15 days for females), throughout mating, and once daily up through gestation day (GD) 12 in females and up to dosing day 50 to 53 in males with oral doses of 0, 10, 30, and 100 mg/kg QD or 0 and 500 mg/kg BID (0 and 1000 mg/kg/day, respectively). Treatment with CCX168 was well-tolerated in male and female hamsters. There were no deaths in the test article-treated groups. CCX168 did not affect fertility or reproductive performance (mating and fertility indices) in male or female rats. The paternal and maternal NOAELs for general and reproductive toxicity of CCX168 was 1000 mg/kg/day.

Embryo-Fetal Development

In a hamster embryo-fetal development (EFD) study, time-mated female hamsters were treated with oral doses of 0 (vehicle), 10, 30, and 100 mg/kg/day and 0 and 500 mg/kg BID (0 and 1000 mg/kg/day) CCX168 administered during the period of organogenesis from GD 6-12. There were no treatment-related effects on maternal performance or on maternal body weight gains. No treatment-related fetal malformations were noted, however, an increase in a skeletal variation described as supernumerary ribs was noted in all litters (40 fetuses) in the 1000 mg/kg/day group. This finding is considered a developmental delay and supernumerary ribs can resolve into the vertebral arch later in development. Toxicokinetic analysis identified saturation of exposure occurred at ≥100 mg/kg/day. The NOAEL for maternal and developmental toxicity was 1000 mg/kg/day.

In a rabbit EFD study, time-mated female rabbits were treated with oral doses of 0 (vehicle), 10, 30, and 200 mg/kg/day CCX168 administered during the period of organogenesis from GD 6-18 and were sacrificed on GD 29. An increase in the number of abortions was noted in the 200 mg/kg/day group. Decreases in body weight gain were seen in the 30 and 200 mg/kg/day groups. No treatment-related changes in cesarean section parameters or fetal malformations or variations were identified. Toxicokinetic analysis identified saturation of exposure occurred at ≥30 mg/kg/day. The NOAEL for maternal toxicity was the low dose of 10 mg/kg/day and the NOAEL for developmental toxicity was the high dose of 200 mg/kg/day.

Prenatal and Postnatal Development

In a hamster pre-and-postnatal development study, mated female hamsters (F0 generation) were treated with oral doses of 0 (vehicle), 10, 30, and 100 mg/kg/day and 0 and 500 mg/kg BID CCX168 from GD 6 to lactation day (LD) 20. F0 dams showed no treatment related effects on reproductive or uterine parameters. There were no treatment related effects on the gestation length, the number of implantation sites, the number of live births, or on viability of F1 offspring. CCX168 and CCX168-M1 were present in the plasma of nursing F1 pups on LD 15. No treatment related effects on body weights of F1 offspring from birth to weaning (LD 1 to LD 21) were seen. There was no effect of CCX168-treatment of the F0 mothers on the postweaning growth, physical, and neurological development of F1 offspring as assessed by measurements of body weight gain, achievements of developmental milestones, motor evaluation, and performance in a passive avoidance test. There was no effect of CCX168-treatment of the F0 mothers on fertility in the F1 offspring. There was no effect of CCX168-treatment in the F0 mothers on numbers of corpora lutea, implantations, pre-and post-implantation losses, and viable embryos in pregnant F1 females. The NOAEL for F0 maternal toxicity and for F1 pup development was the high dose of 500 mg/kg BID (1000 mg/kg/day).

Phototoxicity

While CCX168 absorbed UV light at 290 nm with a molar extinction coefficient of 2989 L mol^{-1} cm^{-1}. CCX168 was negative in a Neutral Red Uptake Phototoxicity Assay in BALB/c 3T3 Mouse Fibroblasts. This assay has a high rate of false positive, so the negative assay indicated that there was minimal concern for potential phototoxicity.

Table 2. Summary of Plasma AUC for Avacopan (CCX168) and Major Metabolite (CCX168-M1) at Dose Level of 30 mg BID in Human Clinical Subjects at Week 52 Based on Phase 3 Study CL010_168

Administered Drug	AUC_{0-12} (ng*hr/mL)	AUC_{0-24} (2X AUC_{0-12}) (ng*hr/mL)
Avacopan (CCX168)	3466	6932
Major Metabolite (CCX168-M1)	1283	2566

Source: Study CL010_168 Population PK modeling Table 5 and Table 7
Abbreviations: ANCA, anti-neutrophilic cytoplasmic ant body; AUC, area under the curve; BID, twice daily.

Table 3. Animal to Human Exposure Margins for Avacopan (CCX168) and Major Metabolite (CCX168-M1) Based on AUC for the Proposed Clinical Dose of 30 mg BID for Pivotal Toxicology Studies

Study No.	NOAEL (mg/kg/day)	ROA	CCX168 or M1	Nonclinical AUC_{0-24} ng*hr/mL	Animal to Human Exposure Margin (Clinical Daily dose 30 mg BID)[1,2]
13-Week Hamster (PC0677_168)	100	Oral	CCX168	39,900	5.8
			M1	2480	0.97
26-Week rat (PC0655_168)	100	Oral	CCX168	73,150	10.5
			M1	2,460	0.96
44-Week Monkey (PC0654_168)	45	Oral	CCX168	29,300	4.2
			M1	9590	3.7

Source: Prepared by the Nonclinical Reviewer. Exposure data was derived from Study No. PC0677_168 (13-Week hamster), Study No. PC0655_168 (26-Week rat), and Study No. PC0654_168 (44-Week Monkey)
[1] Steady state human CCX681 AUC_{0-24}: 6932 ng*hr/mL
[2] Steady state human CCX681-M1 AUC_{0-24}: 2566 ng*hr/mL
Abbreviations: AUC, area under the curve; BID, twice daily; NOAEL, no-observed-adverse-effect-level; ROA, route of administrations.

Table 4. Animal to Human Exposure Margins for Avacopan (CCX168) and Major Metabolite (CCX168-M1) Based on AUC for the Proposed Clinical Dose of 30 mg BID for Reproductive and Developmental Toxicity Studies

Study No.	NOAEL (mg/kg/day)	ROA	CCX168 or M1	Nonclinical AUC ng*hr/mL	Animal to Human Exposure Margin (Clinical Daily dose 30 mg BID)[1,2]
FEED hamster (PC0670-168)	Maternal and Paternal 1000 (HD)	Oral	CCX168	47,339	6.8
			M1	7,795	3.0
EFD hamster (PC0671_168)	Maternal and Developmental 1000 (HD)	Oral	CCX168	36,400	5.3
			M1	1,680	0.7
EFD rabbit (PC0672_168)	Maternal: 10 (LD)	Oral	CCX168	2350	0.34
			M1	364	0.14
	Developmental: 200 (HD)	Oral	CCX168	4180	0.60
			M1	780	0.3
PPND hamster (PC0673_168)	Maternal and Developmental 1000 (HD)	Oral	CCX168	30,900	4.5
			M1	3,260	1.3

Source: Prepared by the Nonclinical Reviewer. Exposure data was derived from Study No. PC0670-168 (FEED hamster, Study No. PC0671_168 (EFD hamster), Study No. PC0672_168 (EFD rabbit), and Study No. PC0673_168 (PPND hamster)
[1] Steady state human CCX681 AUC_{0-24}: 6932 ng*hr/mL
[2] Steady state human CCX681-M1 AUC_{0-24}: 2566 ng*hr/mL
Abbreviations: AUC, area under the curve; BID, twice daily; EFD, embryo-fetal development; FEED, fertility and early embryonic development; HD, high dose; LD, low dose; NOAEL, no-observed-adverse-effect-level; PPND, pre-and-postnatal development; ROA, route of administrations.

Table 5. Exposure Margins for Clinical Dose of 30 mg BID CCX168 and CCX168-M1 Based on the 2-Year Carcinogenicity Study in Rats and Hamsters

Study Type	CCX168		CCX168-M1	
Sex CCX168 (mg/kg/day)	AUC_{0-24} (ng*hr/mL)	Exposure Margin	AUC_{0-24} (ng*hr/mL)	Exposure Margin
2-Year Carcinogenicity Study in Rats				
Males				
10	11,500	1.66	445	0.17
30	25,600	3.7	1140	0.44
100	17,400	2.51	1440	0.56
Females				
10	13,600	1.96	3670	1.43
30	33,400	4.8	1830	0.71
100	21,400	3.09	1970	0.77
2-Year Carcinogenicity Study in Hamster				
Males				
10	5,560	0.8	363	0.1
30	21,600	3.1	1,550	0.6
100	42,000	6.1	2,850	1.1
Females				
10	4,290	0.6	282	0.1
30	24,500	3.5	1,750	0.7
100	35,600	5.1	2,500	1.0

Source: Prepared by the Nonclinical Reviewer. Exposure data was derived from Study No. PC0675_168 (Rat) and Study No. PC0674_168 (Hamster)
Abbreviations: AUC, area under the curve; BID, twice daily.

Recommendation: From the nonclinical perspective, the application is recommended for approval. An evaluation of the product labeling will be conducted in a separate review. There are no outstanding issues. No further nonclinical studies are required.

5.2. Referenced NDAs, BLAs, DMFs

Investigational new drug (IND) 120784

- All nonclinical studies in support of NDA 214487 were conducted under IND 120784

5.3. Pharmacology

The pharmacology studies were reviewed under NDA 214487 and IND 120784 (see NDA 214487 PharmTox Review of CCX168 (avacopan) and Appendix 7, dated March 8, 2021, in the Document Archiving Reporting and Regulatory Tracking System [DARRTS]).

5.4. ADME/PK

The ADME/PK studies were reviewed under NDA 214487 and IND 120784 (see NDA 214487 PharmTox Review of CCX168 (avacopan) and Appendix 7, dated March 8, 2021, in DARRTS).

5.5. Toxicology

5.5.1. General Toxicology

The repeat dose toxicology studies were reviewed under NDA 214487 and IND 120784 (see NDA 214487 PharmTox Review of CCX168 (avacopan) and Appendices 1, 2, and 3 dated March 8, 2021, in DARRTS).

5.5.2. Genetic Toxicology

The genetic toxicology studies were reviewed under IND 120784 (see NDA 214487 Nonclinical Review Appendix 2 dated March 8, 2021, in DARRTS).

5.5.3. Carcinogenicity

The 2-year carcinogenicity studies in rat and hamster were reviewed under NDA 214487 (see NDA 214487 Review of rat and hamster carcinogenicity studies and Executive Carcinogenicity Assessment Committee minutes dated March 8, 2021 in DARRTS).

5.5.4. Reproductive and Developmental Toxicology

The reproductive and developmental toxicology studies were reviewed under NDA 214487 (see NDA 214487 PharmTox review of CCX168 (avacopan) dated March 8, 2021, in DARRTS).

5.5.5. Other Toxicology Studies

Phototoxicity studies were reviewed under NDA 214487 (see NDA 214487 PharmTox review of CCX168 (avacopan) dated March 8, 2021, in DARRTS).

6. Clinical Pharmacology

6.1. Executive Summary

ChemoCentryx, Inc. submitted NDA 214487 on July 07, 2020, seeking the marketing approval for avacopan for the treatment of adult patients with ANCA-associated vasculitis (GPA and MPA). Avacopan (also known as CCX168) is claimed to be an antagonist of the complement 5a receptor (C5aR). The proposed commercial avacopan drug product is formulated as a 10 mg capsules for oral administration. The proposed dosing regimen is 30 mg twice daily (BID) with food.

NDA 214487 consists of ten clinical and clinical pharmacology studies, including seven phase 1 studies, two phase 2 studies, and one phase 3 study. Twenty in-vitro study reports were submitted characterizing protein binding, metabolism, and drug-drug interaction (DDI) potential. In addition, one population pharmacokinetic (PK) modeling and simulation report was submitted.

Recommendation

The Office of Clinical Pharmacology (OCP), Division of Inflammation and Immune Pharmacology (DIIP) and Division of Pharmacometrics have reviewed the clinical pharmacology data submitted under NDA214487. No approvability issue has been identified from a clinical pharmacology perspective for the treatment of patients with ANCA-associated vasculitis.

The Office of Clinical Pharmacology recommends a Post Marketing Requirement to evaluate the effect of repeat doses of avacopan 30 mg twice daily with food at steady state on the pharmacokinetics of a sensitive substrate of CYP3A4 (e.g., simvastatin) to inform appropriate dosing strategies for coadministration of avacopan with CYP3A4 substrates.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Avacopan is claimed to be an antagonist of C5aR. The following are the major findings of the current review and summary of the clinical pharmacokinetics of avacopan:

1. The dose ranging data (10 mg BID and 30 mg BID) from phase 2 studies (CL002_168 and CL003_168) are limited due to study design (different endpoint, short duration, etc., see section 8). Only one dosing regimen (30 mg BID) was selected for the evaluation in the phase 3 study CL010_168 and the efficacy data is highly confounded by concomitant medications (glucocorticoid, rituximab, and cyclophosphamide). Therefore, no exposure-

response analysis was conducted. Refer to Sections 7 and 8 for efficacy and safety assessment for the pivotal phase 3 study (CL010_168) supporting the proposed 30 mg BID dosing regimen of avacopan for the target patient population.

2. Overall, the cumulative total glucocorticoid dose was greater in the prednisone arm compared to the avacopan arm in Study CL010_168. While the potential exposure increase of glucocorticoids when co-administered with avacopan due to drug-drug interactions could not be ruled out, it is unlikely that the absolute glucocorticoid exposure is higher in avacopan arm vs the prednisone arm in Study CL010_168. Nevertheless, the true differences in glucocorticoid exposures could be smaller than the differences in nominal doses of glucocorticoids between the prednisone arm and the avacopan arm. See Sections 7 and 8 for more detailed assessment regarding the use of non-study supplied glucocorticoids in phase 3 study CL010_168.
3. Summary of clinical pharmacokinetics of avacopan:

Absorption: When a single dose of 30 mg avacopan was administered with a high-fat, high-calorie meal, avacopan AUC and Cmax increased by approximately 72% and 8%, respectively, and the median T_{max} delayed by approximately 4 hours (from 2.0 hours to 6.0 hours) as compared to fasted condition. For the active metabolite M1, a high-fat and high-calorie meal did not affect the AUC, but reduced C_{max} by 51% as compared to fasted condition. Following 30 mg avacopan BID administration, the steady state of avacopan was reached by 13 weeks with approximately 4-fold accumulation.

Distribution: The plasma protein binding (e.g., to albumin and α1-acid glycoprotein) of avacopan and metabolite M1 is greater than 99.9%. In patients with ANCA-associated vasculitis, the mean V/F of avacopan is estimated to be 352 L following the administration of 30 mg BID avacopan.

Elimination: Following a single dose of 30 mg avacopan with food, the mean elimination half-lives of avacopan and M1 are 97.6 hours and 55.6 hours, respectively, in healthy subjects.

- **Metabolism:** CYP3A4 is the major enzyme responsible for the metabolism of avacopan. A mono-hydroxylated product of avacopan, M1, is the major circulating metabolite, presenting approximately 12% of the total drug-related materials in plasma and has approximately the same activity as avacopan on the C5aR.
- **Excretion:** The main route of clearance of avacopan is phase I metabolism followed by biliary excretion of the metabolites into feces. In the mass balance study, following oral administration of radiolabelled avacopan, about 77.2% and 9.5% of the radioactivity was recovered in feces and urine, respectively, and 7% and <0.1% of the radioactive dose was recovered as unchanged avacopan in feces and urine, respectively.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen for avacopan is 30 mg BID with food.

Defer to the efficacy/safety assessment of the pivotal phase 3 study (Study CL010_168) regarding the adequacy of the proposed dosing regimen of avacopan for the proposed indication.

Therapeutic Individualization

Hepatic Impairment: Following a single dose of 30 mg avacopan, the systemic exposure (AUC and C_{max}) of avacopan and M1 in subjects with mild (Child-Pugh Class A, score 5 to 6) or moderate (Child-Pugh Class B, score 7 to 9) hepatic impairment were generally comparable to healthy subjects with normal hepatic function. Therefore, no dose adjustment is recommended for patients with mild or moderate hepatic impairment. Avacopan has not been studied in subjects with severe hepatic impairment.

Strong CYP3A4 Inhibitors: Co-administration with itraconazole, a strong CYP3A4 inhibitor, increased avacopan AUC and C_{max} by 119% and 87%, respectively, and increased M1 AUC and C_{max} by 19% and 3%, respectively. Therefore, when co-administered with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin), the dose of avacopan should be reduced to 30 mg once daily.

CYP3A4 Inducers: Co-administration with rifampin, a strong CYP3A4 inducer, decreased avacopan AUC and C_{max} by 93% and 79%, respectively. Similar systemic exposure decrease was observed for M1. Decreased systemic exposure of avacopan and M1 may lead to reduced therapeutic effect of avacopan. The effect of moderate CYP3A4 inducer has not been evaluated. Therefore, co-administration of avacopan with strong or moderate CYP3A4 inducers is not recommended.

CYP3A4 Substrates: Avacopan showed time-dependent inhibition of CYP3A4. After 30 mg avacopan BID administration under fasted condition for 10 days, the AUC and C_{max} of midazolam, a sensitive CYP3A4 substrate, increased by 81% and 55%, respectively. The impact of avacopan at steady state under fed condition on CYP3A4 substrates could be higher as compared to fasted condition but has not been studied. Therefore, closely monitor patients for adverse reactions and consider dose reduction of sensitive CYP3A4 substrates with a narrow therapeutic window when co-administered with avacopan.

Outstanding Issues

When a single dose of 30 mg avacopan was administered with a high-fat, high-calorie meal, avacopan AUC and Cmax increased by approximately 72% and 8%, respectively, as compared to fasted condition. Following 30 mg avacopan twice daily administration, the steady state of avacopan was reached by 13 weeks with approximately 4-fold accumulation. Avacopan showed time-dependent inhibition of CYP3A4. After 30 mg avacopan twice daily administration under fasted condition for 10 days, the AUC and Cmax of midazolam (a sensitive CYP3A4 substrate) increased by 81% and 55%, respectively. The impact of avacopan at steady state under fed condition on CYP3A4 substrates could be higher as compared to fasted condition but has not been studied.

Therefore, OCP recommends one Postmarketing Requirement study to evaluate the effect of repeat doses of avacopan 30 mg twice daily with food at steady state on the pharmacokinetics of a sensitive substrate of CYP3A4 (e.g., simvastatin) to inform appropriate dosing strategies for coadministration of avacopan with CYP3A4 substrates.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Avacopan is a small molecule drug. Its structure is shown in Figure 2. The proposed drug product is 10 mg capsule.

Table 6. Summary of Clinical Pharmacology and Pharmacokinetics

Review Issues	Recommendations and Comments
Pharmacology	
Mechanism of Action	Avacopan is an antagonist of C5aR.
Active Moieties	Avacopan parent drug and its metabolite M1 are the active moieties. Based on the mass balance study, avacopan was the most abundant drug-related component in human plasma, representing 18% of the plasma radioactivity. M1, a mono-hydroxylated metabolite, presents approximately 12% of the total drug-related plasma exposure and has approximately the same activity as avacopan on the C5aR (Study CL004_168).
QT Prolongation	No significant QTc prolongation effect of avacopan was detected at the highest dose evaluated, i.e., 100 mg BID for 7 days (Study CL014-168, refer to QT-IRT review by Dr. Girish Bende dated 10/14/2020).

Review Issues	Recommendations and Comments	
General Information		
Bioanalysis	Avacopan and M1 concentrations in human plasma were measured using validated high-performance liquid chromatographic separation with tandem mass spectrometric (LC-MS/MS) assays.	
Healthy Volunteers vs. Patients	Based on population PK analysis, subjects with ANCA-associated vasculitis are estimated to have 35% lower CL/F of avacopan and similar CL/F of M1 as compared to healthy subjects (Report CMR_168_POP_PK2).	
Drug exposure at steady state following the therapeutic dosing regimen	Based on population PK analysis, the mean $AUC_{0\text{-}12hr,ss}$ and $C_{max,ss}$ of avacopan are estimated to be 3466±1921 ng*h/mL and 349±169 ng/mL, respectively, following 30 mg BID dosing in patients with ANCA-associated vasculitis (Report CMR_168_POP_PK2).	
Dose Proportionality	Avacopan C_{max} and AUC are approximately dose-proportional after a single dose of 30 mg and 100 mg avacopan (Study CL001_168).	
Accumulation	Following 30 mg BID dosing, the steady state could be achieved by 13 weeks with 4-fold accumulation (Study CL010_168 and Report CMR_168_POP_PK2).	
Variability	The between-subject variability (CV %) of avacopan PK is up to 50% based on PK data in healthy subjects and patients with ANCA-associated vasculitis. Based on population PK analysis, the between-subject variability for CL/F and Vc/F of avacopan is 47% and 32%, respectively (Report CMR_168_POP_PK2).	
Absorption		
T_{max} [oral]	Following a single dose administration of 30 mg avacopan, the median T_{max} of avacopan was 2.0 hours (range 1.5-4.0 hours) under the fasted condition and was 6.0 hours (range 2.0-8.0 hours) under fed condition (Study CL007_168).	
Food effect (high-fat and high-caloric) GMR (fed/fasted, 90% CI) (Study CL007_168)	**$AUC_{0\text{-}inf}$**	**C_{max}**
	Avacopan: 1.72 (1.47, 2.00) M1: 0.89 (0.86, 0.93)	Avacopan: 1.08 (0.92, 1.27) M1: 0.49 (0.45, 0.54)
Distribution		
Volume of Distribution	The apparent volume of distribution (Vc/F) of avacopan is estimated to be 345 L (Report CMR_168_POP_PK2).	
Plasma protein binding	The plasma protein binding (e.g., to albumin and α1-acid glycoprotein) of avacopan and M1 is greater than 99.9%.	
Blood to plasma ratio	In vitro study showed avacopan and M1 have limited penetration into red blood cells. In mass balance study, low association of radioactivity with blood cells was observed with a mean blood-to-plasma ratio of 0.6 (Study CL004-168).	
Substrate transporter systems	Avacopan is not a substrate of BCRP and P-gp efflux, and OATP1B1 and OATP1B3 uptake transporters. M1 is a substrate of P-gp but is not a substrate of BCRP efflux, and OATP1B1 and OATP1B3 uptake transporters.	
Elimination		
Elimination half-life	Following a single dose of 30 mg avacopan with food, the mean elimination half-lives of avacopan and M1 are 97.6 hours and 55.6 hours, respectively, in healthy subjects (Study CL007_168).	

Review Issues	Recommendations and Comments
Metabolism	
Primary metabolic pathway(s)	In vitro studies indicated that CYP3A4 plays a major role in *in vitro* clearance of avacopan as well as in the formation and clearance of M1. In the mass balance study in human, M1 is the major circulating metabolite and has approximately the same activity as avacopan on C5aR. Avacopan and M1 accounted for ~18% and ~12%, respectively, of the total radioactivity in plasma. M1 and most other metabolites are products of oxidative metabolism of avacopan (Study CL004_168).
Inhibitor/Inducer	Based on in vitro study results, avacopan showed time-dependent inhibition of CYP3A4 at 1 µM and had a low potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6. Avacopan showed negligible induction of CYP1A2 and CYP2B6, but modest induction of CYP3A4. Based on in vitro study results, M1 did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6 but had the potential to inhibit CYP2C9 and CYP3A4. M1 had a low potential to induce CYP3A4, CYP1A2 and CYP2B6. In vitro studies indicate that avacopan and M1 do not inhibit the transporters P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, and MATE2K at clinically relevant concentrations. Clinical DDI study (Study CL008-168) showed that co-administration with itraconazole, a strong CYP3A4 inhibitor, increased avacopan AUC and Cmax by 119% and 87%, respectively, and increased M1 AUC and Cmax by 19% and 3%, respectively. Co-administration with rifampicin, a strong CYP3A4 inducer, decreased avacopan AUC and Cmax by 93% and 79%, respectively and similar systemic exposure decrease was observed for M1. After 30 mg avacopan BID administration under fasted condition for 10 days, the AUC and Cmax of midazolam, a sensitive CYP3A4 substrate, increased by 81% and 55%, respectively.
Excretion	
Primary excretion pathway	Following a single oral dose solution of approximately (b) (4) mg/(b) (4) µCi [^{14}C] avacopan, 86.7% of the radioactivity was recovered in urine and feces within 216 hours after dosing, in which approximately 77.2% was recovered in feces and 9.5% was recovered in urine. 7% and <0.1% of the radioactive dose was recovered as unchanged avacopan in feces and urine, respectively (Study CL004_168).

Source: Clinical pharmacology reviewer
Abbreviations: ANCA, anti-neutrophilic cytoplasmic ant body; AUC, area under the curve; BID, twice daily; CI, confidence interval; CL/F, oral clearance; C_{max}, maximum concentration; CYP, cytochrome P-450 enzyme; DDI, drug-drug interaction; GMR, geometric mean ratio; QT-IRT, QT-Interdisciplinary Review Team; OATP, organic anion transporting polypeptides; BCRP: breast cancer resistance protein; Pgp, P-glycoprotein; PK, pharmacokinetics; T_{max}, time to reach maximum concentration; Vc/F, apparent volume of distribution

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

This submission consists of ten clinical and clinical pharmacology studies, including seven phase 1 studies in healthy subjects, two phase 2 and one phase 3 clinical studies (Table 7). The use of avacopan for the treatment of the proposed indication was based on the pivotal phase 3 study CL010_168 (see Sections 7 and 8). See OCP Appendix (17.3) for individual study reviews for clinical pharmacology studies.

Table 7. List of Clinical Studies

Study Number/ Country/ Phase	Study Title	Subject Population	Study Size and Treatment	Avacopan Dose Form (oral)
CL001_168 / Switzerland / Phase 1	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	Healthy subjects	48 subjects; single-dose (1 – 100 mg) in Period 1; 1 – 10 mg q.d. or 30 / 50 mg b.i.d. dose for 7 days in Period 2	Dosing solutions and 10 mg capsules[a]
CL004_168 / United States / Phase 1	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	Healthy subjects	6 males; a single dose of 100 mg / 400 µCi ^{14}C-avacopan	Dosing solution
CL007_168 / United States / Phase 1	An Open-Label, Phase 1 Study in Healthy Volunteers to Evaluate the Pharmacokinetic Food Effect of CCX168[b]	Healthy subjects	16 subjects; 3 – 100 mg in 4 periods	Dosing solution for 3 mg dose; 10 mg capsules[c] for other groups
CL008_168 / United States / Phase 1	An Open-Label, Phase 1 Study in Healthy Volunteers to Evaluate the Drug-Drug Interaction Potential of CCX168 with Concomitant Medications	Healthy subjects	32 subjects (16 in each cohort)	10 mg capsules[c]
CL013_168 / United States / Phase 1	An Open-Label, Phase 1 Study to Evaluate the Single-dose Pharmacokinetics of Avacopan (CCX168) in Male and Female	Healthy subjects and subjects with mild or moderate	24 subjects (8 in each cohort; 30 mg single dose)	10 mg capsules[c]

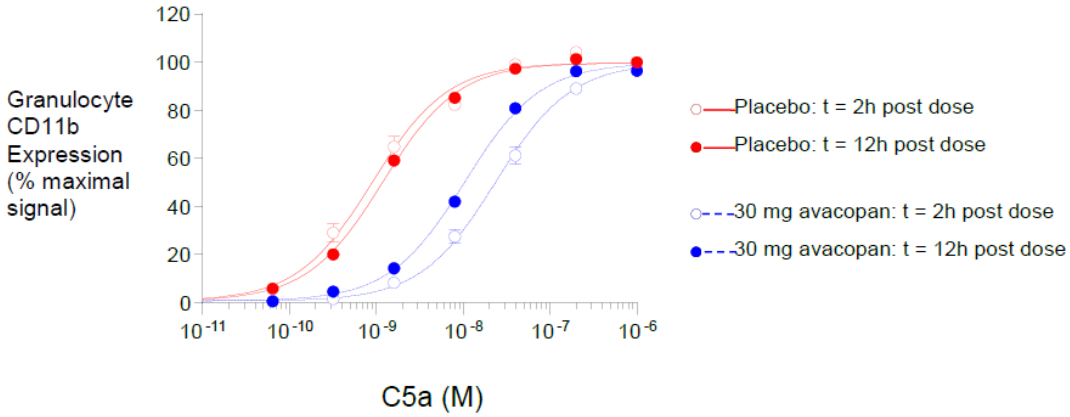
	Subjects with Mild or Moderate Hepatic Impairment	hepatic impairment		
CL014_168/ United States / Phase 1	A Multiple-Dose, Randomized, Double-Blind, Placebo-Controlled, Active-Comparator, Parallel Study to Investigate the Effect of Avacopan at Therapeutic and Supratherapeutic Doses on the QT/QTc Interval in Healthy Subjects	Healthy subjects	58 subjects (29 in Cohort 1 on 30 mg/100 mg each dose level for 7 days; 29 in Cohort 2 on moxifloxacin)	10 mg capsules[c]
CCX1101 / Japan / Phase 1	A Phase 1 Clinical Study of CCX168 in Japanese and Caucasian Healthy Adult Males	Healthy Japanese and Caucasian subjects	80 subjects (10 in each cohort [8 on avacopan, 2 on placebo]; 10, 30, or 100 single dose; 30 or 50 mg b.i.d.)	10 mg capsules[c]
CL002_168 / Europe / Phase 2	A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects with Anti-Neutrophil Cytoplasmic Antibody (ANCA) - Associated Vasculitis on Background Cyclophosphamide or Rituximab Treatment	Subjects with ANCA[d]-associated vasculitis	67 subjects: 23 on placebo b.i.d. + high dose prednisone + CYC or RTX SOC[e]; 22 on 30 mg avacopan b.i.d. + low dose prednisone + CYC or RTX SOC; 22 on 30 mg avacopan b.i.d. + no prednisone + CYC or RTX SOC	10 mg capsules[c]
CL003_168 / US, Canada / Phase 2	A Randomized, Double-Blind, Placebo-Controlled, Dose Assessment Phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis	Subjects with ANCA-associated vasculitis	42 subjects: 13 on placebo + full dose prednisone + CYC or RTX SOC; 13 on 10 mg avacopan b.i.d. + full dose prednisone + CYC or RTX; 16 in Group 3: 30 mg avacopan b.i.d. + full dose prednisone + CYC or RTX	10 mg capsules[c]
CL010_168 / North America, Europe, Australia, New Zealand,	A Randomized, Double-Blind, Active-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of Avacopan (CCX168) in Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Treated Concomitantly with Rituximab	Subjects with ANCA-associated vasculitis	330 subjects Group A (prednisone): avacopan-matching placebo + full dose prednisone + CYT or RTX	10 mg capsules[c]

Japan / Phase 3	or Cyclophosphamide/Azathioprine		Group B (avacopan): 30 mg b.i.d. avacopan + prednisone-matching placebo+ CYT or RTX	

[a] Avacopan was dosed as semi-solid filled gelatin capsules in 100% Cremophor RH40 or 50/50 Cremophor RH40 / PEG-4000.
[b] Study CL007_168 also evaluated cardiac safety.
[c] Avacopan was dosed as semi-solid filled gelatin capsules in 50/50 Cremophor RH40 / PEG-4000.
Source: Table 1 of Summary of Clinical Pharmacology Studies
Semi-solid capsule formulation in (b) (4) Cremophor RH40 / PEG-4000 is the proposed commercial formulation of avacopan.
Abbreviations: ANCA, anti-neutrophil cytoplasmic autoantibody; b.i.d, twice daily; CYC, cyclophosphamide; q.d., once daily; RTX, rituximab; SOC, standard of care.

The Applicant performed an *ex vivo* assay using blood samples from healthy subjects in Study CL001_168 to investigate the PK/pharmacodynamic (PD) relationship of avacopan in humans. The relationship between the avacopan plasma concentration and the inhibition of C5aR-dependent upregulation of the integrin CD11b in peripheral blood neutrophils and inhibition of C5aR-dependent neutrophil chemotaxis was determined. Results indicated that the 30 mg BID dosing regimen provides continuous blockade of the C5aR in an entire 12-hour dosing period (Figure 3). However, the clinical relevance of this PK/PD assessment is unclear.

Figure 3. Ex Vivo Whole Blood Assay Results From Healthy Subjects Dosed With 30 mg Avacopan Twice Daily or Placebo in Study CL001_168



Source: Figure 3 of Summary of Clinical Pharmacology Studies
%C5aR inh bition=(1-[1/x-fold shift])×100
The placebo group (in red solid line) showed no shift in the C5a concentration vs. granulocyte CD11b expression curve, whereas the avacopan 30 mg BID group (in blue dashed line) showed a >10-fold shift in the curve at both the 2-hour and 12-hour (trough level) time points.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The dose ranging data from phase 2 studies (CL002_168 and CL003_168) are limited. Only one dosing regimen, i.e., 30 mg BID, was selected for the evaluation in phase 3 study CL010_168

and was proposed for the target patient population, which is generally reasonable from a clinical pharmacology perspective. The findings from phase 2 studies are briefly discussed below. See Sections 7 and 8 for more detailed interpretation regarding phase 2 study design and assessment. Also refer to Sections 7 and 8 for efficacy and safety assessment for the pivotal phase 3 study (CL010_168) supporting the proposed 30 mg BID dosing regimen of avacopan for the target patient population.

In addition, exposure response was not conducted since only one dose was evaluated in phase 3 study and the efficacy of avacopan is confounded by the use of comedications, including glucocorticoid, rituximab, and cyclophosphamide.

Phase 2 Study CL002_168

It is a prospective, randomized, double-blind, double-dummy, placebo-controlled clinical trial in subjects with active ANCA-associated vasculitis. Only 30 mg BID dosing of avacopan was administered with a full starting dose of prednisone (60 mg once daily) or a reduced starting dose of prednisone (20 mg once daily) plus cyclophosphamide. The prednisone for both treatment groups was tapered based on a prespecified tapering schedule. Results indicated that the primary efficacy endpoint, BVAS response at Week 12, was met (Table 8).

Phase 2 Study CL003_168

It is a randomized, double-blind, placebo-controlled clinical trial to assess the safety, tolerability, and efficacy of avacopan in subjects with new or relapsed AAV on background standard of care treatment plus glucocorticoid treatment. Patients were randomized to the following three treatment groups and prednisone was tapered based on a prespecified tapering schedule for all three groups:

- Full dose prednisone control group: avacopan-matching placebo plus cyclophosphamide or rituximab plus a full starting dose of prednisone (60 mg/day)
- Low dose avacopan group: avacopan 10 mg BID plus cyclophosphamide or rituximab plus a full starting dose of prednisone (60 mg/day)
- High dose avacopan group: avacopan 30 mg BID plus cyclophosphamide or rituximab plus a full starting dose of prednisone (60 mg/day)

Results for the primary efficacy endpoint indicated that the clinical response based on BVAS at Day 85 was similar between 10 mg and 30 mg BID avacopan dose regimens (Table 9). However, 30 mg BID avacopan dose regimen appeared to achieve a more rapid BVAS response at Week 4 (BVAS reached 0 in 33.3% subjects with 30 mg BID, 8.1% subjects with 10 mg BID, and 15.4% subjects in control group) and better renal response (increase of eGFR over 12-week treatment: 6.2 mL/min/1.73 m^2 with 30 mg BID; 1.2 mL/min/1.73 m^2 with 10 mg BID; 2.0 mL/min/1.73 m^2 in control group) than 10 mg BID dose regimen. See Sections 7 and 8 for more detailed interpretation regarding phase 2 study design and assessment.

Table 8. Analysis of Clinical Response Based on BVAS Response at Day 85 (ITT Population) in Study CL002_168

Treatment	N'	n (%)	Difference in Percentages vs Placebo	Two-Sided 90% CI for Difference	Non-Inferior P-Value
Placebo + Full Dose Prednisone (N = 20)	20	14 (70.0)			
CCX168 + Low-Dose Prednisone (N = 22)	22	19 (86.4)	16.4	(-4.3, 37.1)	0.0019
CCX168 + No Prednisone (N = 21)	21	17 (81.0)	11.0	(-11.0, 32.9)	0.0102
All CCX168 (N = 43)	43	36 (83.7)	13.7	(-5.5, 33.0)	0.0020

BVAS response was defined as achieving a 50% reduction from baseline in the BVAS plus no worsening in any body system component.
n = number of subjects who responded.
N' = number of subjects with evaluation.
BVAS = Birmingham Vasculitis Activity Score; CI = confidence interval; ITT = Intent-to-Treat; vs = versus.
Source: Post-text Table 14.2.1.1

Source: Table 13 of Study CL002_168 CSR

Table 9. Analysis of Clinical Response Based on BVAS at Day 85 (ITT Population) in Study CL003_168

Treatment	N'	n (%)	Difference in Percentages vs Placebo	2-Sided 90% CI for Difference
Placebo + Standard of Care (N = 13)	13	11 (84.6%)		
CCX168 10 mg + Standard of Care (N = 12)	12	11 (91.7%)	7.1	(-14.00, 28.10)
CCX168 30 mg + Standard of Care (N = 15)	15	12 (80.0%)	-4.6	(-28.27, 19.04)
All CCX168 (N = 27)	27	23 (85.2%)	0.6	(-19.36, 20.50)

Birmingham Vasculitis Activity Score response was defined as achieving a 50% reduction from baseline in the BVAS plus no worsening in any body system component.
N = number of subjects in the analysis population for the specified treatment group; N' = number of subjects with post-baseline, on-treatment BVAS data; n = number of responders; % = 100*n/N'.
BVAS = Birmingham Vasculitis Activity Score; CI = confidence interval; ITT = Intent-to-Treat; vs = versus.
Source: Post-text Table 14.2.1.1

Source: Table 8 of Study CL003_168 CSR

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Avacopan treatment is not recommended for patients with severe hepatic impairment and no dose adjustment is needed in patients with mild or moderate hepatic impairment. No dose adjustment is needed based on renal function, race, gender, age, or body weight.

Patients With Hepatic Impairment

The main route of clearance of avacopan is metabolism followed by biliary excretion of the metabolites into feces.

The impact of mild and moderate hepatic impairment on avacopan PK was assessed in an open-label, single dose study (Study CL0013_168). Following a single oral dose of 30 mg avacopan,

the systemic exposure (C_{max} and AUC) of both avacopan and M1 in subjects with mild or moderate hepatic impairment were generally comparable to healthy subjects (Table 10). The impact of severe hepatic impairment on avacopan PK has not been studied. Therefore, no dose adjustment is needed for patients with mild or moderate hepatic impairment.

Table 10. Summary of Results of Avacopan and M1 PK Parameters in Subjects With Mild or Moderate Hepatic Impairment Compared With Healthy Subjects

Analyte Parameter Group Comparison	Geo LS Mean	GMR	90% CI of GMR
Avacopan			
$AUC_{0\text{-}inf}$ (ng.h/mL)			
Mild hepatic impairment/healthy	1370/1220	1.12	(0.77, 1.63)
Moderate hepatic impairment/healthy	1360/1220	1.12	(0.69, 1.79)
$AUC_{0\text{-}t}$ (ng.h/mL)			
Mild hepatic impairment/healthy	1030/940	1.09	(0.83, 1.44)
Moderate hepatic impairment/healthy	955/940	1.02	(0.78, 1.33)
C_{max} (ng/mL)			
Mild hepatic impairment/healthy	107/123	0.87	(0.70, 1.10)
Moderate hepatic impairment/healthy	102/123	0.83	(0.66, 1.03)
M1			
$AUC_{0\text{-}inf}$ (ng.h/mL)			
Mild hepatic impairment/healthy	885/799	1.11	(0.83, 1.48)
Moderate hepatic impairment/healthy	943/799	1.18	(0.89, 1.56)
$AUC_{0\text{-}t}$ (ng.h/mL)			
Mild hepatic impairment/healthy	766/665	1.15	(0.88, 1.51)
Moderate hepatic impairment/healthy	776/665	1.17	(0.90, 1.52)
C_{max} (ng/mL)			
Mild hepatic impairment/healthy	46/48	0.95	(0.74, 1.22)
Moderate hepatic impairment/healthy	40/48	0.84	(0.66, 1.06)

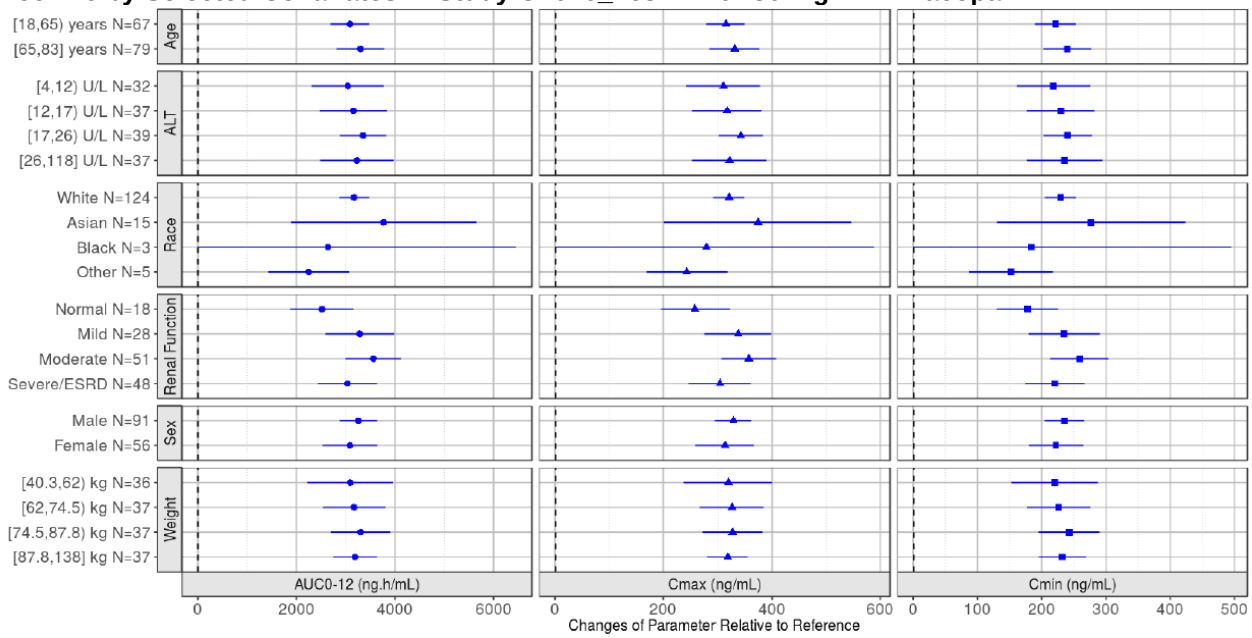
Source: Tables 8 and 11 of Study CL0013-168 CSR
Abbreviations: AUC, area under the curve; CI, confidence interval; C_{max}, maximum concentration; GMR: geometric mean ratio; LS. Least square.

Patients With Renal Impairment

Renal excretion is not a major pathway of avacopan elimination. Therefore, no dedicated study in renal impaired patients has been performed.

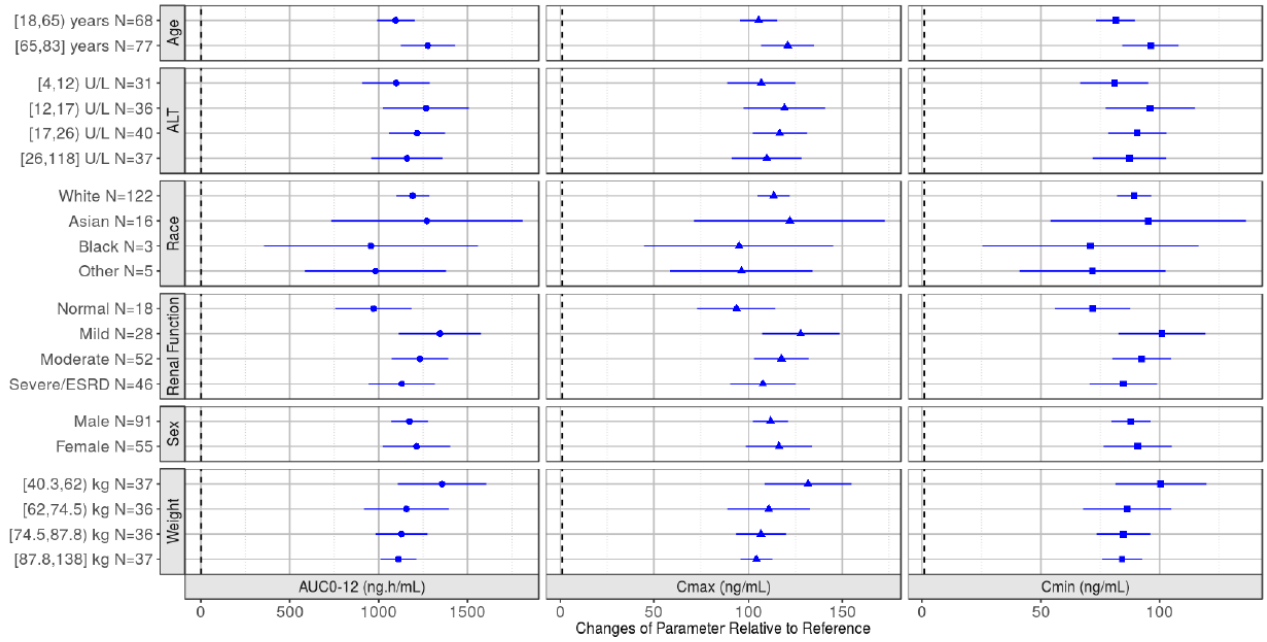
In population PK analysis including data from patients with normal or impaired renal function (normal (eGFR ≥90 mL/min/1.73 m^2): n=128 (34.8%); mild renal impairment (eGFR ≥60 and <90 mL/min/1.73 m^2: n=85 (23.1%); moderate renal impairment (eGFR ≥30 and <60 mL/min/1.73m^2: n=90 (24.5%); severe renal impairment- end stage renal disease (eGFR <30 mL/min/1.73 m^2): n=62 (16.8%)), while eGFR was identified as a significant covariate for clearance and volume of distribution of both avacopan and M1, the impact on avacopan and M1 exposure is not expected to be clinically relevant (Figure 4 and Figure 5).

Figure 4. Distribution of Avacopan Exposures Derived With the Posterior Bayes Parameters at Week 26 by Selected Covariates in Study CL010_168 – With 30 mg BID Avacopan



Source: Figure 7 of Report CMR_168_POP_PK2
Note: The dots and the horizontal blue segments represent mean and 95%confidence interval of pharmacokinetic exposures at Week 26, respectively in each categorical group. Subjects with C_{max} value below limit of quantification (1.0 ng/mL) were removed from the plot.
Abbreviations: ALT, alanine aminotransferase; AUC, area under the curve; BID, twice daily; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; ESRD, end stage renal disease.

Figure 5. Distribution of M1 Exposures Derived With the Posterior Bayes Parameters at Week 26 by Selected Covariates in Study CL010_168 – With 30 mg BID Avacopan



Source: Figure 8 of Report CMR_168_POP_PK2
Note: The dots and the horizontal blue segments represent mean and 95%confidence interval of pharmacokinetic exposures at Week 26, respectively in each categorical group. Subjects with C_{max} value below limit of quantification (1.0 ng/mL) were removed from the plot.
Abbreviations: ALT, alanine aminotransferase; AUC, area under the curve; BID, twice daily; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; ESRD, end stage renal disease

Other Intrinsic Factors

No clinically significant differences in plasma exposure of avacopan and M1 are expected based on age, race, sex, and body weight (Figure 4 and Figure 5). Therefore, no corresponding dose adjustment is needed.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food Effect

After a single dose of 30 mg avacopan, a high-fat high-calorie meal increased avacopan AUC and C_{max} by approximately 72% and 8%, respectively, and the median T_{max} delays by approximately 4 hours (from 2.0 hours to 6.0 hours) as compared to fasted condition. For the active metabolite M1, a high-fat high-calorie meal did not affect AUC, but reduced C_{max} by 51% as compared to fasted condition. In phase 2 and 3 studies, avacopan was administered with food.

Potential for Other Drugs to Affect Avacopan:

Table 11. Potential Drug Interactions of Other Drugs on Avacopan

Co-Administered Drug	Regimen of Co-Administered Drug	Effect on PK (Ratio (90% CI))[1]	Comments and Dosing Recommendation
Strong CYP3A inhibitor: itraconazole	200 mg QD for 4 days	Avacopan: AUC: 2.19 (2.00, 2.41) C_{max}: 1.87 (1.70, 2.06) M1: AUC: 1.19 (1.11, 1.28) C_{max}: 1.03 (0.95, 1.11)	When co-administered with strong CYP3A4 inhibitors, avacopan dose should be reduced.
Strong CYP3A inducer: rifampin	600 mg QD for 11 days	Avacopan: AUC: 0.07 (0.06, 0.10) C_{max}: 0.21 (0.18, 0.25) M1: AUC: 0.07 (0.06, 0.09) C_{max}: 0.27 (0.23, 0.31)	Decreased systemic exposure may lead to reduced therapeutic effect of avacopan. The effect of moderate CYP3A4 inducer has not been evaluated. Co-administration of strong or moderate CYP3A4 inducers is not recommended.

Source: Tables 11-7, 11-9, 11-11, 11-13 of Study CL008_168 CSR
[1] Ratios for C_{max} and AUC compare co-administration of the medication with avacopan vs. administration of avacopan alone.
Abbreviations: AUC, area under the curve; CI, Confidence interval; C_{max}, maximum concentration; CYP, cytochrome P450 enzyme; PK, pharmacokinetic; QD, once daily.

In phase 2 and phase 3 studies, 68.5% (n=50) and 78% (n=124) subjects, respectively, were co-administered proton-pump inhibitors, such as omeprazole. Proton-pump inhibitors are acid-reducing agents, which may result in elevated gastric pH. Avacopan is a weak-acid drug with pKa of 4.7. In vitro dissolution profile at pH (b) (4) showed that 10 mg avacopan capsule was rapidly dissolved and full dissolution (~100%) was reached within 30 minutes. Therefore, co-administration with proton-pump inhibitors is not expected to further increase the rate and/or extent of absorption of avacopan capsules.

Potential for Avacopan to Affect Other Drugs:

Table 12. Potential Drug Interactions of Avacopan on Other Drugs

Co-Administered Drug	Regimen of Avacopan	Effect on PK (Ratio (90% CI))[1]	Comments and Dosing Recommendation
Sensitive CYP3A substrate: midazolam	30 mg BID for 11 days, fasted condition*	AUC: 1.81 (1.65, 1.98) C_{max}: 1.55 (1.41, 1.69)	The impact of avacopan at steady state under fed condition on CYP3A4 substrates could be higher than fasted condition but has not been studied. Closely monitor adverse events and consider dose reduction of sensitive CYP3A4 substrates with narrow therapeutic window when co-administered with avacopan.
Sensitive CYP2C9 substrate: celecoxib	30 mg BID for 11 days, fasted condition	AUC: 1.15 (1.03, 1.28) C_{max}: 1.64 (1.34, 2.00)	No dose adjustment is needed.

Source: Tables 11-3 and 11-5 of Study CL008_168 CSR
[1] Avacopan doses were taken in the fasted state with not more than 100 mL of water. No food was allowed for at least 2 hours post dose for the morning doses.
Abbreviations: AUC, area under the curve; BID, twice daily; CI, confidence interval; C_{max}, maximum concentration; CYP, cytochrome P450 enzyme; PK, pharmacokinetics.

Potential DDI Between Avacopan and Glucocorticoid, and the Implications:

In the phase 3 study CL010_168, prednisone and other non-study supplied glucocorticoids, which are all identified to be CYP3A4 substrates (Table 13), were co-administered with avacopan, a CYP3A4 inhibitor. The mean cumulative total glucocorticoid use, including both protocol-specified prednisone and non-study supplied glucocorticoids, over 52 weeks was greater in the prednisone arm, as expected based on the study design (3654.5 mg in the prednisone arm and 1348.9 mg in the avacopan arm). As the PK of systemic glucocorticoids was not assessed in Study CL010_168, it is not clear whether avacopan increased the exposure of glucocorticoids. While prednisone PK has been compared with or without coadministration of avacopan in phase 2 studies (CL003_168 and CL002_168), the impact of avacopan on prednisone exposure is inconclusive since concentrations of prednisone and its active metabolite prednisolone in most of subjects could not be accurately quantified (below the lower limit of quantification). Based on the existing data, the exposure increase of glucocorticoids when co-administered with avacopan due to drug-drug interactions could not be ruled out.

This reviewer assessed whether there might be higher absolute glucocorticoid exposure in the avacopan arm compared to the prednisone arm, which may compromise the interpretation of efficacy data in the phase 3 study CL010_168. The Glucocorticoid Toxicity Index (GTI), which is intended to quantitatively capture glucocorticoid toxicity, was measured over the first 26 weeks

in Study CL010_168. The data showed a greater improvement (decrease of GTI) from baseline in the avacopan arm on GTI-CWS and GTI-AIS at Weeks 13 and 26 (see Section 8). While the differences in GTI between the treatment groups may be due to the study design and not necessarily reflect the efficacy of avacopan, the lower GTI in the avacopan arm suggests that the glucocorticoid exposure is lower in the avacopan arm compared to the prednisone arm in the first 26 weeks.

GTI was not assessed at later time points after 26 weeks. In weeks 27-52, approximately 12% more patients on the prednisone arm used non-study supplied glucocorticoid compared to the avacopan arm (38.4% vs 26.5%,Table 14). During this period, the mean dose of glucocorticoid is similar in patients who used steroid in both arms (1203 mg in prednisone arm vs 1041 mg in avacopan arm, Table 14). As the major difference in glucocorticoid use is the percentage of patients who use any glucocorticoid, and not the amount of drug each subject used, the potential drug interaction between avacopan and glucocorticoid will not affect patients who do not use glucocorticoid. Therefore, it's unlikely that the avacopan arm has higher absolute glucocorticoid exposure vs the prednisone arm in weeks 27-52.

Overall, the cumulative total glucocorticoid dose was greater in the prednisone arm compared to the avacopan arm in study CL010_168. While the potential exposure increase of glucocorticoids when co-administered with avacopan due to drug-drug interactions could not be ruled out, it is unlikely that the avacopan arm has higher absolute glucocorticoid exposure vs the prednisone arm in study CL010_168. Nevertheless, the true differences in glucocorticoid exposures could be smaller than the differences in nominal doses of glucocorticoids between the prednisone arm and the avacopan arm. See Sections 7 and 8 for more detailed assessment regarding the use of non-study supplied glucocorticoids in phase 3 study CL010_168.

Table 13. Summary of Non-Study Supplied Glucocorticoid Use in Study 010_168

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

Note: the summary is based on the reported Standardized Medication Name
Source: Reviewer's analysis
Abbreviations: CYP, cytochrome P450 enzyme.

Table 14. Non-Study Supplied Glucocorticoid Use (Patients Who Used Steroid)

	Avacopan	Prednisone
Glucocorticoid Use Weeks 0-26		
Number of subjects	143 (86.1%)	149 (90.9%)
Mean dose (mg)	1245.5	884.0
Glucocorticoid Use Weeks 27-52		
Number of subjects	44 (26.5%)	63 (38.4%)
Mean dose (mg)	1041.2	1202.7
Glucocorticoid Use Weeks 0-52		
Number of subjects	145 (87.3%)	149 (90.9%)
Mean dose (mg)	1544.3	1392.5

Source: Statistical Reviewer

Question on Clinically Relevant Specifications (TBD)?

None

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 15. Summary of Clinical Studies Supporting NDA 214487

Study	Study Design	Regimen/Schedule/Route	Treatment Duration/ Follow-up	Patient Population
CL010_168 ADVOCATE 143 clinical sites in North America, Europe, Australia, New Zealand, and Japan	Randomized, double-blind, active-controlled study to evaluate the safety and efficacy of avacopan in AAV on background RTX or CYC/AZA	PBO + prednisone 60 mg taper (n=164) Avacopan 30 mg BID (n=166) All patients received CYC or RTX for induction. Patients induced with CYC received AZA for maintenance. All patients could receive non-study supplied glucocorticoids through the entire study.	Total 60 weeks Treatment: 52 weeks Follow-up: 8 weeks	331 patients with AAV
Phase 2				
CL002_168 CLEAR 60 clinical sites in Europe (Austria, Belgium, Czech Republic, Hungary, France, Germany, Ireland, Netherlands, Poland, Sweden, UK)	Randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of avacopan in AAV on background CYC or RTX	Step 1 Avacopan 30 mg BID + prednisone 20 mg taper + CYC (n=8) PBO + prednisone 60 mg taper + CYC (n=4) Step 2 Avacopan 30 mg BID + NO prednisone + CYC (n=8) PBO + prednisone 60 mg taper + CYC (n=6) Step 3 PBO + prednisone 60 mg taper + CYC/RTX (n=14) Avacopan 30 mg BID + prednisone 20 mg taper + CYC/RTX (n=14) Avacopan 30 mg BID + NO prednisone + CYC/RTX (n=13)	Total: 24 weeks Treatment: 12 weeks Follow-up: 12 weeks	67 patients with AAV Step 1: 12 patients with ANCA-associated renal vasculitis Step 2: 14 patients with ANCA-associated renal vasculitis Step 3: 41 patients with AAV

Study	Study Design	Regimen/Schedule/Route	Treatment Duration/ Follow-up	Patient Population
CL003_168 CLASSIC 47 clinical sites in U.S., Canada	Randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of avacopan in AAV on background CYC or RTX	Avacopan 10 mg BID + prednisone 60 mg taper (n=13) Avacopan 30 mg BID + prednisone 60 mg taper (n=16) PBO + prednisone 60 mg taper (n=13) All patients received CYC or RTX for induction.	Total: 24 weeks Treatment: 12 weeks Follow-up: 12 weeks	42 patients with AAV

Abbreviations: AAV, ANCA-associated vasculitis; ANCA, anti-neutrophilic cytoplasmic antibody; AZA, azathioprine; BID, twice daily; CYC, cyclophosphamide; PBO, placebo; RTX, rituximab.

7.2. Review Strategy

ChemoCentryx conducted a single pivotal trial, CL010_168, that served as the primary support for efficacy and safety.

The efficacy assessment was reviewed by the statistical and clinical reviewers. The Agency statistician confirmed the Applicant's pre-specified analyses and performed additional supplemental analyses as appropriate.

The Division consulted the Division of Clinical Outcome Assessment for input on the Glucocorticoid Toxicity Index, a novel assessment of toxicity due to glucocorticoids that was one of the Applicant's secondary efficacy endpoints. Additionally, the Division requested DCOA's assessment of the hr-QoL measures that are also without regulatory precedent.

The Division also consulted the Division of Cardiology and Nephrology (DCN) for input on the clinical meaningfulness of the kidney-related trial data.

The safety assessment was also reviewed by the statistical and clinical reviewers. The approach to the safety review is presented in Section 8.2.1.

Additionally, ChemoCentryx conducted two phase 2 trials, CL002_168 and CL003_168, as summarized in Table 15. There were notable differences between these studies and the pivotal trial. Importantly, they included different treatment arms with different doses of avacopan and varying concomitant prednisone tapers, shorter treatment duration, small patient populations, and different efficacy evidence. Therefore, the interpretation of data from the phase 2 trials are limited and will be presented briefly in this review.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study CL010_168

Trial Design

Study CL010_168 was a 52-week, randomized, double-blind, 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 background therapy of cyclophosphamide or rituximab. This trial was conducted in North America, Europe, Australia, New Zealand, and Japan.

The treatment period of the study was 52 weeks with an 8-week follow-up period. Eligible patients were stratified based on three factors:

- Receiving IV rituximab, IV cyclophosphamide, or oral cyclophosphamide
- PR3 or MPO ANCA-associated vasculitis
- Newly diagnosed or relapsing ANCA-associated vasculitis

Patients were randomized 1:1 to one of two treatment groups:

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

The prednisone starting dose in Group A for adults was 60 mg/day (if ≥55 kg) or 45 mg/day (if <55 kg). The prednisone dose was tapered to 0 by Day 141. Details of the pre-specified prednisone taper are provided in Table 129 in the Appendix.

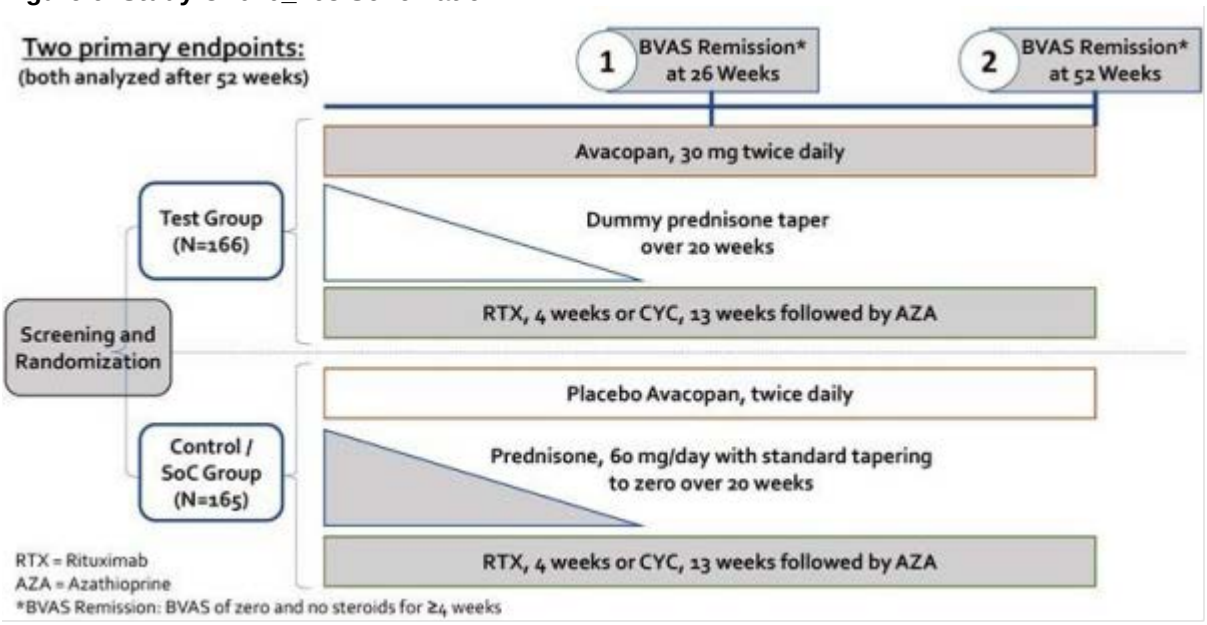
Patients in the IV cyclophosphamide stratum received cyclophosphamide 15 mg/kg IV up to 1.2 g maximum every 2 to 3 weeks for 13 weeks, followed by azathioprine 1 mg/kg/day starting at Week 15 with titration up to 2 mg/kg/day. Subjects in the oral cyclophosphamide stratum received cyclophosphamide 2 mg/kg/day orally for 14 weeks, followed by azathioprine

1 mg/kg/day starting at Week 15 with titration up to 2 mg/kg/day. Patients who had a contraindication to azathioprine received mycophenolate instead. Subjects in the IV rituximab stratum received rituximab 375 mg/m2 IV weekly for 4 weeks.

Patients could receive "extra" (i.e., non-study supplied) glucocorticoids, and the reasons for administration were recorded. Details of glucocorticoid use are presented below under Concomitant Medications.

The study included 3 periods: screening (up to 2 weeks), double-blind treatment (up to 52 weeks), and follow-up (8 weeks). Thus, the last scheduled visit would be at Week 60. Figure 6 shows the study schematic.

Figure 6. Study CL010_168 Schematic



Sources: Pre-NDA Meeting package.

Key Inclusion/Exclusion Criteria

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

- Alveolar hemorrhage requiring invasive pulmonary ventilation support anticipated to last beyond the screening period

- Requirement of dialysis or plasma exchange within 12 weeks prior to screening
- Kidney transplant
- Any other multi-systemic autoimmune disease, e.g., EGPA, systemic lupus erythematosus, IgA vasculitis, rheumatoid vasculitis, Sjogren's syndrome, anti-glomerular basement membrane disease, or cryoglobulinemic vasculitis

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

- Cyclophosphamide within 12 weeks prior to screening
- Azathioprine, MMF, or MTX must be withdrawn prior to Day 1
- IV glucocorticoids (>3000 mg methylprednisolone or equivalent) within 4 weeks prior to screening
- Continuous oral glucocorticoids (>10 mg prednisone or equivalent) for more than 6 weeks prior to screening
- Rituximab or other B-cell antibody within 52 weeks of screening or 26 weeks if there is evidence of B-cell reconstitution
- Other biologics (e.g., anti-tumor necrosis factor (TNFs), abatacept, alemtuzumab, IVIg, belimumab, tocilizumab, or eculizumab) within 12 weeks prior to screening

Dose Selection

ChemoCentryx selected the dose for the pivotal trial based on the clinical experience from two phase 1 studies in health subjects (studies CL001_168 and CL007_168) and the two phase 2 studies. Per the Applicant, doses up to the maximum dose tested (100 mg BID x 7 days) appeared to be tolerated. The dose of 30 mg BID provided trough (Cmin) plasma avacopan concentrations that allowed for at least 95% blockade of C5aR on blood neutrophils continuously throughout the day. The Applicant deemed this level of C5aR blockade to be "optimal," as it blocked C5a-induced CD11b upregulation and C5a-induced migration of neutrophils in *in vitro* assays conducted in blood samples from Study CL001_168.

Dose Modification and Dose Discontinuation

The protocol allowed for study treatment discontinuation for safety and laboratory abnormalities.

If a patient developed a Grade 3 or higher adverse event (AE) considered possibly related to study medication, the study medication was suspended and only could be restarted if the event resolved and the Investigator considered it appropriate.

Liver Function Test Abnormalities

- If a patient developed a ≥ Grade 3 increased hepatic transaminases (>5 times upper limit of normal [ULN]) or if a patient developed a ≥ Grade 2 increased hepatic transaminases

(>3 x ULN) with elevation of bilirubin to >2 times ULN, dose of study drug must be paused. Evaluation for possible drug-induced liver injury (DILI) must be pursued.

- Study drug must be permanently discontinued if any of the following markers of hepatic injury and/or impaired liver synthetic activity were observed and if it could not be attributed a reversible etiology unrelated to study medication (e.g., cholelithiasis):
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8x ULN
    - ALT or AST >5x ULN for more than 2 weeks
    - ALT or AST >3x ULN and (total bilirubin >2x ULN or INR >1.5)
    - ALT or AST >3x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

If complete evaluation ruled out drug-induced liver injury and if all labs returned to normal, then study drug could be resumed after discussion and agreement with the Medical Monitor. Hepatic transaminases and bilirubin were then monitored closely.

Low White Blood Cell (WBC) Count

- If a patient developed ≥ Grade 3 leukopenia (WBC <2 x 109/L) OR neutropenia (<1 x 109/L) OR Grade 4 lymphopenia (<0.2 x 109/L), then study drug was paused.
- If a patient developed Grade 2 leukopenia (WBC <3 x 109/L but ≥2 x 109/L), the patient must be followed closely for infection and for further significant reduction in WBC (i.e., reduction by an additional 0.5 x 109/L or to <2 x 10^9/L). If either occurred, the study drug was paused.

Study drug could be resumed if any abnormal value returned to normal and the Investigator deemed it appropriate.

Creatine Phosphokinase (CPK) Elevation

If a patient develops ≥ Grade 3 CPK increase (>5x ULN), dosing of study drug was paused. Study drug was resumed only if CPK returned to normal levels.

Administrative Structure

The Medical Monitor and clinical staff provided continuous safety monitoring. In addition, an external Data Monitoring Committee (DMC) was established to monitor the safety of subjects over the course of the study. The DMC was comprised of an external physician and a biostatistician. A DMC charter was developed before the start of the study, and the DMC functioned according to the charter. The DMC had regular meetings, once every 3 to 6 months, depending on study enrollment rate. Ad hoc meetings were scheduled if unanticipated safety events occurred. After review of data at each meeting, the DMC made recommendations about further conduct of the study.

Additionally, an Adjudication Committee (AC) was established to perform a blinded, independent adjudication of BVAS and vasculitis damage index (VDI) data. The AC was composed of individuals who were independent of ChemoCentryx, recognized experts in AAV, and experts in the use of BVAS and VDI in clinical trial design and operationalization. The AC operated under a charter. The AC adjudicated BVAS, VDI, and the following endpoints: (1) achievement of early disease remission at Week 4, (2) achievement of disease remission at Week 26 (primary endpoint), (3) achievement of sustained disease remission at Week 52 (primary endpoint), and (4) occurrence of relapse.

Concurrent Medications

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

Patients who relapsed could receive additional immunosuppressive therapy (e.g., rituximab or cyclophosphamide) after discussion with the Medical Monitor. Patients who required immunosuppressive therapy for relapse (defined as occurrence of at least 1 major item on the BVAS or ≥ 3 minor items on the BVAS or 1 or 2 minor items on the BVAS recorded at 2 consecutive visits after achieving remission) continued study drug treatment and continued in the study.

Patients received prophylactic therapy (e.g., *Pneumocystis* pneumonia (PCP) prophylaxis with sulfamethoxazole 400 mg-trimethoprim 80 mg daily) or other precautions/therapies given with RTX, CYC, or AZA. Strong inducers of CYP3A4 were prohibited. Strong inhibitors of CYP3A4 were avoided during the study but were not absolutely contraindicated.

Glucocorticoids

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

The Applicant considered “study-supplied prednisone” as that received by the patients in the control group who received a standardized tapering schedule over the course of the study. The

tapering schedule differed slightly based on body weight. Patients with a body weight ≥55 kg started on prednisone 60 mg per day and tapered to zero over 20 weeks. Adult patients with a body weight <55 kg and adolescent patients with a body weight >37 kg started on prednisone 45 mg per day and tapered to zero over 20 weeks. Adolescent patients with body weight ≤37 kg started on prednisone 30 mg and tapered to zero over 20 weeks. See Table 130 in the Appendix for details of the prednisone taper.

The protocol provided instructions on non-study supplied glucocorticoid use, that is, glucocorticoids not supplied as study drug but allowed for AAV (as described below), pre-treatment for medications (e.g., rituximab), adrenal insufficiency, and other conditions. Non-study supplied glucocorticoids, however, were to be avoided as much as possible during the study. If a patient was still taking a dose of non-study-supplied prednisone ≤20 mg on Day 1, the glucocorticoids should be tapered to zero over a 4-week period.

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

- Relapse of AAV (as defined by at least 1 major item or ≥3 minor items on the BVAS or 1 or 2 minor items on the BVAS after achieving remission, described above): Subjects could be treated with IV glucocorticoids (0.5 to 1 g methylprednisolone per day for 3 days) and/or oral glucocorticoids, tapered according to the subject's condition.
- Worsening of disease (i.e., active disease not meeting the definition of relapse) that involved a major item on the BVAS: Subjects could be treated with IV glucocorticoids (0.5 to 1 g methylprednisolone per day for 3 days) and/or oral glucocorticoids, tapered according to the subject's condition.
- Worsening of disease not involving a major item on the BVAS: Subjects could be treated with a short burst (i.e., not more than 2 weeks) of oral glucocorticoids at a maximum dose of prednisone 20 mg per day or equivalent.

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

Treatment Compliance

Medications were self-administered by study participants. The morning dose of study drug on Day 1 was to be taken in the presence of study site personnel. Patients were instructed to bring the assigned bottles of study medication to the site staff at each study visit, whether empty or not. The study drug dispensed was checked, and a capsule count was done from Week 4 through Week 52 of any remaining avacopan or PBO capsules and from Week 1 through Week 20 of prednisone or PBO. This information was recorded into the Electronic Data Capture system (EDC). Avacopan plasma concentration measurements over the course of the study were also used to assess compliance.

Subject Completion, Discontinuation, or Withdrawal

Investigators were to clearly distinguish between study drug treatment discontinuation and study withdrawal. Patients who discontinued study drug treatment or who initiated medication changes (including prohibited medications) were not automatically withdrawn from the study. Rather, all efforts were to be made to continue to follow the patients for all regularly scheduled visits. Investigators (and staff) took measures to actively maintain contact with patients in the study, such as telephone calls, texts, or e-mails between visits as well as offers for transportation support to study site.

Patients were withdrawn from the study for only one of two reasons:

- Subject withdrawal of consent to contribute additional outcome information
- Loss to follow up

Patients could discontinue study drug treatment for any of the following reasons:

- Subject withdrawal of consent
- The Investigator discontinued study drug treatment if, in his/her clinical judgment, it was in the best interest of the subject
- The Applicant may request discontinuation of study drug treatment for safety reasons

See above for dose discontinuation for safety and laboratory abnormalities.

In the event of early withdrawal, the tests and evaluations listed for the Early Termination visit were to be performed. Data collected from this visit was designated as “Early Termination” visit in the EDC. The Applicant was notified of all study drug treatment and study withdrawals.

Study Endpoints

Primary Endpoint

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

4. The proportion of subjects achieving disease remission at Week 26. Disease remission at Week 26 was defined by the following criteria:

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

5. The proportion of subjects achieving sustained disease remission at Week 52. Sustained remission at Week 52 was defined by the following criteria:

    - Disease remission at Week 26 defined as a BVAS of 0 as determined by the AC
    - No disease relapse between Week 26 and Week 52 as determined by the AC
    - Disease remission at Week 52 defined as a BVAS of 0 as determined by the AC and no administration of glucocorticoids for treatment of AAV within 4 weeks prior to Week 52

The protocol defined that "glucocorticoid use" in the primary endpoint referred to both protocol-specified prednisone and non-study supplied glucocorticoids that may have been given for AAV for the 4 weeks prior to the BVAS assessment at Weeks 26 and 52. The 4-week glucocorticoid-free periods were to be calculated from the actual dates of the Week 26 and Week 52 visits.

Patients were permitted to receive low doses of oral glucocorticoids (no more than 10 mg per day) for treatment of adrenal insufficiency or glucocorticoid treatment for other conditions, e.g., allergic reaction, and were to be classified as responders for purposes of assessment of the primary endpoints if all other requirements for response are met.

Birmingham Vasculitis Activity Score

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

- The BVAS version 3 considers the presence of disease activity within the 28 days prior to assessment. This is what was done in Study CL010_168 for all study visits except for Week 4. For the Week 4 BVAS assessment, disease activity with the 7 days prior to visit was to be recorded, to avoid inclusion of the baseline visit.
- The "persistent" disease aspect of the BVAS version 3 was not used. Rather, only the presence or absence of disease activity was assessed.

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

Disease relapse in the primary endpoint was defined as worsening of disease after having previously achieved remission (BVAS =0) at Week 26, as defined below:

- One or more major item on the BVAS, or
- Three or more minor items on the BVAS, or

- One or two minor items on the BVAS recorded at two consecutive study visits

Secondary Endpoints

1. Glucocorticoid-induced toxicity as measured by a change over the first 26 weeks in the GTI.

   The GTI is a tool intended to quantify toxicity associated with glucocorticoid use. The GTI version 2.0 quantifies changes in glucocorticoid toxicity with 2 scores, the Cumulative Worsening Score (GTI-CWS) and the Aggregate Improvement Score (GTI-AIS).

   - GTI-CWS assesses cumulative glucocorticoid toxicity, regardless of whether the toxicity has lasting effects or is transient. New toxicities that occur are added, but toxicities that resolve on follow-up are not removed. GTI-CWS may increase or remain the same over time but does not decrease. If an investigational agent is effective at decreasing glucocorticoid toxicity over time, the score will be lower in the investigational treatment arm compared to the comparison arms.
   - GTI-AIS is intended to assess whether a therapy is effective at diminishing any glucocorticoid toxicity over time. Toxicities are removed if improvement occurs but can also be added if a new toxicity occurs or if worsening in any item occurs. Therefore, if an investigational agent is effective at decreasing glucocorticoid toxicity over time, the GTI-AIS will decrease over the course of the study in that arm.

2. BVAS of 0 at Week 4, regardless of whether the subjects received glucocorticoids during this period

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

   - SF-36v2 is a multi-purpose, short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. Higher scores represent better functional status. The survey assessments include the following 8 domains: limitations in physical activities because of health problems, limitations in social activities because of physical or emotional problems, limitations in usual role activities because of physical health problems, bodily pain, general mental health (psychological distress and well-being), limitations in usual role activities because of emotional problems, vitality (energy and fatigue), and general health perceptions.

- EQ-5D-5L is a standardized instrument for use as a measure of health outcome that includes a descriptive system consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 5 levels of severity and a EuroQuality of Life VAS. It is applicable to a wide range of health conditions and treatments and provides a simple descriptive profile and a single index value for health status. Higher scores on the EQ-5D-5L index and VAS represent better quality of life.

4. Proportion of subjects with relapse and time to experiencing a relapse

   Relapse was defined as it was in the primary endpoint (i.e., occurrence of at least one major item on the BVAS or ≥3 minor items on the BVAS or 1 or 2 minor items on the BVAS recorded at 2 consecutive visits) but after having achieved BVAS =0 at any time during the treatment period.

Secondary endpoints #5-7 are renal assessments evaluated only in the subgroup of subjects with renal disease at baseline (based on the BVAS renal component).

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

   Urinary MCP-1:creatinine ratio has been studied as a biomarker of active renal disease and a potential prognostic marker in kidney diseases such as AAV. However, its appropriate use and the clinical meaningfulness of a change in MCP-1:creatinine ratio has not been established.

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

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

Statistical Analysis Plan

The primary analysis was performed on the intent-to-treat (ITT) population which includes all subjects who were randomized and received at least one dose of study drug.

In the primary analysis, missing data at Week 26 and Week 52 were imputed as not achieving remission (Week 26) or sustained remission (Week 52), respectively.

The primary analysis compared the remission rates, adjusted for randomization strata, based on the summary score test. Due to the low number of subjects in the oral cyclophosphamide randomization stratum, IV and oral cyclophosphamide strata were combined for the analyses.

The summary score estimate of the common difference in remission rates was to be computed using inverse-variance stratum weights and Miettinen-Nurminen (score) confidence limits for the common difference in remission rates were to be provided for the stratified contingency tables at Weeks 26 and 52.

The two primary endpoints were to be tested sequentially using a gatekeeping procedure to preserve the overall Type I error rate at a 5% two-sided level. The sequence of testing was defined as follows:

1. Test for non-inferiority (H10) of the avacopan group compared to the control group regarding remission at Week 26; if the p-value for non-inferiority for the one-sided test is <0.025, proceed to step 2
2. Test for non-inferiority (H30) of the avacopan group compared to the control group regarding sustained remission at Week 52; if the p-value for non-inferiority for the one-sided test is <0.025, proceed to step 3
3. Test for superiority (H40) of the avacopan group compared to the control group regarding sustained remission at Week 52; if the p-value for superiority for the one-sided test is <0.025, proceed to step 4
4. Test for superiority (H20) of the avacopan group compared to the control group regarding remission at Week 26

The Applicant proposed a non-inferiority margin of -0.20 based on meta-analyses of 20 published studies to assess the historical disease remission rate at Week 26. See Appendix for more details.

Continuous secondary efficacy endpoints, excluding the renal endpoints and GTI, were to be analyzed using a mixed effects model for repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction, and randomization strata as factors, and baseline as covariate. The Applicant proposed a Toeplitz covariance matrix to model within-subject

variance-covariance structure. However, the unstructured covariance matrix which does not require any assumption on within-subject variance-covariance structure was utilized for the analyses in this review.

For the renal endpoints of eGFR, UACR, and urinary MCP-1:creatinine ratio, MMRM models without randomization strata were proposed because of the restriction of the study population to those with renal disease at baseline which resulted in a smaller sample size for the analyses. For the analyses of percent change from baseline, outcomes were to be log-transformed before entering the MMRM analysis, then least square mean differences were to be back transformed to obtain the estimate for the baseline-adjusted percent reduction.

For GTI, the MMRM without any baseline covariates was proposed. The Applicant clarified in the response to an information request stating that "the GTI is designed to measure change in glucocorticoid toxicity between two points in time. In other words, the GTI 2.0 scores are measurements of GTI changes from the beginning of the time interval to the end of the time interval. Therefore, the GTI scores at Weeks 13 and 26 are the GTI scores change at Weeks 13 and 26 from baseline. No baseline GTI scores (AIS or CWS) could be calculated."

In subjects who achieved remission at Week 26, time to relapse was to be analyzed by Kaplan-Meier methodology and log rank testing of the differences between treatment groups.

In Study CL010_168, the following subgroups were included:

- Age (12-17, 18-50, 51-<65, ≥65-<75, ≥75 years)
- Sex (Male or Female)
- Body mass index (BMI, <30 kg/m2 or ≥30 kg/m2)
- Race (White/Caucasian, Black/African American, Asian, and Other)
- Geographic region (North America, Europe, and Japan)
- Background therapy (IV rituximab; IV or oral cyclophosphamide)
- ANCA positivity (PR3; MPO)
- Newly diagnosed AAV; relapsed AAV
- Granulomatosis with Polyangiitis (Wegener's); Microscopic Polyangiitis
- Duration of AAV (<1 year, ≥1 year)

The primary efficacy endpoint was to be examined in these subgroups listed above. The treatment differences between avacopan and prednisone groups were to be presented with point estimate and 95% confidence interval using normal approximation.

Protocol Amendments

The protocol for CL010_168 was amended three times. The original protocol was submitted on November 28, 2016.

Protocol Amendment 1.0, dated June 21, 2017

Significant revisions in this amendment included the following:

- Patients may receive low dose oral glucocorticoids for adrenal insufficiency and would still be classified as responders.
- Patients with active AAV were allowed to receive oral glucocorticoids at low, moderate, or high doses during the 6 weeks prior to screening. Patients would not be considered for screening, however, if the received continuous treatment of moderate to high doses of glucocorticoids (i.e., doses >10 mg prednisone or equivalent).
- Glucocorticoid pre-medication was allowed for all rituximab infusions.
- For concomitant medications:
  - Enteric coated mycophenolate sodium was allowed if mycophenolate mofetil was not tolerated
  - Atovaquone was allowed as PCP prophylaxis
- Discontinuations for laboratory abnormalities (i.e., lymphopenia and CPK increase) were modified to be consistent with the Investigator's Brochure.
- Multiple changes were made to comply with global requests from Regulatory Agencies and Ethics Committees.

Protocol Amendment 2.0, dated June 15, 2018

> Revisions were made in multiple sections to implement additional monitoring for potential hepatotoxicity, as recommended by the DMC.

Protocol Amendment 4.0, dated January 18, 2019

> The most significant revisions in this amendment were related to the DMC's review of unblinded safety data and the subsequent recommendations. For example, additional language was added/updated to describe study drug pause or discontinuation for neutropenia and elevated transaminases.

Of note, Protocol Amendment 3.0 (dated December 6, 2018) and Protocol Amendment 4.1 (dated January 18, 2019) were submitted, but no patients were enrolled under these protocol versions. Protocol Version 4.0 (described above) superseded what was written for these amendments.

8.1.1.1. Study Results

Compliance With Good Clinical Practices

The study was conducted in compliance with the protocol and its amendments and in

accordance with Good Clinical Practice (GCP), as described in the International Conference on Harmonisation Harmonised Tripartite Guidelines for GCP 2000 and the U.S. Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR including parts 50 and 56, concerning informed consent and IRB regulations). The study was also conducted in accordance with local and national regulatory requirements and the Declaration of Helsinki.

Financial Disclosure

The Applicant adequately disclosed financial interests/arrangements with clinical investigators as recommended in the FDA Guidance for Industry: *Financial Disclosure by Clinical Investigators*. See the table in the Appendix 17.2 for details. There were 238 Principal Investigators for Study CL010_168 , and none were employees of the Applicant. Three investigators (Drs. Peter Merkel, John Niles, and David Jayne) disclosed interests/arrangements, namely, significant payments of other sorts from the Applicant of the covered study. These arrangements do not raise concern, as ChemoCentryx took the following steps to minimize the potential bias in assessing study outcomes:

- The Applicant notes that the primary means to minimize/avoid potential bias was the study design. Study CL010_168 was a double-blind, double-dummy, active-controlled randomized study. Study participants, Investigators/study team at the site, and the Applicant study team were all blinded to subject treatment assignments.
    - Avacopan-matching placebo capsules were given to the prednisone control group and prednisone-matching placebo capsules were given to the avacopan group.
    - The study drug bottles and capsule appearance for avacopan and its matching placebo, as well as prednisone and its matching placebo, were identical.
    - Randomization was done with a central interactive web response system to eliminate bias in assignment of subjects to each treatment group.
- Laboratory data that could potentially have led to unblinding (i.e., WBC counts, neutrophil counts, urinary MCP-1:creatinine ratio, urinary albumin: creatinine ratio, hemoglobin A1c, and low-density lipoprotein (LDL)) were not made available to study site personnel, study subjects, personnel responsible for study monitoring, and biostatisticians and data managers during the study unless for safety monitoring.
- This was an international, multicenter study. Therefore, no single country or study center dominated enrollment of study subjects. The 330 study participants were enrolled at 143 sites across multiple continents/countries (North America, Europe, Australia, New Zealand, and Japan). Each site randomized at least 1 subject; therefore, each investigator only

enrolled a small proportion of the total number of subjects, thus, minimizing bias from any one investigator.

- The BVAS was used for the primary endpoints. An AC was constituted at the start of the study to adjudicate the Investigator BVAS assessment which was conducted by Investigators at the different study centers. It was pre-specified that the adjudicated BVAS scores were used for the primary endpoints. This blinded AC comprised of a team of 9 experts in AAV who independently assessed the BVAS scores. If a member of the AC was also an Investigator in the study, they did not participate in the adjudication of study participants from their site.
- An independent external Data Monitoring Committee met regularly to review the unblinded safety data for study participants.

These steps to minimize bias appear appropriate, and the financial disclosures are unlikely to influence the outcome of the study. Therefore, the financial disclosures do not affect the review or recommendation for action.

Data Quality and Integrity

Overall, the data and analysis quality of this NDA submission were determined to be acceptable for the evaluation of efficacy and safety. No significant deficiencies were identified that would impede a thorough analysis of the data presented by the Applicant. While the statistical analysis plan (SAP) was submitted to the Agency after the data were unblinded, the Applicant has confirmed that the final SAP was approved by the Applicant on October 29, 2019, prior to the final database lock on November 20, 2019. The statistical hypotheses to be tested for the primary endpoints, the sequential gatekeeping procedure, and approach to handling missing data were described in the final clinical study protocol submitted to the Agency for review before the database lock. The primary analysis method specified in the protocol was the stratified Newcombe hybrid-score method.

Patient Disposition

Three hundred thirty-one patients were enrolled in the study and randomized to treatment. The first patient was enrolled on March 15, 2017, and the last patient completed the study on November 1, 2019. One hundred sixty-five patients were randomized to the prednisone arm. Of these, 164 received at least 1 dose of study medication, as the Investigator determined that the renal biopsy for 1 patient did not indicate the presence of vasculitis. One hundred sixty-six patients were randomized to the avacopan arm, and all received at least 1 dose of study medication. The ITT population included all patients who were randomized in the study and who received at least 1 dose of blinded study drug. Therefore, the ITT population in Study CL010_168 included 330 patients. Approximately 6% of the randomized patients discontinued

from the study before Week 26 and 8% discontinued study before Week 52, regardless of compliance with randomized treatment (Table 16). Although the protocol stated there were only two reasons for a patient to be withdrawn from the study, Table 16 indicates that patients were considered withdrawn from the study for multiple reasons. The most common reason for study discontinuation was adverse event for the prednisone arm and withdrawal by subject for the avacopan arm.

Table 16. Patient Disposition at Weeks 26 and 52

Patient Disposition	Prednisone (N=164) n (%)	Avacopan (N=166) n (%)
Completed Week 26 Study	154 (93.9)	155 (93.4)
Discontinued Study prior to Week 26	10 (6.1)	11 (6.6)
Withdrawal by subject	2 (1.2)	4 (2.4)
Withdrawal by guardian	-	1 (0.6)
Lost to follow-up	-	1 (0.6)
Lack of efficacy	-	-
Adverse event	5 (3.0)	2 (1.2)
Physician decision	3 (1.8)	2 (1.2)
Other	-	1 (0.6)
Completed Week 52 Study	152 (92.7)	151 (91.0)
Discontinued Study prior to Week 52	12 (7.3)	15 (9.0)
Withdrawal by subject	3 (1.8)	6 (3.6)
Withdrawal by guardian	-	1 (0.6)
Lost to follow-up	-	1 (0.6)
Lack of efficacy	-	-
Adverse event	6 (3.7)	3 (1.8)
Physician decision	3 (1.8)	3 (1.8)
Other	-	1 (0.6)

Source: Statistical Reviewer
Abbreviations: N, total patients randomized who taken at least one dose of drug.

Protocol Violations/Deviations

The Applicant included a per protocol (PP) population for additional analysis of the efficacy endpoints, specifically, the primary endpoints. The PP population included all patients in the ITT population who were compliant with avacopan/placebo and who did not have major protocol deviations that could have significantly affected the interpretation of the results. The PP population included 162 patients (97.6% of the randomized population) in the avacopan arm and 161 patients (97.6%) in the prednisone arm.

Significant protocol deviations (i.e., GCP violations or those that may affect the efficacy evaluation) were captured in the Study Management System as clinical study report (CSR) reportable deviations. These deviations were listed, summarized by category, and reviewed prior to database lock to identify “major deviations” for the PP Population. Patients were excluded from the PP population for (1) missing Week 26 BVAS assessment (n=3 in the

prednisone arm, no patients in the avacopan arm), (2) early study medication withdrawal (Day 7) due to latent tuberculosis at screening (n=2 in the avacopan arm, no patients in the prednisone arm), and (3) lack of proof of ANCA positivity by the Investigator (n=2 in the avacopan arm, no patients in the prednisone arm). Non-responder imputation was applied to patients who had low compliance to study medication (n=19 [11.4%] in the avacopan arm and n=13 [7.9%] in the prednisone arm) or who used non-allowed medications (n=13 [7.8%] in the avacopan arm and n=25 [15.2%] in the prednisone arm) but continued in the study even after early study medication discontinuation.

Table of Demographic Characteristics

The patients randomized in Study CL010_168 generally had similar baseline demographics across treatment arms (Table 17). However, the proportion of patients from North America was higher in the avacopan arm compared to the prednisone arm. Overall, there were slightly more males (56.5%) in Study CL010_168, and most patients were between the ages of 51 and 75 years (67.6%).

Three adolescent patients were enrolled in the study from outside of the US (Spain, Sweden, and United Kingdom); the low enrollment as compared to the target of 10 adolescent patients was attributed to the fact that many Health Authorities (e.g., FDA) were unwilling to enroll adolescents. These 3 patients (ages 13, 15, and 16 years) were all White females with MPO-positive AAV (1 patient with GPA and 2 patients with MPA). Baseline disease characteristics for the general population are described further in the section below.

Table 17. Baseline Demographics of Patient Population in CL010_168

Demographic Parameter	Prednisone (N=164)	Avacopan (N=166)
Sex, n (%)		
Male	88 (53.7)	98 (59.0)
Female	76 (46.3)	68 (41.0)
Age		
Mean years (SD)	60.5 (14.5)	61.2 (14.6)
Min-max (years)	15-88	13-83
Race, n (%)		
White	140 (85.4)	138 (83.1)
Black or African American	2 (1.2)	3 (1.8)
Asian	15 (9.1)	17 (10.2)
Other	7 (4.3)	8 (4.8)
Ethnicity, n (%)		
Hispanic or Latino	5 (3.0)	7 (4.2)
Not Hispanic or Latino	157 (95.7)	151 (91.0)
Not reported/unknown	2 (1.2)	8 (4.8)

Demographic Parameter	Prednisone (N=164)	Avacopan (N=166)
Region, n (%)		
North America	25 (15.2)	34 (20.5)
Europe and rest of world except Japan	129 (78.7)	121 (72.9)
Japan	10 (6.1)	11 (6.6)
Height		
Mean cm (SD)	170.0 (11.2)	168.4 (10.7)
Min-max (cm)	141-197	139-188
Weight		
Mean kg (SD)	77.8 (19.3)	76.4 (20.3)
Min-max (kg)	41.9-133.6	40.3-138
BMI		
Mean kg/m^2 (SD)	26.8 (5.2)	26.7 (6.0)
Min-max (kg/m^2)	17.0-41.7	16.5-46.6

Source: Statistical Reviewer
Abbreviations: BMI, body mass index; N, total patients randomized who taken at least one dose of drug; Min, minimum; Max, maximum; SD, standard deviation.

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Treatment arms were generally balanced with respect to disease-related baseline characteristics (Table 18). More patients had newly diagnosed disease (69.4%), a diagnosis of GPA (54.8%), and MPO positivity (57.0%). Based on BVAS components, most patients had clinical manifestations that fell within the renal component (81.2%), general component (68.2%), ear/nose/throat component (43.6%), and chest component (43.0%); these clinical manifestations were similar across treatment arms. For induction treatment, more patients received RTX (64.8%). Of the 116 patients who received CYC, 96 patients received azathioprine, and 30 patients received mycophenolate as maintenance treatment; use of maintenance AZA and MMF was generally balanced by treatment arm. Twenty-four patients received both azathioprine and mycophenolate (n=14 in the prednisone arm and n=10 in the avacopan arm).

Table 18. Disease-Related Baseline Characteristics of Patient Population in CL010_168

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

Source: Statistical Reviewer
Abbreviations: AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic autoantibody; BVAS, Birmingham Vasculitis Activity Score, Max, maximum; SD, standard deviation; Min, minimum; N, total patients randomized who taken at least one dose of drug; n, number of patients with non-missing baseline characteristics.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

As shown in Table 19, 86.0% of patients in the prednisone arm and 80.7% of patients in the avacopan arm completed treatment through Week 26, and 79.7% of patients in the prednisone arm and 77.7% of patients in the avacopan arm completed treatment through Week 52. Thus, over the course of the study, the proportion of patients who discontinued treatment was similar in each arm, 20.7% in the prednisone arm and 22.3% in the avacopan arm. The most common reason for treatment discontinuation was adverse events for both time periods and was reported by a similar proportion of patients in each treatment arm. Patients who discontinued study drug treatment or who initiated medication changes (including those prohibited by the protocol) were not automatically withdrawn from the study, but efforts were made to continue to follow the patients for all regularly scheduled visits. Of the patients who discontinued treatment, 22 out of 34 in the prednisone arm and 22 out of 37 in the avacopan arm completed the study through the Week 52 assessment.

Table 19. Patient Disposition for Completing Study Treatment at Weeks 26 and 52

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

Source: Statistical Reviewer
Abbreviations: N, total patients randomized who taken at least one dose of drug.

Mean study drug compliance was high for avacopan and its matching placebo (86.4% and 91.5%, respectively) as well as for prednisone and its matching placebo (98.4% and 89.5%, respectively). The most common concomitant medication was sulfonamides and trimethoprim (92.7% in the prednisone arm and 91.6% in the avacopan arm), in accordance with the protocol recommendation for PCP prophylaxis. Concomitant glucocorticoid use is presented in detail below in the discussion of efficacy assessments. Concomitant use of immunosuppressive therapies during the study treatment period was similar across treatment arms, n=29 (17.5%) in the avacopan arm and n=36 (22.0%) in the prednisone arm. These non-protocol allowed immunosuppressants included rituximab (most common), cyclophosphamide, azathioprine, MTX, mycophenolate/mycophenolic acid, and tacrolimus.

Efficacy Results – Primary Endpoint

Approximately 72% of the patients on the avacopan arm and 70% of the patients on the prednisone arm achieved remission at Week 26 (Table 20). The estimated difference in remission rate between avacopan and prednisone was approximately 3%. At Week 26, the non-inferiority comparison was statistically significant (based on the non-inferiority margin proposed by Applicant), but superiority was not demonstrated.

Avacopan was superior to prednisone in achieving sustained remission at Week 52 (two-sided p-value=0.0132). The estimated treatment difference in sustained remission rate between avacopan and prednisone was 12.5%.

Table 20. Primary Efficacy Endpoints

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

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

To assess the impact of missing data on the primary analysis results, a tipping point sensitivity analysis was conducted. For the primary endpoint of 'remission at Week 26' in which the superiority was not met, the lower bound of the 95% confidence interval for the difference in the proportion of responders for each pair of shift parameters are presented (Table 21). For the primary endpoint of 'sustained remission at Week 52', the p-values obtained from the superiority testing are presented (Table 22).

The tipping point analyses were two-dimensional, i.e., the imputation of missing data was performed independently for both treatment arms. Following treatment policy strategy, all observed data was utilized in the sensitivity analysis 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. These results were aggregated using Rubin's method.

For the primary endpoint of 'remission at Week 26', there were a total of 10 patients with missing data on each of the treatment arms. In the most extreme cases where all missing avacopan patients were imputed as non-responder and all missing prednisone patients were imputed as responder, the lower bound of the 95% confidence interval for the treatment difference was -11.2%. This is within the pre-specified non-inferiority margin of -20%, however, it should be noted that the margin was not agreed upon with the Agency. Concerns regarding the proposed margin are discussed in Section 8.3.

Table 21. Tipping-Point Analyses of the Endpoint of Remission at Week 26

Parameter		Number of Missing Prednisone Patients Imputed as Responder										
		0	1	2	3	4	5	6	7	8	9	10
Number of missing avacopan patients imputed as responder	0	-6.0[1]	-6.5	-7.0	-7.6	-8.1	-8.6	-9.1	-9.7	-10.2	-10.7	-11.2[1]
	1	-5.4	-5.8	-6.4	-6.9	-7.5	-8.2	-8.6	-9.1	-9.6	-10.2	-10.4
	2	-4.8	-5.4	-6.0	-6.4	-6.9	-7.5	-7.8	-8.6	-9.1	-9.6	-9.8
	3	-4.1	-4.7	-4.9	-5.7	-6.4	-6.9	-7.3	-7.9	-8.4	-8.9	-9.5
	4	-3.4	-4.0	-4.4	-5.2	-5.4	-6.4	-6.8	-7.1	-7.8	-8.4	-8.8
	5	-2.9	-3.3	-4.1	-4.4	-5.2	-5.4	-6.1	-6.3	-7.4	-7.8	-8.2
	6	-2.4	-2.7	-3.3	-3.9	-4.3	-4.8	-5.5	-5.8	-6.5	-6.7	-8.0
	7	-1.7	-2.3	-2.6	-3.2	-3.7	-4.3	-5.0	-5.6	-5.8	-6.4	-6.5
	8	-1.0	-1.6	-1.9	-2.7	-3.1	-3.9	-4.4	-4.6	-5.1	-5.8	-6.0
	9	-0.3	-0.8	-1.4	-1.9	-2.5	-3.0	-3.5	-3.9	-4.6	-5.1	-5.7

Source: Statistical Reviewer
[1] 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.

For the primary endpoint of 'sustained remission at Week 52', there were a total of 15 patients with missing data on the avacopan arm and a total of 12 patients with missing data on the prednisone arm. At Week 52, in order to tip the superiority conclusion, the hypothesized remission rate for early dropouts in prednisone arm should be larger than in avacopan arm by at least 40% across all possible outcomes in the placebo arm. Considering that the estimated treatment difference was 12.5% in favor of avacopan based on the primary analysis, a 40% greater treatment effect in favor of prednisone among missing patients is considered implausible.

Table 22. Tipping-Point Analyses of the Endpoint of Sustained Remission at Week 52

Parameter		Number of Missing Prednisone Patients Imputed as Responder								
		3	4	5	6	7	8	9	10	11
Number of missing avacopan patients imputed as responder	0	0.0335	0.0433	0.0567	0.0728	0.0950	0.1175	0.1465	0.1841	0.2215
	1	0.0233	0.0292	0.0455	0.0605	0.0669	0.0866	0.1066	0.1346	0.1705
	2	0.0166	0.0215	0.0276	0.0436	0.0556	0.0668	0.0917	0.1170	0.1436
	3	0.0111	0.0187	0.0227	0.0311	0.0324	0.0568	0.0769	0.0862	0.1054
	4	0.0107	0.0120	0.0129	0.0231	0.0290	0.0448	0.0599	0.0656	0.0806
	5	0.0059	0.0090	0.0109	0.0160	0.0247	0.0293	0.0412	0.0559	0.0570
	6	0.0033	0.0078	0.0075	0.0118	0.0138	0.0178	0.0257	0.0290	0.0518
	7	0.0027	0.0035	0.0048	0.0082	0.0114	0.0132	0.0168	0.0278	0.0419
	8	0.0013	0.0022	0.0034	0.0053	0.0055	0.0066	0.0119	0.0187	0.0273
	9	0.0012	0.0018	0.0013	0.0021	0.0034	0.0045	0.0112	0.0104	0.0185
	10	0.0007	0.0008	0.0011	0.0023	0.0026	0.0057	0.0070	0.0076	0.0149
	11	0.0001	0.0004	0.0010	0.0011	0.0021	0.0017	0.0026	0.0043	0.0048
	12	0.0002	0.0002	0.0004	0.0009	0.0007	0.0014	0.0022	0.0037	0.0049
	13	<.0001	0.0002	0.0003	0.0004	0.0006	0.0007	0.0010	0.0014	0.0030
	14	<.0001	<.0001	<.0001	0.0002	0.0003	0.0007	0.0005	0.0012	0.0018
	15	<.0001	<.0001	<.0001	<.0001	0.0002	0.0003	0.0004	0.0006	0.0009

Source: Statistical Reviewer

Another supplementary analysis based on Investigator BVAS assessments was conducted and presented in Table 23. Remission rates and sustained remission rates on both arms were lower using the Investigator assessments compared to the Adjudication Committee assessments. Of note, avacopan was no longer superior to prednisone regarding the primary endpoint of sustained remission at Week 52 when analyzed based on Investigator assessments.

Table 23. Analyses Based on Investigator Assessments

Endpoint	Prednisone (N=164)	Avacopan (N=166)	Difference	Non-inferiority p-value	Superiority p-value
Remission at Week 26	102 (62.2%)	104 (62.7%)	1.4%	<0.0001	0.79
95% CI	(54.3, 69.6)	(54.8, 70.0)	(-8.7, 11.4)		
Sustained Remission at Week 52	77 (47.0%)	91 (54.8%)	8.5%	<0.0001	0.1026
95% CI	(39.1, 54.9)	(46.9, 62.5)	(-1.7, 18.6)		

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

As described in the CSR, only signs and symptoms ascribed to the presence of active AAV were to be reported in the standardized form of the BVAS version 3 used in Study CL010_168. The "persistent" disease aspect of the BVAS version 3 was not used. Vasculitis items that were persistent for at least 3 months and did not show evidence of worsening disease were not scored on the BVAS.

The Applicant explained that "The reason for discrepancies between Investigator and Adjudicator assessments is that Investigators tended to score items that did not show evidence of new or worsening active disease after the baseline assessment."[2] Many of the discrepancies can be attributed to scoring of persistent activity and whether or not it is considered "active."

Table 132 in the Appendix presents the BVAS scores of all patients who had a discrepancy between the Investigator assessment and the Adjudicator assessment and how the BVAS scores were changed. Nearly all BVAS scores were decreased to 0 by the Adjudication Committee. The Adjudication Committee increased the BVAS score in 3 patients in the study (1 patient in the avacopan arm and 2 patients in the prednisone arm at Week 52). Of the 56 patients (29 patients in the avacopan arm and 27 patients in the prednisone arm) for which the Adjudicator changed an Investigator response at Weeks 26 and 52, most of the changes were related to differences in the renal assessment (n=34). The other organ systems with the most discrepancies were General (n=9) and ear, nose, and throat (n=8). The number of patients with discrepancies was balanced across treatment arms at both time points of assessment. At the

[2] ChemoCentryx Response to IR #13, dated February 16, 2021

Week 26 assessment, there were 45 discrepancies in 39 patients (21 patients in the avacopan arm and 18 patients in the prednisone arm). At the Week 52 assessment, there were 18 discrepancies in 17 patients (8 patients in the avacopan arm and 9 patients in the prednisone arm).

Glucocorticoid Use

The primary endpoint was a composite including assessment of disease activity and also absence of GC use within 4 weeks of the timepoint of assessment (Week 26) or (Week 52) to be considered as a responder. In this section, glucocorticoid use in this trial will be reviewed. "Cumulative glucocorticoid use" refers to all glucocorticoids used in each treatment arms, i.e., the protocol-specified, 20-week prednisone taper in the prednisone arm, as well as the non-study supplied glucocorticoids in both treatment arms. Also, of interest, is an evaluation of only non-study supplied glucocorticoids (i.e., use beyond what was prespecified), and this is discussed separately. There are limitations in some of the comparisons presented as they are based on point estimates from a small number of patients.

Cumulative Glucocorticoid Use

The mean cumulative glucocorticoid use per patient over 52 weeks was 3654.5 mg in the prednisone arm compared to 1348.9 mg in the avacopan arm. The cumulative glucocorticoid use over 52 weeks was 10.5 mg/patient-day in the prednisone arm compared to 3.9 mg/patient-day in the avacopan arm.

Although glucocorticoids were not protocol-specified for the avacopan arm, 86% of patients in the avacopan arm received glucocorticoids in the first half of the study. The mean cumulative glucocorticoid use at Week 26 was 1072.9 mg in the avacopan arm and 3192.5 mg in the prednisone arm. As the protocol-specified taper allowed for prednisone through Week 20, it is expected that patients in the prednisone arm would receive more glucocorticoids during the first half of the study. The cumulative glucocorticoid use over 26 weeks was 17.9 mg/patient-day in the prednisone arm compared to 6.1 mg/patient-day in the avacopan arm.

In the second half of the study, glucocorticoid use was not protocol-specified but could be administered for reasons as previously described (vasculitis, adrenal insufficiency, and other conditions). From Week 27 to 52, patients in both treatment arms received non-study supplied glucocorticoids. The mean cumulative glucocorticoid use from Week 27 to 52 was 462 mg in the prednisone arm and 276 mg in the avacopan arm. In the prednisone arm, the cumulative dose was 2.7 mg/patient-day; in the avacopan arm, the cumulative dose was 1.6 mg/patient-day.

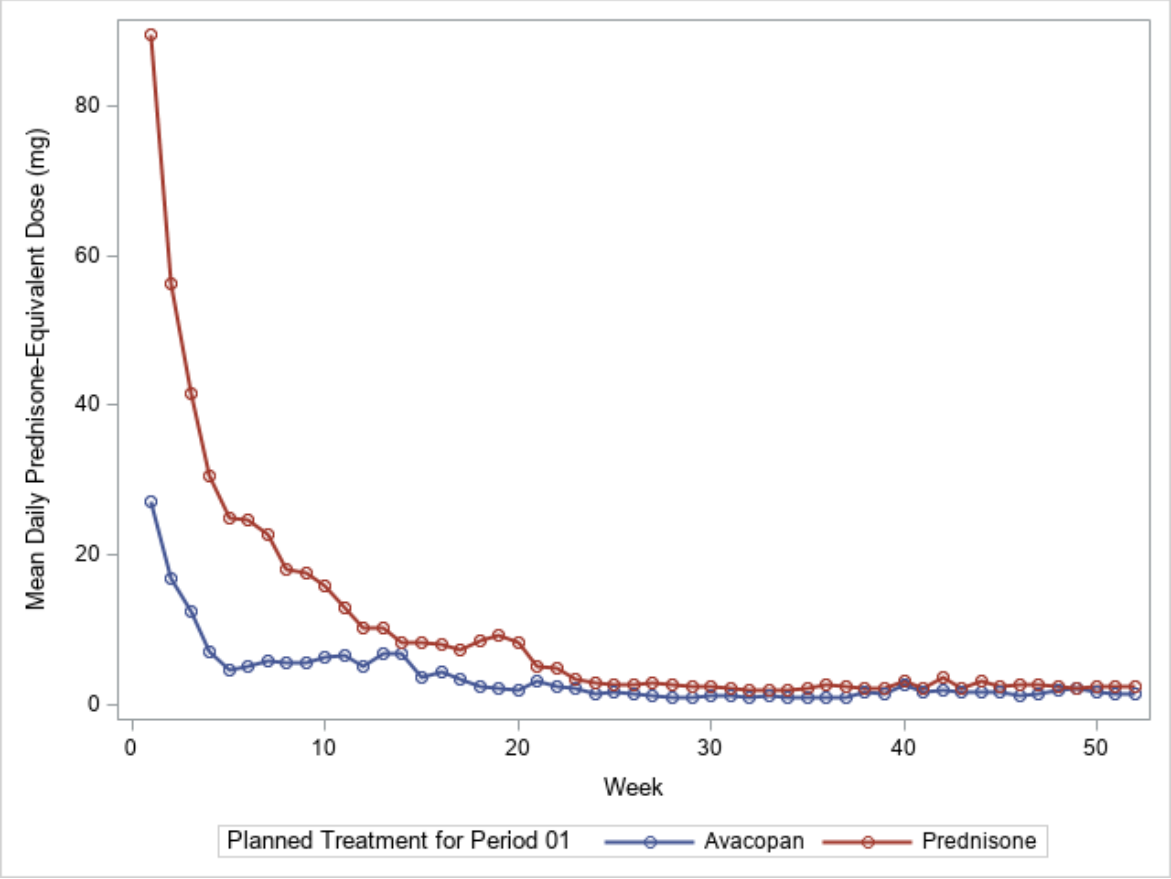
Table 24. Cumulative Glucocorticoid Use

Glucocorticoid Use by Time	Prednisone (N=164)	Avacopan (N=166)
Glucocorticoid use Weeks 0-26		
Total dose (mg)	523,553.89	178,105.14
Number of subjects	164 (100%)	143 (86.1%)
Mean dose (mg)	3,192.4	1,072.9
Patient day	29,228	29,203
Total/patient-day	17.9	6.1
Glucocorticoid use Weeks 27-52		
Total dose (mg)	75,768.65	45,812.3
Number of subjects	63 (38.4%)	44 (26.5%)
Mean dose (mg)	462.0	276.0
Patient day	27,966	27,883
Total/patient-day	2.7	1.6
Glucocorticoid use Weeks 0-52		
Total dose (mg)	599,322.54	223,917.44
Number of subjects	164 (100%)	145 (87.3%)
Mean dose (mg)	3,654.4	1,348.9
Patient day	57,194	57,086
Total/patient-day	10.5	3.9

Source: Statistical Reviewer
Dose by prednisone or prednisone equivalent in mg

Figure 7 is a graphical representation of the cumulative glucocorticoid use, including protocol-specified prednisone and non-study supplied glucocorticoids, by mean daily dose in each treatment arm. In the initial portion of the study, because of the protocol-specified prednisone taper, there is a large difference in the mean daily dose between the two arms. Because the steroid use in the prednisone arm was specified in the study design between Week 0 and 20, it is challenging to attribute differences in steroid use to avacopan's control of disease activity, and the clinical relevance of the differences in the glucocorticoid doses used from Week 0 to 26 between the prednisone and avacopan arms is uncertain. After completion of the 20-week prednisone taper, the mean daily dose is comparable during the second half of the study.

Figure 7. Mean Daily Dose of Cumulative Glucocorticoid Use (Prednisone Equivalent Dose)



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

Non-Study Supplied Glucocorticoid Use

Because glucocorticoid use was specified for only the prednisone arm, there is an interest in comparing the amount of glucocorticoids used beyond the protocol-specified amount, i.e., non-study supplied glucocorticoid use, provided at the Investigator's discretion. An analysis of non-study supplied glucocorticoid use showed that similar numbers of patients in both treatment arms required glucocorticoids (Table 25). Over 52 weeks, 87.3% of patients in the avacopan treatment group and 90.9% of patients in the prednisone group received non-study supplied glucocorticoids.

Table 25. Number of Patients Who Received Non-Study Supplied Steroids (Week 0 to 52)

Treatment Arm	Glucocorticoid Use	No Glucocorticoid Use
Avacopan (N=166)	145 (87.3%)	21 (12.7%)
Prednisone (N=164)	149 (90.9%)	15 (9.1%)

Source: Statistical Reviewer

An analysis of non-study supplied glucocorticoid use showed that a similar dose of glucocorticoids per patient-day was required in both treatment arms over 52 weeks (Table 26). The cumulative non-study supplied glucocorticoid use over 52 weeks was 3.6 mg/patient-day in the prednisone arm compared to 3.9 mg/patient-day in the avacopan arm.

More non-study supplied glucocorticoids were used in the first half of the study in both treatment arms. Mean dose of non-study supplied glucocorticoids in the first half of the study was greater in the avacopan arm than in the prednisone arm, 6.1 mg/patient-day vs. 4.5 mg/patient-day, respectively. Mean dose of non-study supplied glucocorticoids in the second half of the study was numerically lower in the avacopan arm (1.6 mg/patient-day) than in the prednisone arm (2.7 mg/patient-day), although differences between treatment arms were relatively small.

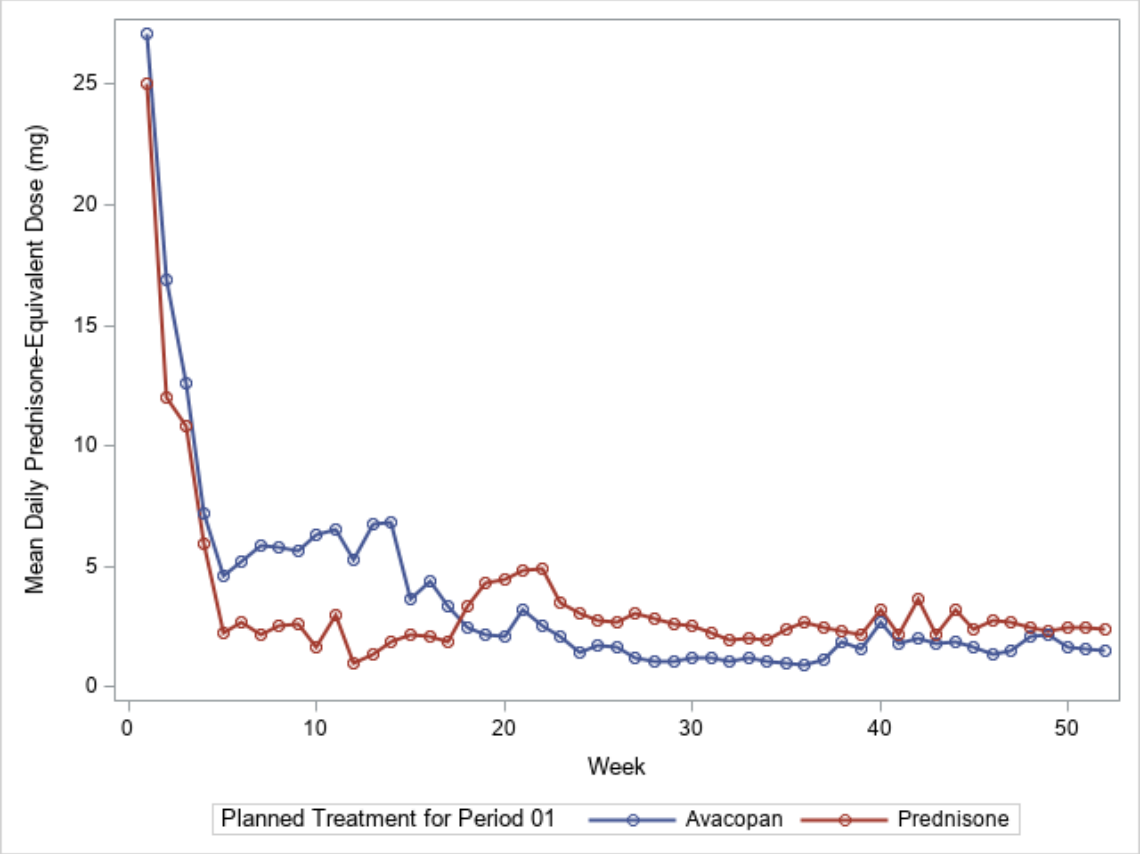
Table 26. Non-Study Supplied Glucocorticoid Use Adjusted for Time in Study

Glucocorticoid Use by Time	Prednisone (N=164)	Avacopan (N=166)
Glucocorticoid use Weeks 0-26		
Total dose (mg)	131718.89	178105.14
Patient day	29228	29203
Total/patient-day	4.5	6.1
Glucocorticoid use Weeks 27-52		
Total dose (mg)	75768.65	45812.3
Patient day	27966	27883
Total/patient-day	2.7	1.6
Glucocorticoid use Weeks 0-52		
Total dose (mg)	207487.54	223917.44
Patient day	57194	57086
Total/patient-day	3.6	3.9

Source: Statistical Reviewer
Dose by prednisone or prednisone equivalent in mg

Figure 8 is a graphical representation of mean daily dose of non-study supplied glucocorticoids by treatment arm. Both treatment arms required non-study supplied glucocorticoids. During the induction period, the avacopan arm required more non-study supplied glucocorticoids. Following induction, all glucocorticoid use was non-study supplied, and the amount of use was similar across treatment arms.

Figure 8. Mean Daily Dose of Cumulative Non-Study Supplied Glucocorticoids (Prednisone Equivalent Dose)



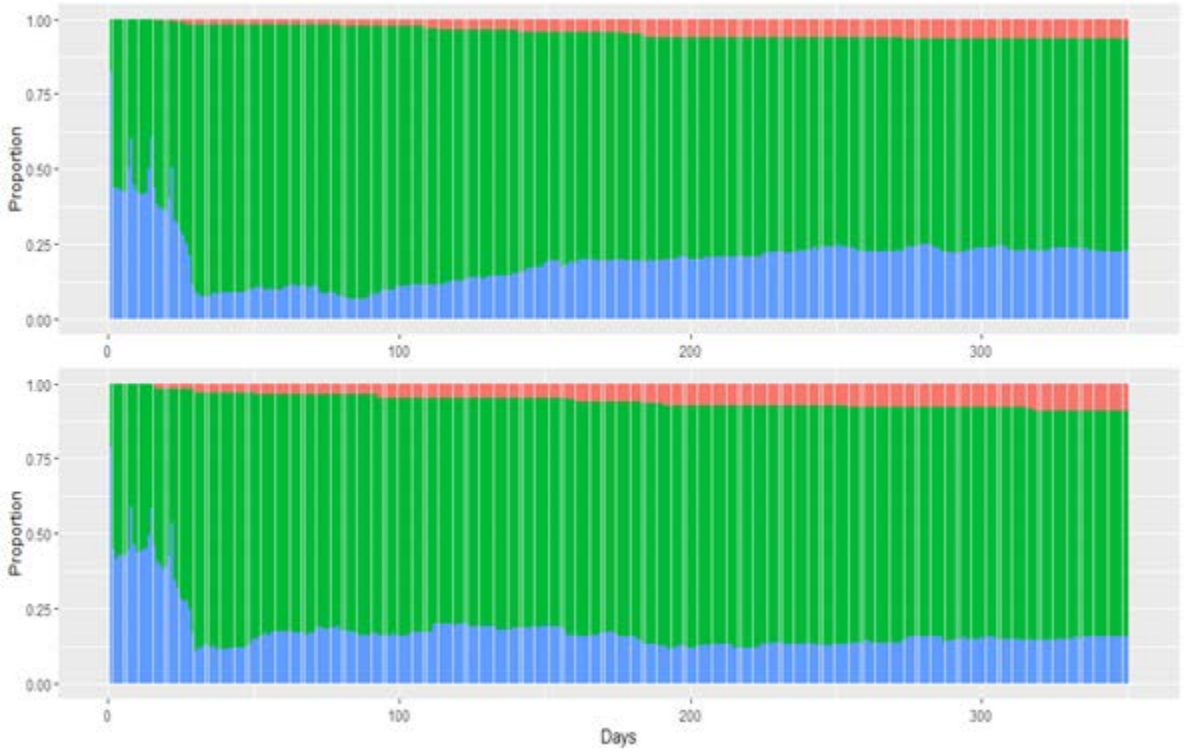
Source: Statistical Reviewer.
Mean daily dose is calculated by dividing the total use in a week by (7 times the total number of subjects in each arm).

To examine how many patients used non-study supplied glucocorticoids throughout the study period, the Agency statistical reviewer analyzed the proportion of patients who used non-study supplied glucocorticoids on each day.

Higher proportions of patients used non-study supplied glucocorticoids in the first month in both treatment arms. Three peaks in the first month occur at Week 1, Week 2, and Week 3 study visits corresponding with the administration of pre-medication for rituximab.

In the first half of the study, the proportion of patients who used non-study supplied glucocorticoids on each day was higher in the avacopan arm compared to that in the prednisone arm. For the prednisone arm, the proportion of patients who used non-study supplied glucocorticoids was greater after completion of the prespecified prednisone taper. In the second half of the study, the proportion of patients who used non-study supplied glucocorticoids on each day was slightly lower in the avacopan arm (approximately 16% at Day 350) compared to that in the prednisone arm (approximately 23% at Day 350).

Figure 9. Proportion of Patients Who Used Non-Study Supplied Glucocorticoids on Each Day of the 52-week Treatment Period in CL010_168



Source: Statistical Reviewer
Top: Prednisone; Bottom: Avacopan. Red: missing; Green: no use of non-study supplied glucocorticoids; Blue: use of non-study supplied glucocorticoids

Reasons for Non-Study Supplied Glucocorticoid Use

Investigators could treat study subjects with non-study supplied glucocorticoids for a variety of reasons. Specifically, for the treatment of AAV, non-study supplied glucocorticoids were used to treat persistent vasculitis, worsening vasculitis, and relapse. Worsening vasculitis and relapse are defined above in the description of the protocol. Patients had persistent vasculitis if they had one or more major items on the BVAS before study entry and did not show improvement or stabilization of these major items within the first 4 weeks of the study. Glucocorticoids for maintenance of remission were to be avoided as much as possible, but patients were included in this category if they had achieved a BVAS of 0 but still required glucocorticoids.

Over the 52-week study period, 117 patients (71.3%) in the prednisone arm received glucocorticoids for vasculitis, and 106 patients (63.9%) in the avacopan arm received glucocorticoids for vasculitis. A similar number of patients in each treatment arm received glucocorticoids for persistent vasculitis (n=85 [51.8%] in the prednisone arm, n=80 [48.2%] in the avacopan arm), worsening vasculitis (n=29 [17.7%] in the prednisone arm, n=31 [18.7%] in the avacopan arm), and maintenance of remission (n=26 [15.9%] in the prednisone arm, n=32

[19.3%] in the avacopan arm). However, numerically more patients in the prednisone arm (n=38 [23.2%]) received glucocorticoids to treat a relapse compared to patient in the avacopan arm (n=17 [10.2%]).

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

Table 27. Reasons for Use of Non-Study Supplied Glucocorticoids in Study CL010_168 (Weeks 0 to 26 and Weeks 27 to 52)

Reason for Glucocorticoid Use	Prednisone (N=164) n (%)	Avacopan (N=166) n (%)
Weeks 0 to 26		
Treatment of AAV	113 (68.9)	103 (62.0)
Treatment of worsening vasculitis	22 (13.4)	27 (16.3)
Treatment of relapse	29 (17.7)	11 (6.6)
Treatment of persistent vasculitis	83 (50.6)	77 (46.4)
Maintenance of remission	20 (12.2)	27 (16.3)
Treatment of other disorder, not vasculitis	17 (10.4)	20 (12.0)
Treatment of adrenal insufficiency	8 (4.9)	3 (1.8)
Pre-medication for rituximab	99 (60.4)	100 (60.2)
Pre-medication for other agent	8 (4.9)	5 (3.0)
Weeks 27 to 52		
Treatment of AAV	50 (30.5)	33 (19.9)
Treatment of worsening vasculitis	14 (8.5)	10 (6.0)
Treatment of relapse	25 (15.2)	8 (4.8)
Treatment of persistent vasculitis	14 (8.5)	10 (6.0)
Maintenance of remission	16 (9.8)	13 (7.8)
Treatment of other disorder, not vasculitis	8 (4.9)	10 (6.0)
Treatment of adrenal insufficiency	5 (3.0)	-
Pre-medication for rituximab	16 (9.8)	10 (6.0)
Pre-medication for other agent	-	-

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

Table 129 in the Appendix presents similar data by background induction therapy. Over the course of the study, a numerically greater proportion of patients in the rituximab subgroup on both arms received non-study supplied glucocorticoids for the treatment of relapse (prednisone 28.0%, avacopan 11.2%) as compared to the cyclophosphamide group (prednisone 14.0%, avacopan 8.5%). Interpretation of this analysis is limited, as patients were not randomized to these subgroups.

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

It is important to recognize that the requirement for glucocorticoids did not necessarily preclude patients from being categorized as responders. Patients who experienced a relapse after achieving remission at Week 26 and patents who were treated with glucocorticoids for vasculitis within 4 weeks of the endpoint assessment (at Week 26 or 52) were considered non-responders. Otherwise, patients could receive glucocorticoids for vasculitis and were still considered responders. Selected examples of patients who received glucocorticoids for vasculitis or a clinical finding potentially concerning for vasculitis but who were still considered responders are described in the Table 133. Examples of patients who were considered responders despite non-study supplied glucocorticoids include patients who received multiple courses of prednisone for vasculitis, who received IV glucocorticoids for pulmonary hemorrhage, and who received multiple doses of IV glucocorticoids for vasculitis and lung nodules. These cases highlight how challenging it is to interpret the glucocorticoid use and the contribution to therapeutic benefit in this study.

Efficacy Results – Secondary and Other Relevant Endpoints

Glucocorticoid Toxicity Index

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

Glucocorticoid toxicity was assessed based on the GTI-CWS and GTI-AIS. Table 28 shows the GTI-CWS at Weeks 13 and 26. At both time points, the GTI-CWS increased compared to baseline, consistent with greater toxicity. As noted above, the GTI-CWS assesses cumulative glucocorticoid toxicity and can increase or remain the same over time. The magnitude of the increase in the GTI-CWS was lower in the avacopan arm compared to the prednisone arm at Weeks 13 and 26.

Table 28. Glucocorticoid Toxicity Index-Cumulative Worsening Score (GTI-CWS) at Weeks 13 and 26

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

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

Unlike GTI-CWS which only scores worsening, GTI-AIS measures both worsening and improvement in the different body systems. GTI-AIS is presented in Table 29 and shows an increase from baseline in both treatment arms. The magnitude of the increase in GTI-AIS was lower in the avacopan arm compared to the prednisone arm at Weeks 13 and 26.

Table 29. Glucocorticoid Toxicity Index-Aggregate Improvement Score (GTI-AIS) at Weeks 13 and 26

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

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

Table 30 and Table 31 present the GTI-CWS and GTI-AIS scores, respectively, by domains. No domains appeared to drive the treatment difference in the overall score. The greatest differences in the prednisone and avacopan arms was seen in the Infection, Lipids, and BMI domains for both GTI-CWS and GTI-AIS at Weeks 13 and 26. Larger differences between treatment arms in Glucose Intolerance were observed at Week 13 than Week 26. Some domains showed no difference between treatment arms (e.g., blood pressure).

Table 30. GTI-CWS by Domains at Weeks 13 and 26 in Study CL010_168

CWS Parameter	Prednisone Mean (SD)[1]	Avacopan Mean (SD)[1]
CWS at Week 13	37.6 (35.47)	26.7 (31.48)
Body Mass Index	3.8 (8.10)	1.1 (5.12)
Glucose Tolerance	2.9 (9.61)	0.2 (2.53)
Blood Pressure	8.6 (12.32)	8.9 (13.17)
Lipids	7.6 (6.66)	5.7 (5.68)
Steroid Myopathy	1.1 (6.70)	0.3 (1.57)
Skin Toxicity	1.9 (4.83)	0.8 (2.34)
Neuropsychiatric Toxicity	3.7 (13.15)	3.0 (12.73)
Infection	8.0 (24.59)	6.8 (22.72)
CWS at Week 26	56.7 (52.79)	39.8 (38.77)
Body Mass Index	3.8 (8.15)	1.9 (6.29)
Glucose Tolerance	3.4 (10.10)	2.9 (9.23)
Blood Pressure	13.8 (14.35)	13.8 (15.75)
Lipids	10.6 (7.54)	8.1 (6.67)
Steroid Myopathy	1.9 (9.85)	0.4 (1.88)
Skin Toxicity	2.2 (4.65)	1.2 (3.44)
Neuropsychiatric Toxicity	5.3 (15.71)	2.9 (11.67)
Infection	15.6 (38.63)	8.7 (25.29)

Source: Statistical Reviewer
[1] Mean and standard deviation calculated from all observed data at corresponding week
Abbreviations: GTI-CWS, Glucocorticoid Toxicity Index-Cumulative Worsening Score; SD, standard deviation.

Table 31. GTI-AIS by Domains at Weeks 13 and 26 in Study CL010_168

AIS Parameter	Prednisone Mean (SD)[1]	Avacopan Mean (SD)[1]
AIS at Week 13	24.5 (40.92)	11.0 (37.15)
Body Mass Index	3.7 (8.32)	0.6 (6.19)
Glucose Tolerance	-1.3 (15.47)	-6.3 (13.37)
Blood Pressure	4.0 (17.85)	3.9 (19.14)
Lipids	6.7 (8.20)	4.2 (7.89)
Steroid Myopathy	0.7 (7.99)	0.2 (1.73)
Skin Toxicity	1.7 (5.01)	0.1 (3.94)
Neuropsychiatric Toxicity	1.0 (17.72)	1.5 (14.55)
Infection	8.0 (24.59)	6.8 (22.72)
AIS at Week 26	24.1 (45.22)	11.9 (38.49)
Body Mass Index	3.3 (8.72)	1.1 (7.70)
Glucose Tolerance	-4.5 (14.38)	-5.3 (16.30)
Blood Pressure	4.7 (19.24)	4.5 (20.45)
Lipids	6.5 (9.62)	4.2 (9.41)
Steroid Myopathy	0.6 (8.64)	0.2 (1.44)
Skin Toxicity	0.8 (4.22)	-0.3 (4.29)
Neuropsychiatric Toxicity	-0.7 (16.72)	-0.9 (9.34)
Infection	13.3 (31.34)	8.5 (25.09)

Source: Statistical Reviewer
[1] Mean and standard deviation calculated from all observed data at corresponding week
Abbreviations: GTI-AIS, Glucocorticoid Toxicity Index-Aggregate Improvement Score; SD, standard deviation.

There are limitations to the interpretation of the GTI-CWS and GTI-AIS. The GTI is a clinician-reported instrument and is not considered a direct measure of how a patient feels, functions, or survives. The GTI does not include the patients' perspectives, rather it is a measure of clinician-reported outcomes and biomarkers. The clinically meaningful within-patient change is not known. Certain rare but serious events (in the domains of "endocrine," "gastrointestinal," "musculoskeletal," and "ocular") are omitted from the GTI score. Additionally, the bone domain was not included in the GTI assessment, consistent with modifications allowed for trials of less than 12 months duration. Although Study CL010_168 was a 52-week study, the Applicant only assessed the GTI at Weeks 13 and 26. In addition, the clinical meaningfulness of a measure of glucocorticoid toxicity is unclear when one arm required glucocorticoids (protocol-specified prednisone) and one did not. There was no comparable measure of the potential toxicities associated with avacopan (i.e., hepatotoxicity). Thus, this could lead to an inherently biased assessment in this study. Finally, differences in GTI between the treatment groups may reflect the study design which specified the prednisone doses to be used in the control group, rather than dosing glucocorticoids based on Investigator assessment of active disease. GTI was not assessed at later timepoints to assess the effects of glucocorticoids after completion of the pre-specified prednisone taper.

As there is no regulatory precedent for GTI, the Division of Clinical Outcome Assessments was consulted to evaluate the GTI as an instrument to support the efficacy of avacopan in AAV. DCOA determined that the GTI is not "fit-for-purpose" (i.e., the level of validation associated with a tool is sufficient to support its context of use) to measure glucocorticoid-related toxicities or glucocorticoid-sparing effects for the context of use of this drug development program. The DCOA team noted 5 issues, specifically, (1) measure not comprehensive of the intended claim; (2) score interpretability; (3) clinically meaningful within-patient change; (4) study design (i.e., the pre-specified glucocorticoid taper is in the control arm and the measure is an assessment of glucocorticoid toxicity. As detailed by DCOA, "the assessment is potentially biased, because while the comparator arm had toxicity systematically assessed in the endpoint, the investigational arm did not have a comparable measure of its potential toxicity profile for comparison, e.g., hepatotoxicity."); (5) adjustment for multiplicity. See the full consult from DCOA reviewer Dr. Ji Li for full details.

In conclusion, GTI is not "fit-for-purpose" to measure glucocorticoid-related toxicities in this program. The interpretation of the results is limited because of multiple concerns including the study design which included a protocol-specified prednisone taper in one arm, the lack of longer term assessments after Week 26, the lack of information to inform the clinical meaningfulness of the difference in the change in GTI between treatment arms, and the lack of a comparable measure to assess toxicities associated with avacopan.

Early Remission and Time to Remission

In Study CL010_168, 68.9% of patients in the prednisone arm achieved early remission (defined as BVAS of 0 at Week 4), while 62.7% of patients in the avacopan arm achieved early remission. Although achieving remission is important, the clinical meaningfulness of achieving early remission is unclear without sustained, long-term remission.

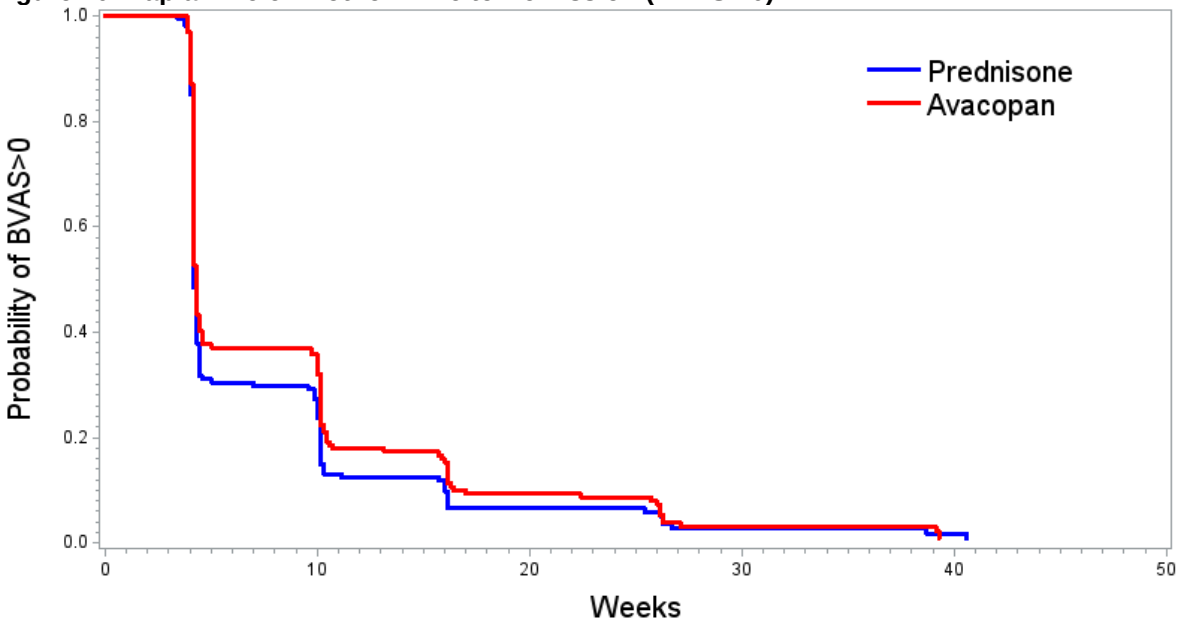
Table 32. Early Remission Defined as a BVAS of 0 at Week 4, Regardless of Whether the Subjects Received Glucocorticoids During This Period of Time

Treatment Arm	N	Count (%)	Diff (%) [95% CI]
Prednisone	164	113 (68.9)	-5.6% [-15.4, 4.2]
Avacopan	166	104 (62.7)	

Source: Statistical Reviewer.
Abbreviations: BVAS, Birmingham Vasculitis Activity Score CI, confidence interval.

The Agency statistical reviewer further conducted an exploratory analysis to evaluate and compare time to remission in the two treatment arms (Figure 10). Patients in the prednisone arm achieved remission generally faster than patients in the avacopan arm. Estimated hazard ratio of avacopan versus prednisone, obtained by fitting the Cox model, was 0.880 with 95% confidence interval of (0.705, 1.098).

Figure 10. Kaplan-Meier Plot for Time to Remission (BVAS =0)



Source: Statistical Reviewer
Abbreviations: BVAS, Birmingham Vasculitis Activity Score.

Relapse

The Applicant evaluated relapse, i.e., proportion of patients with relapse and time to relapse based on the subset of patients who achieved remission, as secondary endpoints. As previously noted, relapse was defined as worsening of disease after having previously achieved remission (BVAS =0) as defined by ≥1 major item on the BVAS or ≥3 minor items on the BVAS or 1-2 minor items on the BVAS at 2 consecutive study visits. As described in the Regulatory History (Section 3.2), the Agency recommended at the IND stage that the Applicant revise the definition of ”relapse” so that all patients could be considered as having a flare, regardless of whether remission was achieved. However, this advice was not incorporated in the definition of ‘relapse’. The Applicant’s analysis of relapse is limited, as it depends on post-randomization variables, i.e., having first achieved remission and the timing of the remission. As a result, the subset of subjects included in this analysis and the time those subjects are at risk for relapse can no longer be assumed to be similar across treatment arms. The advantages of randomization are eliminated because the treatment arms are no longer balanced with respect to possible confounders, leading to potentially biased comparisons between treatment arms and limiting the interpretability of these results. In this case, the overwhelming majority of subjects in both arms did achieve remission; however, there are differences in the time at which remission is achieved. Patients who achieve remission at earlier time point, are at risk of relapse for a longer duration. Therefore, these may not be comparable groups. The analysis solely of relapse after remission is considered exploratory.

The Agency performed an alternative exploratory analysis to assess relapse that instead incorporates all patients and addresses the concerns of conditioning on a post-randomization variable to define a subset of patients. Table 33 presents patients who did not achieve remission in both treatment arms, as well as patients who relapsed after achieving remission (before or after Week 26). In the primary endpoints, patients who achieved remission after Week 26 (e.g., Week 39) would have been considered non-responders at both Week 26 and Week 52. In contrast to the primary endpoint assessment, patients who achieved remission after Week 26 but did not suffer a relapse before the Week 52 assessment are considered responders in this analysis. Thus, this exploratory analysis attempts to evaluate the patients with refractory and/or relapsing disease based on the overall population.

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

It is important to note that this post-hoc exploratory analysis does not account for the time to achieving BVAS of 0 and do not, on their own, support a determination that avacopan decreases relapses or helps to achieve remission.

Table 33. Proportion of Patients Who Did Not Achieve Remission (BVAS =0) or Relapsed after Remission (BVAS =0)

BVAS Outcome	Prednisone (N=164) n (%)	Avacopan (N=166) n (%)
Did not achieve BVAS =0	7 (4.3)	8 (4.8)
Achieved BVAS =0	157 (95.7)	158 (95.2)
Relapse	33 (20.1)	16 (9.6)
Between Week 0-Week 26[1]	16 (9.1)	3 (1.8)
Between Week 27-Week 52[2]	17 (11.0)	13 (7.8)
Did not achieve BVAS =0 OR Relapsed	40 (24.4)	24 (14.5)
Difference (95% CI)	-9.9% (-18.4%, -1.5%)	

Source: Statistical Reviewer.
[1] Day 1 to Day 183
[2] Day 184 to End of treatment
Point estimate and 95% confidence interval using normal approximation were reported.
Counts and percentages relative to N.
Abbreviations: BVAS, Birmingham Vasculitis Activity Score; CI, confidence interval; Diff, difference; N, the number of patients randomized who received at least one dose of drug.

Vasculitis Damage Index

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

Table 34 shows the change from baseline in VDI in both treatment arms at Week 26 and Week 52. The change from baseline in VDI was similar between treatment arms at both timepoints.

Table 34. Change From Baseline in Vasculitis Damage Index (VDI) at Weeks 26 and 52

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

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

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

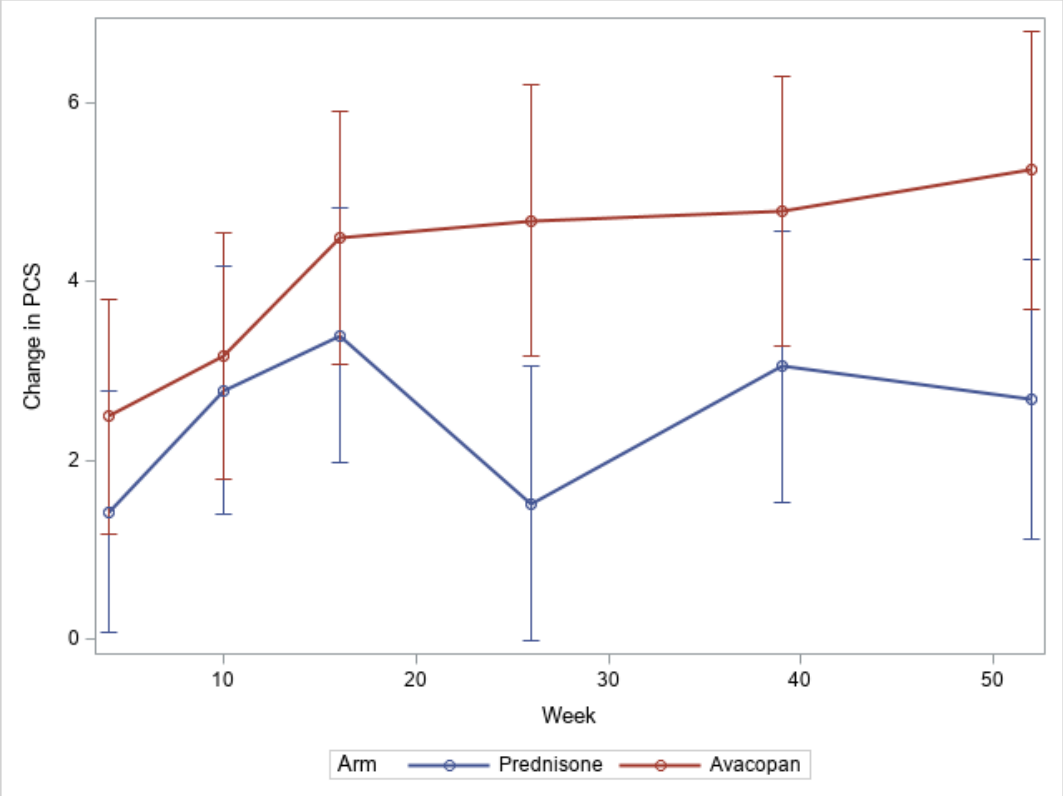
Quality of Life Measures

Quality of life was assessed based on the SF-36 and EQ-5D-5L, both general quality of life instruments, not specific to the assessment of vasculitis.

SF-36 Physical Component Score

Figure 11 shows the change from baseline in SF-36 Physical Component Score (PCS) over the 52-week treatment period. There was a trend toward a greater improvement in SF-36 PCS over time in the avacopan arm. At Week 52, the mean change in PCS was 5.2 in the avacopan arm compared to 2.7 in the prednisone arm, with the treatment difference of 2.6 (95% CI: [0.5, 4.7]). A supplemental analysis based on ANCOVA, however, resulted in a smaller treatment difference of 1.8 with 95% CI of (-0.3, 3.9).

Figure 11. Change From Baseline in SF-36 Physical Component Score (PCS)

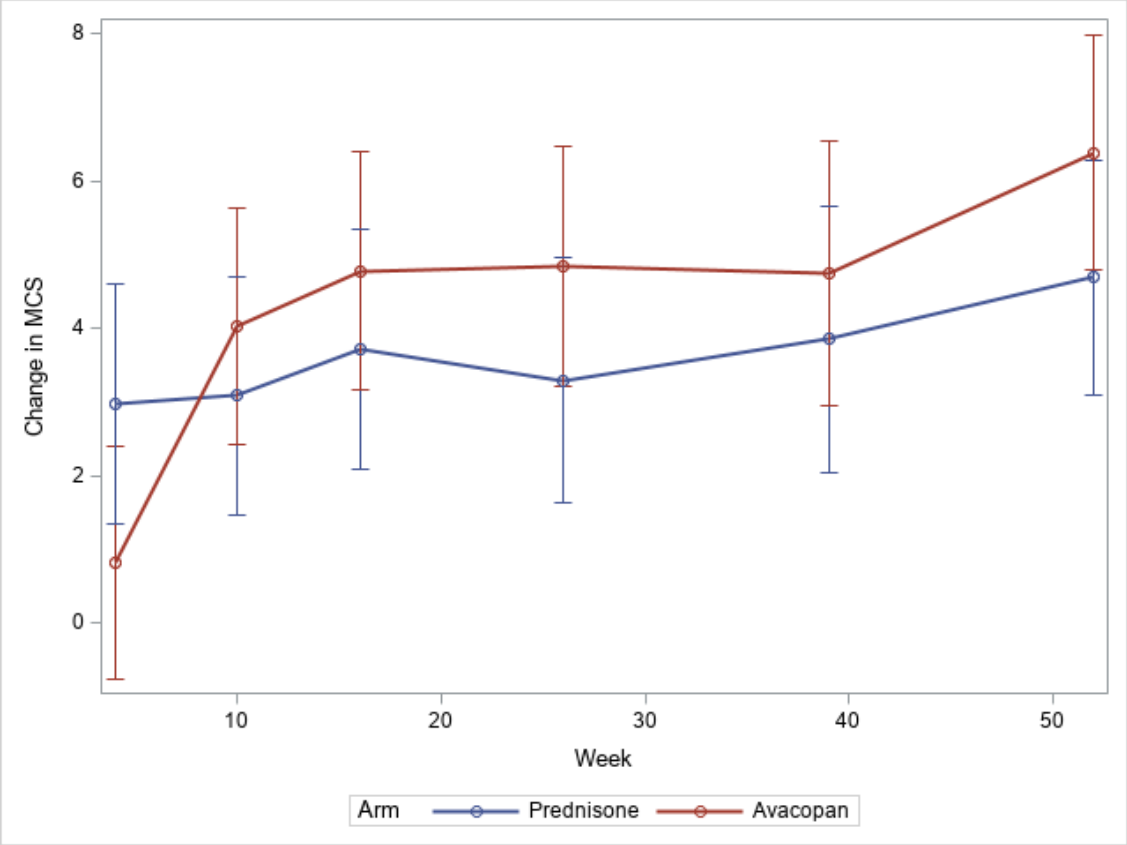


Sources: Statistical reviewer.
Least Squares (LS) means with 95% confidence intervals. Derived from a mixed effects model for repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction, and randomization strata as factors, and baseline as covariate. An unstructured covariance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

SF-36 Mental Component Score

Similarly, there was a trend toward a greater improvement in SF-36 Mental Component Score (MCS) over time in the avacopan arm. Results for the mean changes from baseline in SF-36 MCS score over the 52-week treatment period is shown in Figure 12. In Study CL010_168, LS mean treatment difference between avacopan and prednisone arms was 1.7 with 95% confidence interval of (-0.4, 3.8).

Figure 12. Change From Baseline in SF-36 Mental Component Score (MCS)



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

For SF-36 PCS and especially for SF-36 MCS, the confidence intervals did not rule out zero effect in most of the domains. Specifically, for PCS, the domains of Physical Functioning and General Health Perception ruled out zero effect at Week 52, but the domains of Role Physical and Bodily Pain did not. For MCS, no domains ruled out zero effect at Week 52. Table 35 presents the change from baseline in each of the SF-36 domains at Week 52.

Table 35. SF-36 PCS and MCS at Baseline and Week 52

	Prednisone Mean (SD)[1]			Avacopan Mean (SD)[1]			Avacopan - Prednisone
SF-36 Domains	**Baseline**	**Week 52**	**Change[2,3]**	**Baseline**	**Week 52**	**Change[2,3]**	**Diff (95% CI)[3]**
PCS							
Physical functioning	64.1 (27.29)	70.2 (26.09)	4.7 (1.0, 8.4)	63.7 (26.81)	73.5 (25.10)	9.8 (6.1, 13.5)	5.1 (0.1, 10.1)
Role physical	47.5 (31.18)	62.2 (29.51)	12.3 (7.8, 16.8)	46.1 (30.54)	65.9 (29.16)	17.6 (13.2, 22.1)	5.3 (-0.7, 11.3)
Bodily pain	52.7 (32.73)	65.2 (27.53)	12.1 (7.6, 16.6)	51.4 (30.62)	68.8 (27.63)	16.5 (12.0, 20.9)	4.4 (-1.6, 10.4)
General health	51.1 (19.21)	52.2 (22.62)	-0.4 (-3.5, 2.7)	51.4 (20.65)	57.3 (20.46)	5.9 (2.9, 9.0)	6.3 (2.2, 10.4)
MCS							
Mental health	62.5 (22.38)	75.4 (17.98)	9.6 (7.0, 12.3)	67.2 (20.19)	78.2 (17.94)	10.8 (8.2, 13.4)	1.2 (-2.3, 4.7)
Role emotional	67.1 (29.95)	74.1 (26.46)	4.0 (0.0, 8.0)	67.8 (30.24)	79.0 (24.57)	9.3 (5.4, 13.3)	5.3 (-0.01, 10.6)
Social functioning	59.1 (31.22)	75.6 (28.14)	13.6 (9.6, 17.7)	61.1 (31.08)	80.6 (22.25)	18.1 (14.1, 22.1)	4.5 (-0.9, 9.9)
Vitality	42.9 (24.60)	55.3 (23.82)	10.5 (7.0, 14.0)	44.7 (23.19)	59.5 (21.72)	14.4 (11.0, 17.9)	4.0 (-0.7, 8.6)

Source: Statistical Reviewer
[1] Mean and standard deviation calculated from all observed data at corresponding week
[2] Model-based mean change from baseline
[3] Derived from a mixed effects model for repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction, and randomization strata as factors, and baseline as covariate. An unstructured covariance matrix was used to model the within-subject variance-covariance structure for the model errors.
Abbreviations: CI, confidence interval; Diff, difference; MCS, mental component score; PCS, physical component score; SD, standard deviation

DCOA was consulted to provide an assessment of the SF-36 in the context of the avacopan program. DCOA noted that the SF-36 has been widely deployed to measure hr-QoL in clinical research and the Agency has accepted the instrument in certain contexts of use. However, in the AAV patient population, DCOA's assessment is that there is insufficient evidence of content validity either from the literature or in the avacopan program-specific research to ensure adequate interpretation of hr-QoL in the proposed context. The SF-36 is a measure of general health status, which makes it difficult to ascertain the effect of treatment on the underlying disease or condition under treatment. For other rheumatologic diseases (OA, RA, SLE, etc.), a minimum clinically important difference (MCID) has been proposed to be a change of 2.5 to 5 points in the summary scores and a change of 5 to 10 points in each of the domain scores (Strand et al. 2011). Because there is insufficient evidence of content validity, there are limitations to interpreting what would be a clinically meaningful change in this study. Even if content validity was established, a preferred analysis would be a clinically meaningful within-patient change from the patient perspective rather than an MCID compared between groups. Given the complexity of hr-QoL, (b) (4) (b) (4) a robust outcome on the primary endpoint, a clear estimand, and an *a priori* endpoint model with appropriate control for multiplicity are necessary considerations for regulatory decision-making.

EQ-5D-5L

EQ-5D-5L is based on a VAS and a population norm-based Index. Results for the mean changes from baseline in EQ-5D-DL at Week 52 is shown in Table 36. LS mean treatment difference between avacopan and prednisone arms in EQ-5D-5L VAS was 6.1 with 95% confidence interval of (2.3, 9.8). LS mean treatment difference in EQ-5D-5L Index score was 0.05 with 95% confidence interval of (0.01, 0.09).

Table 36. Change From Baseline in EQ-5D-5L at Week 52

	Change From Baseline	
Treatment Arm	**LS Mean[1] (95% CI)**	**Diff (95% CI)**
VAS		
Prednisone	7.0 (4.2, 9.9)	6.1 (2.3, 9.8)
Avacopan	13.1 (10.2, 15.9)	
Index		
Prednisone	-0.003 (-0.03, 0.03)	0.05 (0.01, 0.09)
Avacopan	0.05 (0.02, 0.08)	

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

DCOA was also consulted to provide an assessment of the EQ-5D-5L results in the avacopan clinical program. DCOA noted that there is no regulatory precedent of using EQ-5D-5L. The EQ-5D-5L is a generic preference-based measure intended to provide a single health utility index

value for use in economic analyses [redacted] (b) (4)

Renal Assessments

DCN was consulted to provide subject matter expertise on the interpretation of the results of the renal endpoints.

Baseline Renal Disease

Patients were categorized as having baseline renal disease by meeting criteria for the BVAS renal component. Table 37 presents the BVAS criteria utilized to define patients with baseline renal disease in Study CL010_168 and the proportion of patients who met each criterion. One hundred thirty-four patients (80.7%) in the avacopan arm and 134 patients (81.7%) in the prednisone arm had renal disease at baseline based on these criteria.

Table 37. Proportion of Patients With Baseline Renal Disease (Based on BVAS criteria) in Study CL010_168

BVAS Criteria for Renal Disease at Baseline		Prednisone (N=164) n (%)	Avacopan (N=166) n (%)
Renal disease at baseline based on the following BVAS criteria		134 (81.7)	134 (80.7)
Hypertension (HTN)	Diastolic blood pressure >95 mm Hg Related to ANCA-associated vasculitis	21 (12.7)	23 (14.0)
Proteinuria	>1+ on urinalysis or >0.2 g/g creatinine on a urine sample	110 (66.3)	107 (65.2)
Hematuria	≥10 RBC per high power field on microscopy	77 (46.4)	68 (41.5)
Serum creatinine elevation at first assessment	Serum creatinine 1.41-2.82 mg/dL	60 (36.1)	61 (37.2)
	Serum creatinine 2.83-5.64 mg/dL	26 (15.7)	20 (12.2)
	Serum creatinine ≥5.6 mg/dL	1 (0.6)	0
Rise in Serum creatinine >30% or fall in creatinine clearance >25%		20 (12.2)	17 (10.2)
Other	RBC casts and/or glomerulonephritis	60 (36.1)	59 (36.0)

Source: ChemoCentryx Response to IR#13, Table 40.1
Abbreviations: ANCA, anti-neutrophilic cytoplasmic ant body; BVAS, Birmingham Vasculitis Activity Score; RBC, red blood cell.

The most commonly observed renal criterion was proteinuria (65.2% in the prednisone arm and 66.3% in the avacopan arm). The other renal criteria observed in the study patient population included hematuria (41.5% prednisone arm vs. 46.4% avacopan arm), increase in serum creatinine (49.4% prednisone arm vs. 52.4% avacopan arm), and red blood cell (RBC) casts/glomerulonephritis (36.0% prednisone arm vs. 36.1% avacopan arm). Patients in each treatment arm met a similar mean number of criteria (2.7 in the prednisone group and 2.8 in the avacopan group). Identifying baseline glomerulonephritis with BVAS criteria only may have limitations. Concerns include using diastolic blood pressure alone in the assessment of hypertension (HTN), inability to differentiate acute versus chronic kidney disease in the elevated serum creatinine criterion, and a lack of guidance on time course for change to

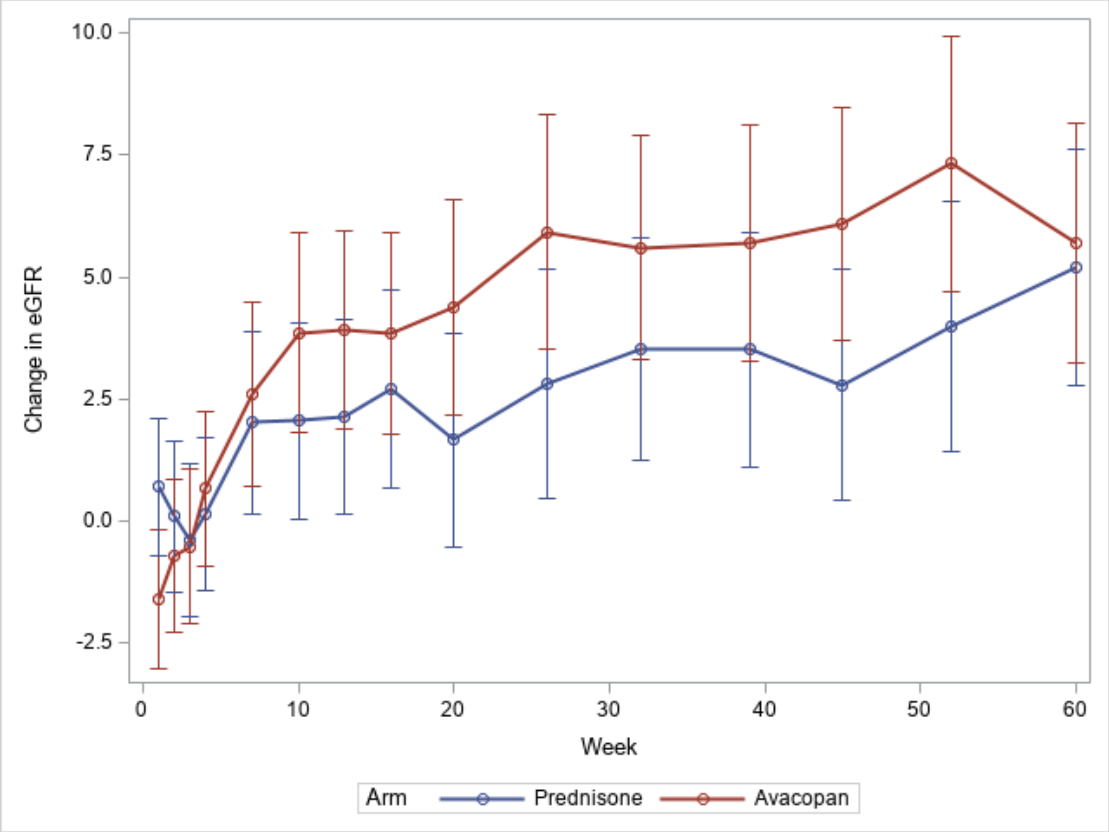
determine an increase in creatinine or fall in creatinine clearance. For example, it is not clear whether patients had evidence of chronic kidney disease before the current diagnosis or flare of vasculitis. Together, these criteria make it challenging to understand the type and degree of renal disease attributed to AAV (i.e., active glomerulonephritis) compared to chronic kidney damage at baseline and makes it difficult to understand the nature of any benefit and the clinical importance of the trial's renal assessments.

eGFR

The change in eGFR from baseline was evaluated for all patients with baseline renal disease. Eighty-one percent (268 out of 330) patients had renal disease at baseline.

Figure 13 shows the change from baseline in eGFR over the 52-week treatment period and the 8-week follow-up period (off therapy). There is a trend toward a greater improvement in eGFR over time in the avacopan arm. At Week 52, the change in eGFR was 7.3 mL/min/1.73 m^2 in the avacopan arm compared to 4.0 mL/min/1.73 m^2 in the prednisone arm. The LS mean difference between treatment arms on eGFR was 3.3 mL/min/1.73 m^2 with 95% confidence interval of (-0.4, 6.9). The clinical meaningfulness of this magnitude of difference between treatment groups is unclear, and 95% confidence interval contains 0. Additionally, the fact that the treatment benefit appears to be lost within 8 weeks after study drug discontinuation further questions the clinical importance of the results (mean change in eGFR at Week 60: 3.6 for avacopan and 3.2 for prednisone).

Figure 13. Change From Baseline in eGFR in Patients With Baseline Renal Disease



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

The Applicant also performed an exploratory subgroup analysis in patients with stages of kidney disease based on GFR (i.e., eGFR <30 mL/min/1.73 m^2, 30 to 59 mL/min/1.73 m^2, and >59 mL/min/1.73 m^2) and noted that the greatest change from baseline occurred in patients with <30 mL/min/1.73 m^2 at baseline. The treatment difference in patients with baseline GFR <30 mg/min/1.73 m^2 was small (5.7 mL/min/1.73 m^2 at Week 52) and decreased at Week 60, similar to the analysis in the overall population of patients with baseline renal disease. Similar to the overall population, the clinical relevance of the small and non-sustained change in eGFR is uncertain.

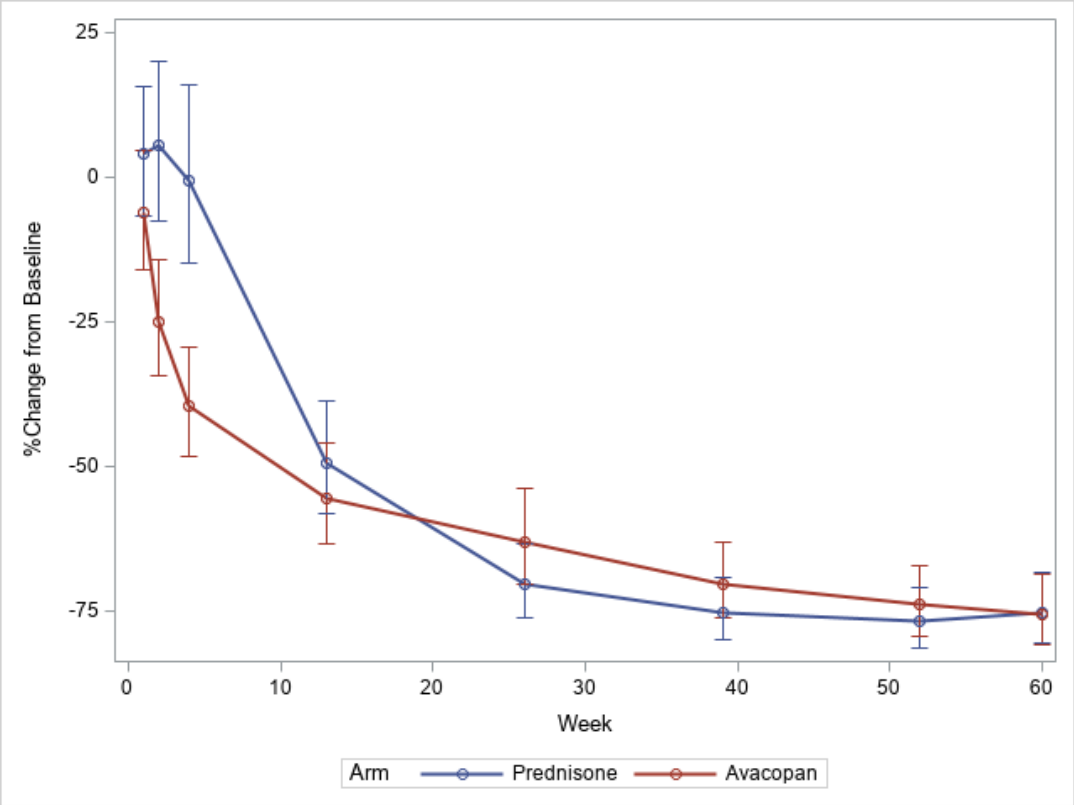
Urinary Albumin:Creatinine Ratio

The UACR analysis was only performed in patients who met BVAS criteria for renal disease at baseline who also had a UACR ≥10 mg/g creatinine, a value that is generally considered to be in the normal range. Seventy-seven percent of patients (253 out of 330) were included in this

analysis. Figure 14 shows the percent change from baseline in the UACR in this subset of patients.

Percent change in UACR at Week 52 was similar in the avacopan and prednisone arms (-74% change from baseline and -77% change from baseline, respectively).

Figure 14. Percent Change From Baseline in Urinary Albumin:Creatinine Ratio (UACR) in Patients With Baseline Renal Disease and Baseline UACR ≥10 mg/g (60-week Study Period)



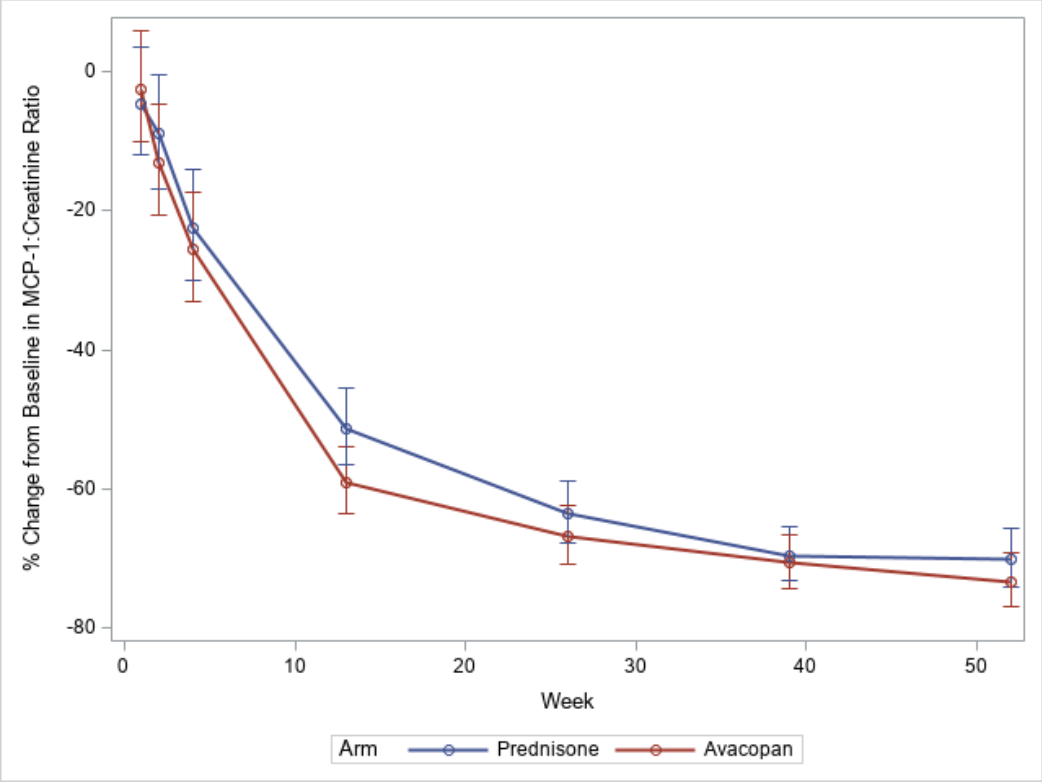
Sources: Statistical reviewer.
Least Squares (LS) means with 95% confidence intervals. Derived from a mixed effects model for repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction as factors, and baseline as covariate. An unstructured covariance matrix was used to model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

The improvement appears to occur more quickly in the avacopan arm with a 40% decrease in UACR at Week 4 compared to no change in the prednisone arm. However, the improvement in UACR becomes more similar after Week 13 in both treatment arms without a major difference over time through Week 60, as seen in Figure 14. It is challenging to interpret the clinical significance of percent change in albuminuria in a population that includes patients with near-normal albuminuria levels at baseline. In addition, the Applicant did not provide data supporting the use of UACR as a surrogate for clinical outcomes in ANCA-associated vasculitis; however, it seems unlikely that the difference seen at Week 4 but not at later timepoints would predict a meaningful clinical benefit of avacopan over prednisone.

MCP-1:Creatinine Ratio

Percent change in MCP-1:creatinine ratio at Week 52 was similar in the avacopan and prednisone arms (-73% change from baseline and -70% change from baseline, respectively). The clinical meaningfulness of changes in this biomarker as a measure of inflammation or glomerulonephritis in AAV is unknown.

Figure 15. Percent Change From Baseline in MCP-1:Creatinine Ratio



Sources: Statistical reviewer.
Least Squares (LS) means with 95% confidence intervals. Derived from a mixed effects model for repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction as factors, and baseline as covariate. An unstructured covariance matrix was used to model the within-subject variance-covariance structure for the model errors.
Abbreviations: MCP-1, monocyte chemoattractant protein-1

Dialysis

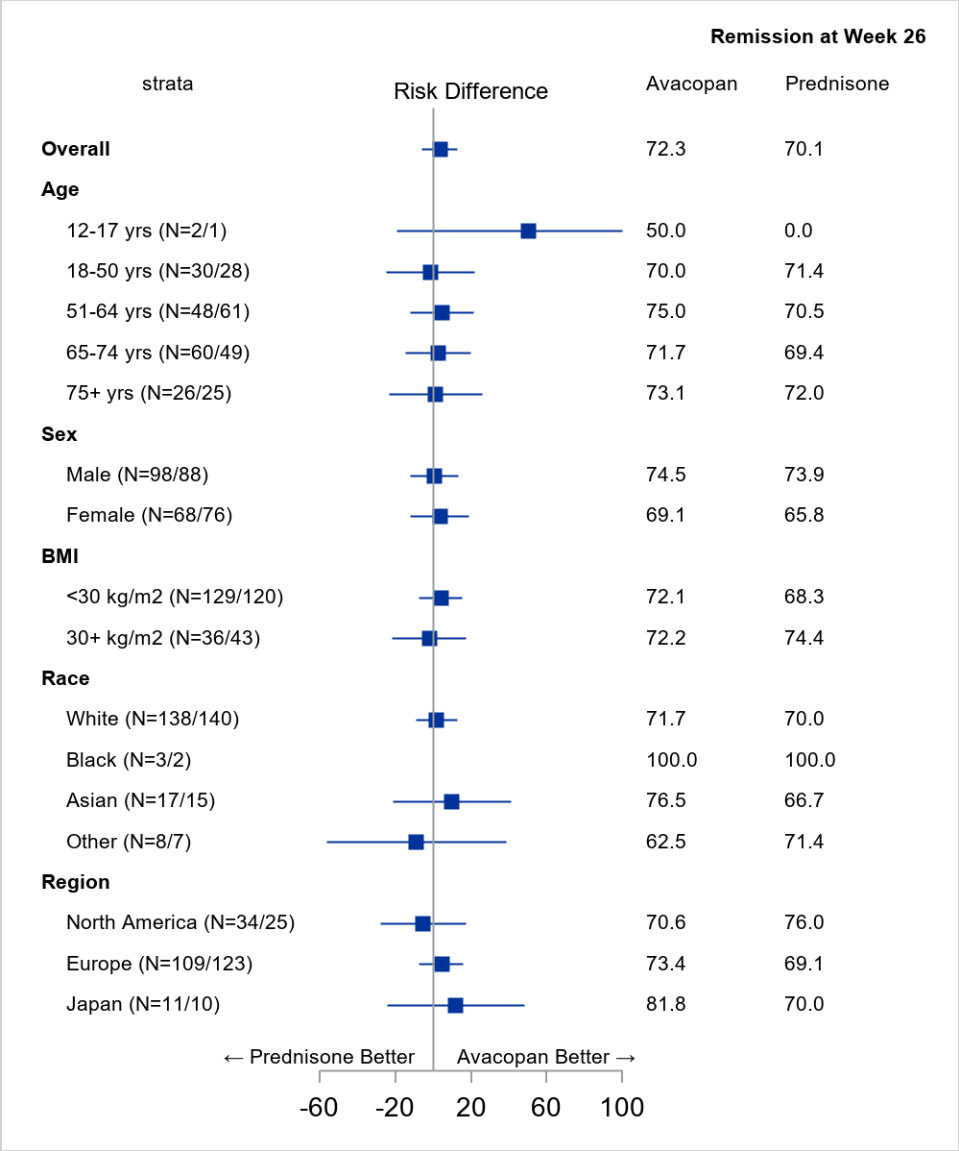
Few patients required dialysis during the study, balanced by treatment arms. Overall, 4 patients in the prednisone group required dialysis and 3 patients in the avacopan arm required dialysis.

Findings in Special/Subgroup Populations

Results from subgroup analyses by demographics were consistent with findings in the overall population (i.e., remission rates in the two arms are similar at Week 26 and greater in the

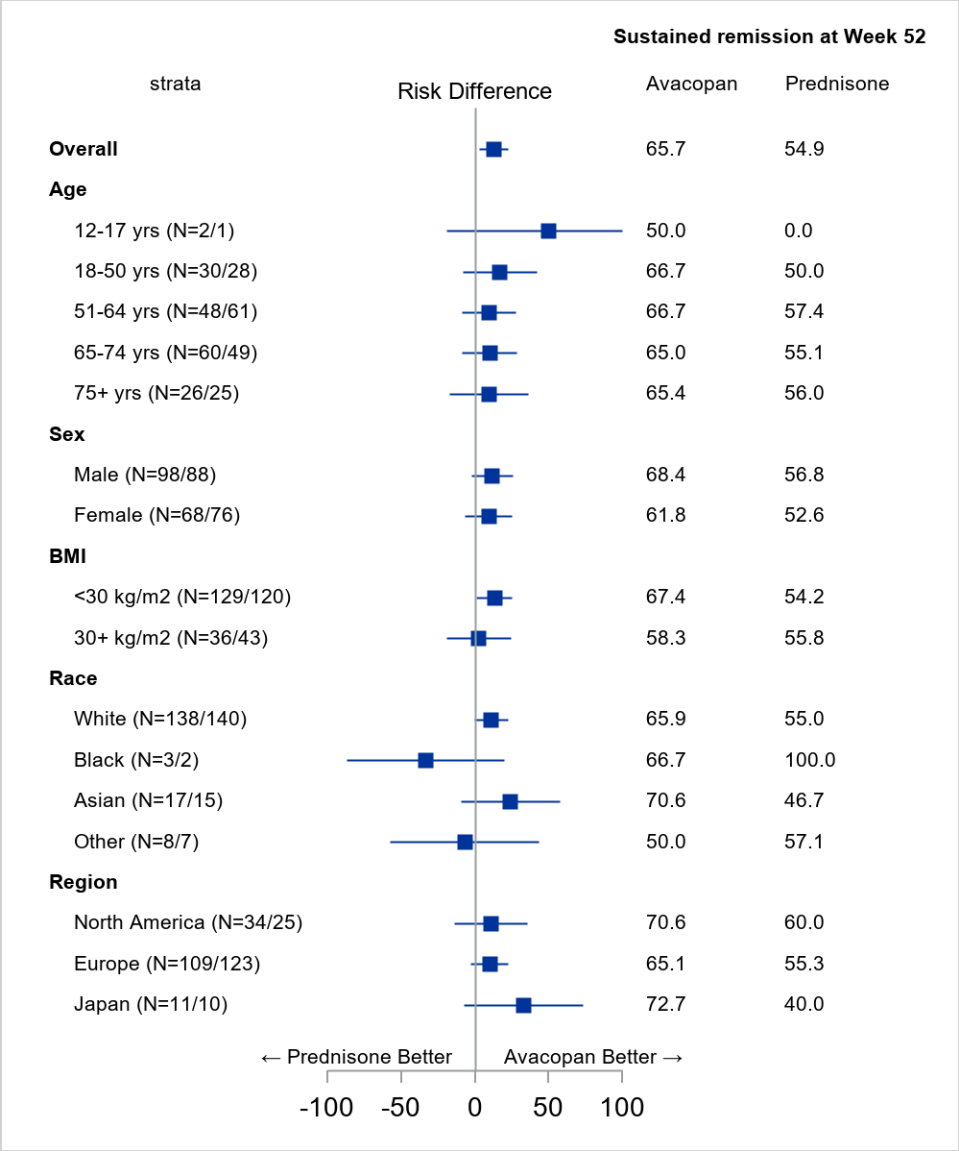
avacopan arm at Week 52), based on the primary endpoints comparing patients randomized to avacopan vs prednisone (Figure 16 and Figure 17). The age subgroup of "12-17 years" and the race subgroup of "Black/African American" could not be reliably assessed due to an extremely limited sample sizes. Of the 3 adolescent patients (n=1 in the prednisone group and n=2 in the avacopan group), only 1 patient stayed on study drug (avacopan) through the end of the study.

Figure 16. Remission at Week 26 by Demographic Subgroup



Source: Statistical reviewer.
Point estimate and 95% confidence interval using normal approximation.
The notation N = XXX/YYY indicates the sample size for avacopan and prednisone, respectively.
Abbreviations: BMI, body mass index.

Figure 17. Sustained Remission at Week 52 by Demographic Subgroup

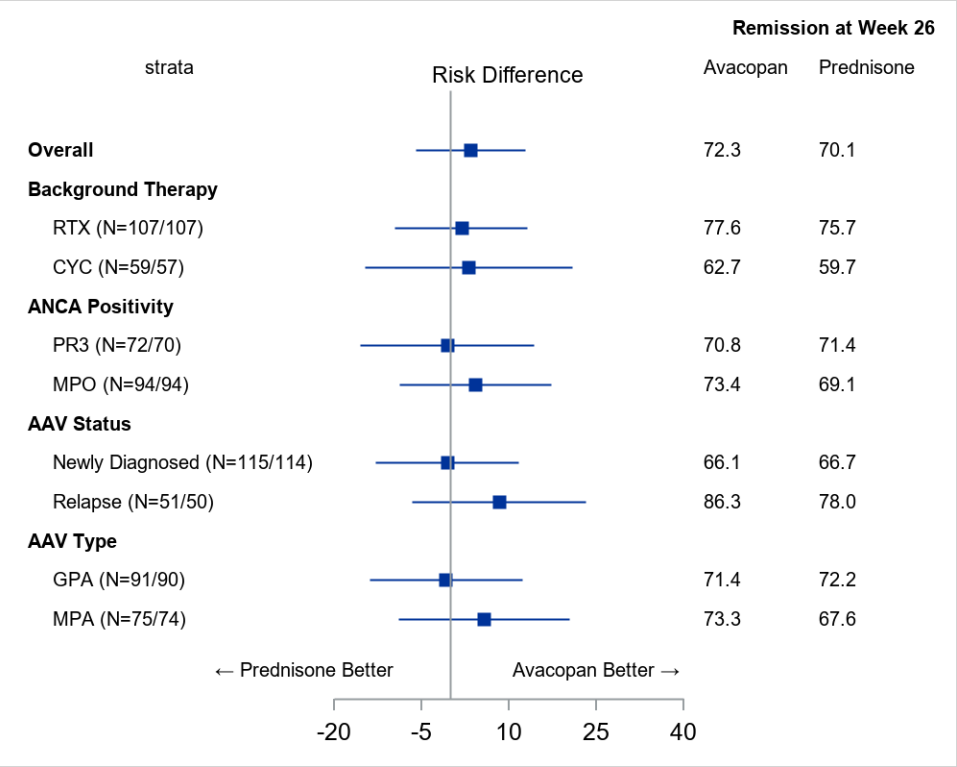


Source: Statistical reviewer.
Point estimate and 95% confidence interval using normal approximation.
The notation N = XXX/YYY indicates the sample size for avacopan and prednisone, respectively.
Abbreviations: BMI, body mass index.

Results from subgroup analyses by randomization strata or disease-related characteristics at baseline are shown in Figure 18 and Figure 19.

Subgroup analyses for the primary endpoint of remission at Week 26 were generally consistent with findings in the overall population, comparing patients randomized to avacopan vs prednisone, as presented in Figure 18.

Figure 18. Remission at Week 26 by Randomization Strata or Baseline Characteristics



Source: Statistical reviewer.
Point estimate and 95% confidence interval using normal approximation.
The notation N = XXX/YYY indicates the sample size for avacopan and prednisone, respectively. Subgroup findings should be interpreted with caution due to small sample sizes and overlapping subgroups.
Abbreviations: AAV, ANCA-associated vasculitis; ANCA, anti-neutrophilic cytoplasmic antibody; CYC, cyclophosphamide; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase-3; RTX, rituximab.

At Week 52 (Figure 19), multiple subgroups (RTX induction therapy, MPO positivity, baseline relapsing disease, and underlying MPA) appeared to have larger magnitude of treatment effect.

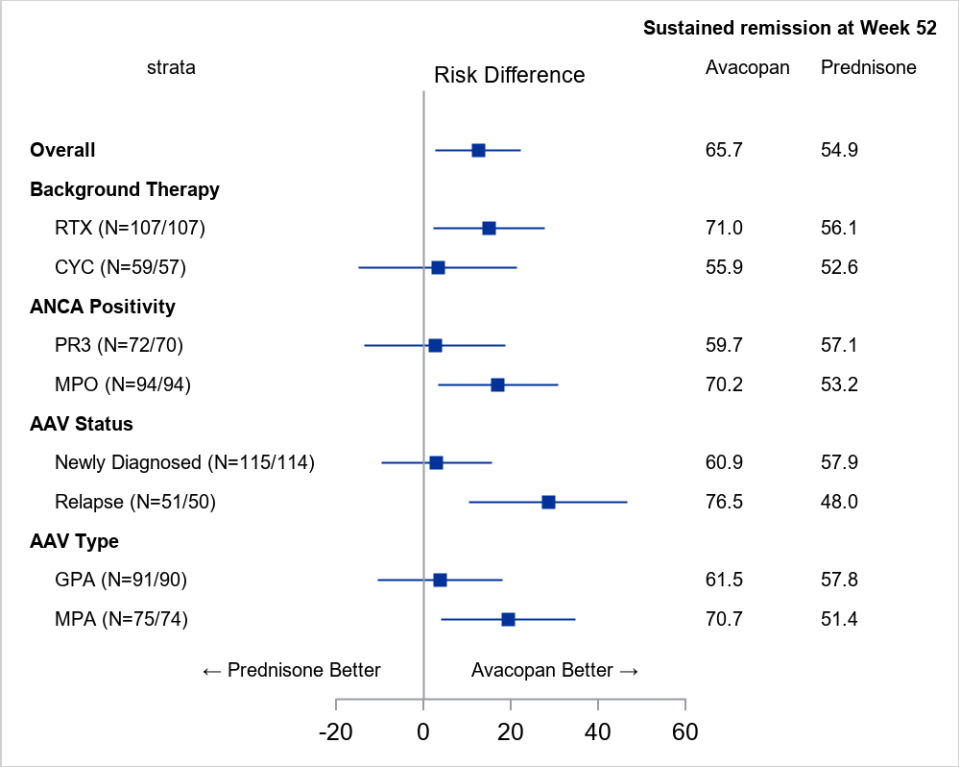
The larger treatment effect in patients who are MPO positive and those with MPA may be expected based on clinical experience in these populations. PR3-positivity and GPA are associated with increased risk relapse, treatment failure, and more organ involvement (Hilhorst et al. 2015; Geetha and Jefferson 2020; Wallace and Miloslavsky 2020).

A larger treatment effect was also observed in the subgroup of patients who received background induction therapy with RTX, compared to those who received CYC. The proportion of patients who received RTX induction and achieved sustained remission at Week 52 was 71.0% in the avacopan arm vs. 56.1% in the prednisone arm. Responses were similar in patients who received CYC induction, 55.9% in the avacopan arm and 52.6% in the prednisone arm. In this study, the RTX subgroup did not receive maintenance therapy between Weeks 26 and 52.

Induction treatment was selected based on Investigator discretion, and the patients were not randomized to background therapy. Acknowledging the limitations of subgroup analyses, these findings suggest the possibility that the observed treatment effect of avacopan may not be consistent across standard-of-care maintenance therapy.

The baseline disease characteristic that seemed to have the greatest influence on treatment effect was relapsing disease. The proportion of patients who achieved sustained remission in patients with relapsing disease was 76.5% in the avacopan arm compared to 48% in the prednisone arm. However, 89 out of 101 relapsing patients received RTX, posing the same limitations discussed in the previous paragraph. In addition, for newly diagnosed disease, responses were similar between the two treatment arms, 60.9% in the avacopan arm and 57.9% in the prednisone arm.

Figure 19. Sustained Remission at Week 52 by Randomization Strata or Baseline Characteristics



Source: Statistical reviewer.
Point estimate and 95% confidence interval using normal approximation.
The notation N = XXX/YYY indicates the sample size for avacopan and prednisone, respectively. Subgroup findings should be interpreted with caution due to small sample sizes and overlapping subgroups. Abbreviations: AAV, ANCA-associated vasculitis; ANCA, anti-neutrophilic cytoplasmic ant body; CYC, cyclophosphamide; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase-3; RTX, rituximab.

Although these subgroup analyses were pre-specified, the results should be interpreted with caution, as there are several limitations. Due to the large number of evaluated subgroups,

subgroups are overlapping, and the probability of accidental findings could be large. The analyses are exploratory and are not controlled for multiplicity. Furthermore, given the small sample sizes for subgroups, the estimates of treatment effect may not have sufficient precision.

Durability of Response

AAV is a chronic disease with a relapsing and remitting course, and durability of response is an important goal of treatment. The Applicant's primary endpoint of sustained remission at Week 52 assessed a sustained response of BVAS remission from Week 26 to Week 52 without relapse between Weeks 26 and 52, as well as lack of steroid use in the 4 weeks prior to assessment. This endpoint supports the durability of response.

Persistence of Effect

The Applicant continued to follow the patients in Study CL010_168 for 8 weeks (Weeks 52 to 60) after treatment discontinuation. During this time, the Applicant made several efficacy assessments. Importantly, the treatment difference seen in eGFR was lost after discontinuation of study treatment (discussed above). The Applicant notes that there were relapses and worsening of BVAS reported during this follow-up period, and they were generally similar in both treatment arms.

- Relapse (determined by AC): 6 patients in avacopan arm (3.8%) vs. 7 patients in prednisone arm (4.5%)
- Relapse (determined by Investigator): 6 patients in the avacopan arm (3.8%) vs. 10 patients in the prednisone arm (6.4%)
- Worsening in BVAS (determined by AC): 9 patients in the avacopan arm (5.7%) vs. 12 patients in the prednisone arm (7.6%)

The evaluation of persistence of effect after study treatment discontinuation is limited, but the proportion of patients with relapse or worsening in BVAS in the 8 weeks after treatment discontinuation was numerically lower in the avacopan arm.

8.1.2. Study CL002_168

Trial Design

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

57 as background therapy. In step 3, background therapy could be either CYC (same regimen as steps 1 and 2) or rituximab 375 mg/m^2 on days 1, 8, 15, and 22.

In step 1, 12 patients were randomized in a 2:1 ratio to receive avacopan 30 mg BID orally plus low dose prednisone (20 mg daily) or placebo avacopan plus full dose prednisone (60 mg, also referred to as the "standard-of-care arm"). If step 1 was successful, step 2 would be initiated. In step 2, 14 patients were randomized in a 2:1 ratio to receive avacopan 30 mg BID plus placebo prednisone or the standard-of-care arm. If step 2 was successful, then step 3 would proceed. In step 3, 41 patients were randomized in a 1:1:1 ratio to three treatment arms: avacopan 30 mg BID plus low dose prednisone, avacopan 30 mg BID plus placebo prednisone, or full dose prednisone. In the treatment arms with a protocol-specified prednisone taper, the prednisone taper varied depending on the starting dose. For the standard of care arm, prednisone was tapered from 60 mg to no prednisone by Week 20. For the avacopan/low dose prednisone arm, prednisone was tapered from 20 mg to no prednisone by Week 14. The avacopan/no prednisone group had a placebo prednisone taper. The key efficacy endpoints were assessed at Week 12 followed by a 12-week follow-up period during which patients who received CYC were switched to azathioprine and patients who received RTX did not receive any additional treatment.

Key Inclusion/Exclusion Criteria

Patients were enrolled in the study if they were males or females (surgically sterile or post-menopausal) with a clinical diagnosis of GPA, MPA, or renal-limited vasculitis consistent with the Chapel-Hill consensus definition. Other key inclusion criteria included patients with new or relapsed AAV where treatment with CYC or RTX were required, positive ANCA antibodies (anti-PR3 or anti-MPO) at screening or prior documentation, and at least 1 major item or at least 3 non-major items or at least 2 renal items on BVAS. In the original protocol (prior to Amendment 3.0), all patients were required to have renal vasculitis based on renal biopsy performed within 4 weeks prior to screening OR have hematuria (≥30 RBCs/hpf or ≥2+ on dipstick) and proteinuria (UACR ≥0.5 g/g) compatible with nephritis. Exclusion criteria were significant for any major end-organ involvement (i.e., rapidly progressive glomerulonephritis, DAH, rapid-onset mononeuritis multiplex, or CNS involvement) or for any other multi-system autoimmune disease.

Dose Selection

Avacopan 30 mg twice daily was selected for this study. ChemoCentryx believed that this dose was supported by the phase 1 study CL001_168, which evaluated single doses from 1 to 100 mg and multiple doses of 1, 3, and 10 mg once daily as well as 30 and 50 mg twice daily. ChemoCentryx concluded that all of these doses were tolerated. Dose regimens ≥30 mg twice daily provided at least 95% C5aR coverage on blood neutrophils continuously throughout the

day, and, as described for the pivotal trial, ChemoCentryx believed that this level of C5aR coverage was most appropriate to achieve optimal pharmacology.

Concomitant Medications

Any medication that was not protocol-specified to treat AAV was prohibited over the treatment period. The allowed medications included avacopan, oral prednisone, IV CYC or RTX, or rescue glucocorticoids (IV/PO, described below). Prophylactic treatment for osteoporosis, gastroprotection, pneumocystis pneumonia (PCP), and anti-nausea medication was allowed.

Rescue glucocorticoids were used in the following circumstances:

- Successive deterioration of eGFR over 3 days suggesting that, in the view of the Principal Investigator, if no extra intervention was taken, the renal function would continue to deteriorate
- Worsening of renal function (eGFR decrease >10 mL/min from baseline) either during the 84-day treatment period or during the 84-day follow-up period
- Persistence or new occurrence of a major non-renal item per BVAS, e.g., gangrene, sudden vision loss, retinal changes, sensorineural hearing loss, massive hemoptysis/alveolar hemorrhage, respiratory failure, cardiomyopathy, ischemic abdominal pain indicative of mesenteric ischemia, or nervous system disease
- If the study site's physician deems it to be in the best interest of the patient

Rescue glucocorticoids included IV methylprednisolone 500 mg once daily for 3 days or high-dose oral prednisone (e.g., prednisone 200 mg) with appropriate tapering. Patients were deemed a treatment failure if they needed rescue glucocorticoids, and study medication was discontinued.

Study Endpoints

For efficacy analyses, the sponsor pooled the data from all 3 steps, resulting in 3 groups:

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

The primary endpoint for Study CL002_168 was the proportion of 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.

Multiple other efficacy endpoints were also assessed.

1. In patients with hematuria and albuminuria at baseline, the proportion of patients achieving renal response at Day 85. Renal response was defined as an improvement in the following parameters:
    - An increase from baseline to Day 85 in eGFR (utilizing the Modification of Diet in Renal Disease serum creatinine equation)
    - A decrease from baseline to Day 85 in hematuria (central laboratory microscopic count of urinary RBCs)
    - A decrease from baseline to Day 85 in albuminuria (first morning UACR)
2. Proportion of patients achieving disease remission at Day 85, defined as BVAS of 0 or 1 plus no worsening in eGFR and urinary RBC count <10/hpf
3. % change from baseline to Day 85 in BVAS
4. Change and % change from baseline to Day 85 in eGFR
5. In patients with baseline hematuria >5 RBCs/hpf, the proportion of patients and time to first achieving urinary RBC count ≤5 RBCs/hpf at any time during 84-day treatment period
6. In patients with baseline hematuria ≥30 RBCs/hpf, the proportion of patients and time to first achieving urinary RBC count <30 RBCs/hpf at any time during the 84-day treatment period
7. In patients with hematuria at baseline, the % change from baseline to Day 85 in urinary RBC count
8. In patients with albuminuria at baseline, the % change from baseline to Day 85 in UACR
9. % change from baseline to Day 85 in urinary MCP-1: creatinine ratio
10. Proportion of patients requiring rescue IV or oral glucocorticoid treatment
11. Change from baseline to Day 85 in VDI
12. Change from baseline to Day 85 in hr-QoL, as measured by SF-36 v2 and EQ-5D-5L

The Applicant also performed the following assessments.

- Total cumulative study-supplied prednisone dose and duration of dosing during the 84-day treatment period
- Total cumulative systemic glucocorticoid dose (any use) and duration of dosing during the 84-day treatment period
- Total cumulative CYC or RTX dose and duration during the 84-day treatment period
- % change from baseline in hsCRP
- % change from baseline in ANCA (anti-PR3 and anti-MPO) at Day 85
- Proportion of patients becoming ANCA negative at Day 85
- Change and % change from baseline in plasma and urine biomarkers

Protocol Amendments

The original protocol was dated March 31, 2011; subsequently, there were 4 protocol amendments. Additionally, there were country-specific amendments for Sweden, the Netherlands, and the United Kingdom. Briefly, the 4 major amendments can be summarized as follows: Amendment 1.0 (April 23, 2012): Changes included but were not limited to local laboratory results within 72 hours of Screening being sufficient, clarifications on inclusion/exclusion criteria based on Investigator's questions, immunosuppressive medications allowed during 12-week follow-up period, and a plan for combining data of all patients in the standard-of-care arm for all steps.

Amendment 2 (March 14, 2013): Changes included but were not limited to adjusting the upper age limit of study participants to 80 years and the lower limit of eGFR to 25 mL/min/1.73 m^2, oral glucocorticoids allowed for rescue, and plan for combining data from steps 1 and 2.

Amendment 3 (May 30, 2014): Changes included but were not limited to modifications to the inclusion/exclusion criteria to allow for patients with AAV with or without renal disease as well as baseline labs (e.g., eGFR down to 20 mL/min/1.73 m^2, hemoglobin ≥9 g/dL, liver enzymes no more 3x ULN), addition of rituximab as an option for background therapy, immunosuppressive therapy after day 99 (azathioprine for patients who received cyclophosphamide and no medication for patients who received rituximab), addition of SF-36 v2 and EQ-5D-5L as hr-QoL measures, and additional safety assessments with adverse events associated with glucocorticoid use.

Amendment 4 (September 18, 2018): Changes included but were not limited to changes to the statistical methodology and additional clarification regarding stopping criteria for WBC and neutrophil counts.

8.1.2.1. Study Results

Compliance With Good Clinical Practices

The study was conducted in accordance with the Declaration of Helsinki and with all applicable laws and regulations of the locale and country where the study was conducted and in compliance with Good Clinical Practice Guidelines.

Financial Disclosure

Study CL002_168 was not considered a covered clinical study. Therefore, a financial disclosure review was not conducted.

Patient Disposition

A total of 67 patients were randomized into the treatment arms as shown in Table 38, which also presents the overall patient disposition in Study CL002_168. The Safety Population included all patients who were randomized and received at least 1 dose of study medication. The Safety Population is consistent with all who were randomized. The ITT population included all patients who were randomized and received at least 1 dose of study medication and had at least 1 post-baseline, on-treatment BVAS assessment. Of the 67 patients who randomized, 63 patients were included in the ITT population, as shown in Table 38.

Table 38. Patient Disposition in Study CL002_168

Patient Disposition	PBO + CYC/RTX + High Dose Prednisone (SOC)	Avacopan + CYC/RTX + Low Dose Prednisone	Avacopan + CYC/RTX + No Prednisone
Randomized, N	23	22	22
Safety population	23	22	22
Intent-to-treat (ITT) population	20 (87.0)	22 (100.0)	21 (95.5)
Completed	18 (78.3)	19 (86.4)	18 (81.8)
Early withdrawal (total)	5 (21.7)	3 (13.6)	4 (18.2)
Early withdrawal on/before Day 85	2 (8.7)	0	2 (9.1)
Early withdrawal after Day 85	3 (13.0)	3 (13.6)	2 (9.1)

Source: CL002_168 CSR
% are based on total number of subjects randomized
Abbreviations: CYC, cyclophosphamide; PBO, placebo; RTX, rituximab; SOC, standard of care.

A total of 4 randomized patients withdrew from the study before Day 85. Two patients were in the avacopan + no prednisone arm and withdrew due to physician decision and adverse event. The other 2 patients were in the standard-of-care arm and withdrew consent.

An additional 8 patients withdrew during the follow-up period. These included 3 patients in the avacopan + low dose prednisone arm, 2 patients in avacopan + no prednisone arm, and 3 patients in the standard-of-care arm. The most common cause for withdrawal was adverse event (n=2 in the avacopan + low-dose prednisone arm, n=1 in the avacopan + no prednisone arm, and n=2 in the standard-of-care arm).

Table of Demographic Characteristics

Table 39 presents the baseline demographics of patients randomized in the study. The baseline demographics were comparable across treatment arms. More patients were male (70.1% vs. 29.9%), and the mean age was 57.9 years. All patients were White. As previously noted, this study was conducted entirely in Europe and likely reflects the racial characterization of this population.

Table 39. Baseline Demographics of Patient Population in Study CL002_168

Demographic Parameter	PBO + CYC/RTX + High Dose Prednisone (SOC) N=23	Avacopan + CYC/RTX + Low Dose Prednisone N=22	Avacopan + CYC/RTX + No Prednisone N=22
Age at Screening, mean ± SD (years)	59.1 (14.0)	57.0 (14.2)	57.4 (14.0)
Gender			
Male, n (%)	17 (73.9)	14 (63.6)	16 (72.7)
Female, n (%)	6 (26.1)	8 (36.4)	6 (27.3)
Race			
White, n (%)	23 (100)	22 (100)	22 (100)
BMI (kg/m2), mean ± SD	27.3 (7.1)	24.9 (4.1)	26.5 (4.7)

Source: CL002_168 CSR
% are based on total number of patients randomized
Abbreviations: BMI, body mass index; CYC, cyclophosphamide; PBO, placebo; RTX, rituximab; SD, standard deviation; SOC, standard of care.

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant drugs)

Significant baseline disease characteristics are presented in Table 40 and were evenly distributed across treatment arms.

The majority of patient had newly diagnosed disease (n=49 [73.1%]) in the entire study. Slightly more patients had GPA (n=33 [49.3%]) compared to MPA (n=28 [41.8%]), and a smaller number had renal-limited disease (n=5 [7.5%]). As Steps 1 and 2 only allowed induction with CYC, the majority of patients received CYC as background therapy (n=54 [80.6%]). The mean BVAS for all patients was 13.7 and was similar across treatment arms. The extent of baseline disease is unclear, particularly in terms of baseline renal manifestations, as the Applicant utilized different criteria to capture active renal vasculitis. Steps 1 and 2 required evidence of glomerulonephritis based on renal biopsy or baseline hematuria/albuminuria, whereas, in Step 3, renal disease at baseline was defined based on the BVAS renal criterion. Using the total number of patients for whom “renal response” was assessed, the Applicant’s assessment of baseline renal vasculitis includes 56 patients (n=36 in both avacopan arms and n=20 in the standard-of-care arm).

Table 40. Baseline Disease Characteristics in Study CL002_168

Parameter	PBO + CYC/RTX + High Dose Prednisone (SOC)	Avacopan + CYC/RTX + Low Dose Prednisone	Avacopan + CYC/RTX + No Prednisone
Randomized, N	23	22	22
Baseline Disease Characteristics of Randomized Population			
Duration of ANCA disease in months, median (range)	0 (0-162)	0 (0-61)	1 (0-108)
Newly Diagnosed ANCA disease, n (%)	18 (78)	15 (68)	16(73)
Relapsing ANCA disease, n (%)	5 (22)	7 (32)	6 (27)
BVAS, mean ± SD	13.2±5.8	14.3±6.0	13.8±6.4
Type of AAV, n (%)			
GPA, n (%)	10 (43.5)	11 (50.0)	12 (54.5)
MPA, n (%)	10 (43.5)	9 (40.9)	9 (40.9)
Renal-limited vasculitis, n (%)	2 (8.7)	2 (9.1)	1 (4.5)
Unknown	1 (4.3)	0	0
Background treatment of ITT population			
CYC, n (%)	17 (85)	17 (77)	16 (76)
RTX, n (%)	3 (15)	5 (23)	5 (24)

Source: CL002_168 CSR
[1] Intent-to-treat population is defined as all patients randomized who received at least one dose of drug.
Abbreviations: AAV, ANCA-associated vasculitis; ANCA, anti-neutrophilic cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; CI, confidence interval; CYC, cyclophosphamide; GPA, granulomatosis with polyangiitis; ITT, intent-to-treat; MPA, microscopic polyangiitis; PBO, placebo; RTX, rituximab; SOC, standard of care; SD, standard deviation.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was high for avacopan or its placebo across treatment arms, ranging from 83.7% to 108.1%. Six patients were noted to have lower compliance to prednisone or its placebo (4.4% to 73.8%), but the other patients had good compliance ranging from 80.7% to 123.7% across all 3 treatment arms.

The number of patients requiring concomitant immunosuppressive therapy in addition to what was allowed in the protocol was generally similar across treatment arms. Use of azathioprine (n=7 [31.8%] in the avacopan + low dose prednisone arm; n=6 [27.3%] in the avacopan + high dose prednisone arm; n=7 [30.4%] in the standard-of-care arm) and methotrexate (n=1 [4.3%] in the standard-of-care arm) was reported.

Non-study supplied glucocorticoids were administered in all treatment arms, 43.5% of patients in the standard-of-care arm, 72.7% in the avacopan + low dose prednisone arm, and 50.0% of patients in the avacopan + no prednisone arm. Rescue glucocorticoid use is reviewed in more detail as a secondary endpoint below.

Efficacy Results

Table 41 presents the primary endpoint, BVAS 50% response, in Study CL002_168. Additionally, two of the secondary endpoints most comparable to the primary endpoint of the pivotal trial are included in this table, BVAS remission and BVAS 0.

Table 41. BVAS 50% Response and Other Efficacy Assessments at Week 12 in Study CL002_168

Parameter	PBO + CYC/RTX + High Dose Prednisone (SOC)	Avacopan + CYC/RTX + Low Dose Prednisone	Avacopan + CYC/RTX + No Prednisone
Randomized, N	23	22	22
Intent-to-Treat (ITT) Population[1], N	20	22	21
Efficacy Assessments in ITT Population			
BVAS 50% Response at Week 12, n (%)	14 (70.0)	19 (86.4)	17 (81.0)
Difference in percentage vs. control	--	16.4%	11.0%
Two-sided 90% CI for difference, avacopan minus control	--	-4.3%, 37.1%	-11.0%, 32.9%
BVAS remission at Week 12, n (%)	7 (35.0)	6 (27.3)	4 (19.0)
Difference in percentage vs. control	--	-7.7	-16.0
Two-sided 90% CI for difference, avacopan minus control	--	-31.2, 15.8	-38.5, 6.6
BVAS 0 at Week 12, n (%)	8 (40.0)	10 (45.5)	7 (33.3)
Difference in percentage vs. control	--	5.5	-6.7
Two-sided 90% CI for difference, avacopan minus control	--	-19.6, 30.5	-31.4, 18.1

Source: CL002_168 CSR
[1] Intent-to-treat population is defined as all patients randomized who received at least one dose of drug.
Abbreviations: AAV, ANCA-associated vasculitis; ANCA, anti-neutrophilic cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; CI, confidence interval; CYC, cyclophosphamide; GPA, granulomatosis with polyangiitis; ITT, intent-to-treat; MPA, microscopic polyangiitis; PBO, placebo; RTX, rituximab; SOC, standard of care; SD, standard deviation.

The proportion of patients who achieved BVAS 50% response was greater in the treatment arms with avacopan and concomitant glucocorticoids. The highest response was noted in the avacopan plus low dose prednisone background therapy (86.4%) compared to 81.0% in the avacopan plus no prednisone arm and 70.0% in the standard-of-care arm. However, the Applicant's definition of disease response has unknown clinical significance. Whether a 50% improvement, as compared to complete resolution of BVAS to 0, is clinically meaningful is unknown. Further, it is unknown if treatment effects assessed at Week 12 in AAV are predictive of long-term clinical outcomes.

BVAS remission at Week 12 was a secondary endpoint. BVAS remission was defined as a BVAS score of zero or one plus no worsening in eGFR and urinary RBC count <10/hpf. Importantly, there are limitations to the remission assessment in this study. Because of the protocol-specified prednisone tapering schedule, patients may be treated with concomitant prednisone (10 mg) at Week 12, depending on the treatment arm and patient weight. Thus, it is difficult to

isolate the treatment effect of avacopan with that of the different concomitant glucocorticoid regimens used at the time of assessment. However, despite these limitations, more patients on standard of care (35.0%) achieved BVAS remission compared to patients on avacopan (27.3% in patients on low dose prednisone and 19.0% in patients on no prednisone).

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

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

Data Quality and Integrity

Investigators' meetings were held on 2 occasions (September 9, 2011, and May 30, 2014) to prepare for the study and to standardize performance. Clinical research associates conducted periodic on-site visits to ensure adherence to the protocol, review electronic Case Report Forms (eCRFs) and site source documents for accuracy and completeness of information, examine site records for documentation of study medication receipt and administration, observe the progress of the study, and review Investigator files for required documents. All Investigators and/or sub-investigators who performed the BVAS and VDI assessments were trained in proper completion of these instruments prior to enrolling patients at their sites. The eCRFs were created by (b) (4) and data were frequently reviewed with computer generated checks, manual edit checks, etc. Adverse events, medical/surgical history, physical examination data, and concomitant medications were coded by a coding specialist and reviewed by a medical monitor prior to the study being unblinded. Adverse events and medical history were coded to a system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) version 14.0. Concomitant medications were coded to Anatomical Therapeutic Chemical class and preferred term using the World Health Organization (WHO) Dictionary (June 2011).

There are no issues concerning the submitted data quality or integrity that raise questions about the purported efficacy results.

Efficacy Results – Secondary and Other Relevant Endpoints

Not all the efficacy endpoints are discussed in this review. A summary of the renal assessments, health-related QoL measures, vasculitis disease index (VDI), and non-study supplied glucocorticoid use are reviewed.

Renal Assessments

Renal Response

Renal response was defined as an improvement in eGFR, hematuria, and albuminuria, without any specific parameters to define what improvement is. Numerically more patients achieved renal response in the avacopan + low dose prednisone arm (n=10 [55.6%]) compared to the avacopan + no prednisone arm (n=6 [33.3%]) and the standard-of-care arm (n=8 [40.0%]). Differences between groups were due to small numbers of patients.

eGFR

At the end of the 12-week treatment period, the mean increase in eGFR from baseline was greatest in the avacopan + low dose prednisone arm (6.0 mL/min/1.73 m^2 [19.9%]), compared to the avacopan + no prednisone arm (0.8 mL/min/1.73 m^2 [0.9%]) and the standard-of care arm (5.6 mL/min/1.73 m^2 [15.4%]).

Hematuria

The mean % change from baseline in urinary RBC count (as measured by geometric mean ratio of visit over baseline) was greatest in the standard-of-care arm (0.08 [92.0%]), compared to avacopan + low dose prednisone (0.17 [83.0%]) and avacopan + no prednisone (0.15 [85.0%]).

Albuminuria (UACR)

The first UACR decreased from baseline in all 3 treatment arms. The mean decrease from baseline was greatest in the avacopan + low dose prednisone arm (0.44 [56.0%]), compared to avacopan + no prednisone arm (0.57 [43.0%]) and standard-of-care arm (0.79 [21.0%]).

Overall, renal response as well as change in eGFR and in albuminuria were greatest in the avacopan + low dose prednisone group, while change in hematuria from baseline was greatest in the standard-of-care group. As noted, the small sample size limits conclusions regarding an effect on renal assessments, but there was no consistent benefit of avacopan + no prednisone over the other treatment arms observed.

Rescue Glucocorticoids

Three patients received rescue IV or oral glucocorticoids during the 84-day treatment period. This included 2 patients in the avacopan + no prednisone arm and 1 patient in the standard-of-care arm. Some patients required lower doses of non-study supplied glucocorticoids (i.e., not "rescue" doses): 6 patients in avacopan + low-dose prednisone arm, 4 patients in the avacopan + no prednisone arm, 3 patients in the standard-of-care arm.

Vasculitis Damage Index (VDI)

The mean increase from baseline in VDI was lower in the avacopan arms compared to that in the standard-of-care arm. The mean increase was 0.3 in the avacopan + low dose prednisone arm, 0.2 in the avacopan + no prednisone arm, and 0.7 in the standard-of-care arm. Overall, change was small in each group. Additionally, the study was 12 weeks, and VDI is a measure of persistent disease activity (i.e., present for more than 3 months). Thus, its clinical meaningfulness in this short study is limited.

SF-36 and EQ-5D-5L

For hr-QoL measures, the Applicant evaluated both SF-36 and EQ-5D-5L in Step 3. For SF-36, the Physical Component Summary score increased in all 3 treatment arms, greatest in the avacopan + low-dose prednisone arm (mean increase from baseline through Day 85 was 6.7 in avacopan + low-dose prednisone arm, 4.8 in the avacopan + no prednisone arm, 5.4 in the standard-of-care arm). The Mental Component Summary score increased in the 2 avacopan arms (greatest in the avacopan + low-dose prednisone arm) but not in the standard-of-care arm (mean change from baseline through Day 85 was 11.8 in avacopan + low-dose prednisone arm, 2.8 in the avacopan + no prednisone arm, -0.8 in the standard-of-care arm). The mean EQ-5D-5L VAS score also increased in both avacopan arms but decreased in the standard-of-care arm. The mean EQ-5D-5L health scale index only showed a minimal increase from baseline in the avacopan + low dose prednisone arm. Thus, there did appear to be greater improvement in the hr-QoL measures in the avacopan arms. However, as previously discussed under Study CL010_168, there is insufficient evidence of content validity to ensure adequate interpretation of hr-QoL in the proposed context.

Durability of Response

The treatment duration of Study CL002_168 was 12 weeks, and the efficacy endpoints were primarily assessed at this time point. Over the 12-week period, there was continued improvement in mean BVAS over time in all treatment arms with greater improvement in the avacopan arms, -79.1% in the avacopan + low dose prednisone arm, -73.0% in the avacopan + no prednisone arm, and -56.5% in the standard-of-care arm. This assessment is different from that of BVAS 50% response or BVAS remission; thus, it is not the primary endpoint. A post-hoc

analysis evaluated BVAS of 0 at Day 29 which was sustained at Day 85. As noted above, this endpoint would be more comparable to that studied in the pivotal trial. This analysis showed that sustained remission (over 12 weeks) was achieved in a greater number of patients in the avacopan arms, specifically, 6 patients (28.6%) in the avacopan + no prednisone arm and 3 patients (13.6%) in the avacopan + low-dose prednisone arm compared to 1 patient (5.0%) in the standard-of-care arm. This post-hoc analysis in a very small sample size has many limitations to interpretation.

Persistence of Effect

At the end of the 12-week follow-up portion of the study (Day 169, when avacopan was discontinued), the proportion of patients with BVAS 50% response had decreased in the avacopan arms but had increased in the standard-of-care arm. On Day 169, the proportion of patients with BVAS 50% responses was similar across all three treatment arms (17 patients [77.3%] in the avacopan + low dose prednisone arm, 15 patients [71.4%] in the avacopan + no prednisone arm, 16 patients [80.0%] in the standard-of-care arm). Thus, there appeared to be a loss in BVAS 50% response in the avacopan arms but not in the standard-of-care arm. Evaluation of BVAS remission was also conducted at Day 169 In addition, the BVAS mean percent change from baseline was greater on Day 169 compared to Day 85, but there was no treatment difference across treatment arms at the end of the follow-up period (Day 169), -86.5% in the avacopan + low dose prednisone arm, -84.6% in the avacopan + no prednisone arm, and -83.5% standard-of-care prednisone arm. Evaluation of the more pertinent efficacy endpoints of BVAS remission and BVAS of 0 showed similar results on Days 85 and 169. The proportion of patients with BVAS remission on Day 169 was 23.8% in the avacopan + no prednisone arm (19.0% on Day 85), 45.5% in the avacopan + low-dose prednisone arm (27.3% on Day 85), and 50.0% in the standard-of-care arm (35.0% on Day 85). The proportion of patients with BVAS of 0 on Day 169 was 52.4% in the avacopan + no prednisone arm (33.3% on Day 85), 68.2% in the avacopan + low-dose prednisone arm (45.5% on Day 85), and 70.0% in the standard-of-care arm (40.0% on Day 85).

In the follow-up portion of the study, four patients (3 patients in the avacopan + low-dose prednisone group and 1 patient in the avacopan + no prednisone arm) received rescue IV or oral glucocorticoids.

In conclusion, persistence of effect after discontinuation of avacopan is difficult to assess in this study in a small number of patients. BVAS Remission and BVAS of 0 appeared to be sustained in the avacopan arms and standard-of-care arms, although only patients in the avacopan arms required rescue glucocorticoids.

Efficacy Results – Secondary or Exploratory Clinical Outcome Assessment (PRO) Endpoints

Health-related quality of life measures are reviewed above.

8.1.3. Study CL003_168

Trial Design

CL003_168 was a randomized, double-blind, placebo-controlled, dose assessment study to assess the safety, tolerability, and efficacy of avacopan in patients with new or relapsing AAV on background standard of care cyclophosphamide or rituximab treatment plus prednisone. The study design for CL003_168 is described in Table 15. Forty-two patients were stratified based on (1) newly diagnosed or relapsing AAV, (2) MPO or PR3 ANCA positivity, and (3) cyclophosphamide or rituximab standard of care treatment. These patients were then randomized 1:1:1 to the following 3 treatment arms:

- Group A: Avacopan 10 mg twice daily plus CYC/RTX plus prednisone
- Group B: Avacopan 30 mg twice daily plus CYC/RTX plus prednisone
- Group C: Placebo twice daily plus CYC/RTX plus prednisone

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

Key Inclusion/Exclusion Criteria

Patients were enrolled in the study if they were patients with a clinical diagnosis of GPA, MPA, or renal-limited vasculitis consistent with the Chapel-Hill consensus definition. Women of childbearing potential or men with partners of childbearing potential could be enrolled if they used adequate contraception. Other key inclusion criteria/exclusion criteria were similar to that in the most updated protocol for CL002_168. These included patients with new or relapsed AAV where treatment with CYC or RTX were required, positive ANCA antibodies (p-ANCA or c-ANCA) at screening or positive, and at least 1 major item or at least 3 non-major items or at least 2 renal items on BVAS. Exclusion criteria were significant for any major end-organ involvement (i.e., rapidly progressive glomerulonephritis, DAH, rapid-onset mononeuritis multiplex, or CNS involvement) or for any other multi-system autoimmune disease.

Dose Selection

Avacopan 10 mg twice daily and 30 mg twice daily were selected for this study. Avacopan 30 mg BID was the dose tested in Study CL002_168. As this was a dose-ranging study, the Applicant planned to evaluate safety and efficacy at another dose regimen. The Applicant

anticipated that avacopan at 10 mg BID and 30 mg BID should be well-tolerated based on Study CL002_168. Based on PK-PD modeling, this lower dose regimen provided less C5aR coverage in the circulation compared to the 30 mg BID regimen but could also improve efficacy.

Concomitant Medications

Study CL003_168 had the same rules for concomitant medications and rescue glucocorticoids as Study CL002_168. Any medication that was not protocol-specified to treat AAV was prohibited over the treatment period. The allowed medications included avacopan, oral prednisone, IV CYC or RTX, or rescue glucocorticoids (IV/PO, described below). Prophylactic treatment for osteoporosis, gastroprotection, PCP, and anti-nausea medication was allowed.

Rescue glucocorticoids were used in the following circumstances:

- Successive Deterioration of eGFR over 3 days suggesting that, in the view of the Principal Investigator, if no extra intervention was taken, the renal function would continue to deteriorate
- Worsening of renal function (eGFR decrease >10 mL/min from baseline) either during the 84-day treatment period or during the 84-day follow-up period
- Persistence or new occurrence of a major non-renal item per BVAS, e.g., gangrene, sudden vision loss, retinal changes, sensorineural hearing loss, massive hemoptysis/alveolar hemorrhage, respiratory failure, cardiomyopathy, ischemic abdominal pain indicative of mesenteric ischemia, or nervous system disease
- If the study site's physician deems it to be in the best interest of the patient

Rescue glucocorticoids included IV methylprednisolone 500 mg once daily for 3 days, followed by oral glucocorticoids per standard of care. Patients were deemed a treatment failure if they needed rescue glucocorticoids, and study medication was discontinued.

Study Endpoints

The primary efficacy endpoint was BVAS 50% response at Day 85. The definition of BVAS 50% response in Study CL003_168 was the same as the definition used in Study CL002_168.

Other efficacy endpoints were also the same as those assessed in Study CL002_168, as already described in Section 8.1.2. A notable difference is that disease remission was defined as BVAS of 0 without inclusion of a renal assessment in Study CL003_168.

Protocol Amendments

Study CL003_168 was the opening study for the IND, and the original protocol was dated May 31, 2014. Several amendments were made following Agency recommendations.

Amendment 1.0 (August 13, 2014)

Per Agency recommendations, all patients were required to receive PCP prophylaxis. Additionally, for rescue glucocorticoids, IV glucocorticoids would be used, instead of the high dose oral glucocorticoids (which is not a regimen used in the U.S.). The prednisone taper (in all arms) was standardized to start at 60 mg.

Amendment 2.0 (May 12, 2015)

Based on the Agency's pharm-tox review of the nonclinical studies, the Applicant added monitoring for lipase and amylase as well as CNS changes (e.g., assessment of speech, consciousness level, etc.). In addition, definition of SAEs was expanded to include severe infections requiring antibiotics. Modifications to the Canadian version of the protocol were also incorporated into the general protocol; these were mostly refinements to the inclusion/exclusion criteria.

Amendment 3.0 (August 19, 2015)

Based on recommendations from the DMC due to 2 cases of leukopenia/neutropenia in this study, more specific medication stopping criteria were provided for low WBC count.

Amendment 4.0 (February 19, 2016)

The statistical analysis of the primary endpoint was modified because of the small sample size. Additionally, the endpoint of early remission was added. The remission criterion removed hematuria, as not all patients had renal disease at baseline.

8.1.3.1. Study Results

Compliance With Good Clinical Practices

The study was conducted in accordance with the Declaration of Helsinki and with all applicable laws and regulations of the locale and country where the study was conducted and in compliance with Good Clinical Practice Guidelines.

Financial Disclosure

Study CL003_168 was not considered a covered clinical study. Therefore, a financial disclosure review was not conducted.

Patient Disposition

Forty-two patients with AAV were randomized as described below in Table 42. Forty patients completed the study. One patient in each of the avacopan arms discontinued the study before

the end of the 12-week treatment period due to an adverse event. There were no discontinuations in the follow-up period.

Table 42. Patient Disposition in Study CL003_168

Patient Disposition	PBO + CYC/RTX + Prednisone (SOC) n (%)	Avacopan 10 mg BID + CYC/RTX + Prednisone n (%)	Avacopan 30 mg BID + CYC/RTX + Prednisone n (%)
Randomized, N	13	13	16
Safety Population	13 (100)	13 (100)	16 (100)
Intent-to-Treat (ITT) Population	13 (100)	12 (92.3)	15 (93.8)
Completed	13 (100)	12 (92.3)	15 (93.8)
Early withdrawal (total)			
Early withdrawal on/before Day 85	0	1 (7.7)	1 (6.3)
Early withdrawal after Day 85	0	0	0

Source: CL003_168 CSR
% are based on total number of subjects randomized
Abbreviations: BID, twice daily; CYC, cyclophosphamide; PBO, placebo; RTX, rituximab; SOC, standard of care

Table of Demographic Characteristics

Table 43 presents the baseline demographics of patients enrolled in Study CL003_168. Demographics were similar across treatment arms. In the entire patient population, there were more females (54.8%) with a mean age of 57.7 years, and most patients were White (90.5%). The demographics in this study are more similar to that in the pivotal trial than the demographics in Study CL002_168 was to the pivotal trial.

Table 43. Baseline Demographics in Patient Population of CL003_168

Demographic Parameter	PBO + CYC/RTX + Prednisone (SOC)	Avacopan 10 mg BID + CYC/RTX + Prednisone	Avacopan 30 mg BID + CYC/RTX + Prednisone
Age at screening, mean ± SD (years)	58.5 (15.4)	60.0 (10.8)	55.3 (13.8)
Gender, n (%)			
Male	4 (30.8)	8 (61.5)	7 (43.8)
Female	9 (69.2)	5 (38.5)	9 (56.3)
Race, n (%)			
Black or African American	0	2 (15.4)	1 (6.3)
White	13 (100)	11 (84.6)	14 (87.5)
Other	0	0	1 (6.3%)
BMI (kg/m2), mean ± SD	31.0 (12.5)	27.6 (8.9)	31.5 (7.6)

Source: CL003_168 CSR
% are based on total number of subjects randomized
Abbreviations: BID, twice daily; BMI, body mass index; CYC, cyclophosphamide; PBO, placebo; RTX, rituximab; SD, standard deviation; SOC, standard of care

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Important baseline disease characteristics are described below in Table 44. Disease characteristics were similar across treatment arms. More patients in Study CL003_168 had newly diagnosed disease (64.3% of the overall population). The distribution of types of AAV in the study included GPA (69.0%), MPA (26.2%), and renal-limited vasculitis (4.8%). It is unclear how many patients met the BVAS renal criteria, but to evaluate "renal response" (see below), the Applicant evaluated 19 patients with baseline hematuria and albuminuria. More patients in all treatment arms were treated with rituximab, i.e., 92.9% of the entire patient population. The baseline mean BVAS was 15.3.

Table 44. Baseline Disease Characteristics in Study CL003_168

Parameter	PBO + CYC/RTX + Prednisone (SOC)	Avacopan 10 mg BID + CYC/RTX + Prednisone	Avacopan 30 mg BID + CYC/RTX + Prednisone
Randomized, N	13	13	16
Baseline disease characteristics of randomized Population			
Duration of ANCA disease in months, median (range)	1 (0-95)	1 (0-347)	2.5 (0-170)
Newly Diagnosed ANCA disease, n (%)	8 (61.5)	10 (76.9)	9 (56.3)
Relapsing ANCA disease, n (%)	5 (38.5)	3 (23.1)	7 (43.8)
BVAS, mean ± SD	15.0 (4.45)	15.8 (8.84)	15.1 (6.43)
Background treatment of randomized population, n (%)			
CYC	1 (7.7)	0	2 (12.5)
RTX	12 (92.3)	13 (100)	14 (87.5)

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

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant reported that 5 patients (n=2 in the avacopan 10 mg arm, n=2 in the avacopan 30 mg arm, and n=1 in the standard-of-care arm) had lower treatment compliance with avacopan or avacopan placebo (as low as 28.6% in 1 patient in the avacopan 10 mg arm) and that an additional patient in the avacopan 30 mg arm had incomplete drug accountability. Otherwise, the remainder of the patients had compliance to avacopan or avacopan placebo ranging from 75.3% to 104.2%. Additional immunosuppression was administered in 5 patients, 4 of whom were in the avacopan arms and 1 in the standard-of-care arm. These included rituximab (n=1 in the avacopan 30 mg arm), azathioprine (n=2 in the avacopan 30 mg arm), cyclophosphamide (n=1 in the avacopan 10 mg arm), and methotrexate (n=1 in standard-of-care arm).

Non-study supplied glucocorticoids were administered in all treatment arms (69.2% of patients in the standard-of-care arm, 76.9% of patients in the avacopan 10 mg arm, and 81.3% of patients in the avacopan 30 mg arm).

Efficacy Results – Primary Endpoint

Table 45 includes the results of the primary endpoint analysis. In this small study, the greatest BVAS 50% response was seen in the avacopan 10 mg BID arm at 91.7% compared to 80.0% in the avacopan 30 mg BID arm and 84.6% in the placebo arm.

Table 45. BVAS 50% Response and Other Efficacy Assessments in Study CL003_168

Parameter	PBO + CYC/RTX + Prednisone (SOC)	Avacopan 10 mg BID + CYC/RTX + Prednisone	Avacopan 30 mg BID + CYC/RTX + Prednisone
Randomized, N	13	13	16
Intent-to-treat (ITT) population[1], N	13	12	15
Efficacy Assessments in ITT Population			
BVAS 50% Response at Day 85, n (%)	11 (84.6)	11 (91.7)	12 (80.0)
Difference in percentage vs. control	--	7.1%	-4.6%
Two-sided 90% CI for difference, avacopan minus control	--	-14.0, 28.1	-28.3, 19.0
BVAS 0 at Day 85, n (%)	7 (53.8)	8 (66.7)	7 (46.7)
Difference in percentage vs. control	--	12.8%	-7.2%
Two-sided 90% CI for difference, avacopan minus control	--	-19.1, 44.7	-38.3, 23.9
BVAS 0 at Days 29 and 85, n (%)	2 (15.4)	1 (8.3)	3 (20.0)
Difference in percentage vs. control	--	-7.1	4.6
Two-sided 90% CI for difference, avacopan minus control	--	-28.1, 14.0	-19.0, 28.3

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

Additionally, Table 45 presents secondary endpoints of interest that are most similar to the primary endpoint in the pivotal trial. These include the proportion of patients who achieved "disease remission," defined as BVAS of 0 at Day 85, and "early disease remission," defined as BVAS of 0 at Days 29 and 85. As all patients were treated with prednisone, at Day 85, all patients were receiving at least 10 mg of prednisone in this assessment of remission. Note, this differs from the pivotal study which required patients to have discontinued glucocorticoids at least 4 weeks prior to the endpoint assessment. As with BVAS response, disease remission in Study CL003_168 was greatest in the avacopan 10 mg BID arm (66.7%) and lowest in the avacopan 30 mg BID arm (46.7%). Early remission was highest in the avacopan 30 mg BID arm (20.0%) and lowest in the avacopan 10 mg BID arm (8.3%). Differences between groups were due to differences in small numbers of patients.

The greatest BVAS 50% response was observed in the avacopan 10 mg BID arm, which is not the dose selected for the pivotal trial. Additionally, as already noted in the discussion of Study CL002_168, the clinical meaningfulness of BVAS 50% response is unknown. Whether remission at Week 12, and even more so at Week 4, correlates with long-term remission is unknown. The small number of patients in this study further limits the conclusions of efficacy.

Data Quality and Integrity

The Applicant had a similar process to that for Study CL002_168 to ensure data quality and integrity. An Investigators' meeting was held on October 18, 2014, to prepare Investigators for the study and to standardize performance. Clinical research associates conducted periodic on-site visits to ensure adherence to the protocol, review eCRFs and site source documents for accuracy and completeness of information, examine site records for documentation of study medication receipt and administration, observe the progress of the study, and review Investigator files for required documents. All Investigators and/or sub-investigators who performed the BVAS and VDI assessments were trained in proper completion of these instruments prior to enrolling patients at their sites. The eCRFs were created by (b) (4) and data were frequently reviewed with computer generated checks, manual edit checks, etc. Adverse events, medica/surgical history, physical examination data, and concomitant medications were coded by a coding specialist and reviewed by a medical monitor prior to the study being unblinded. Adverse events and medical history were coded to a SOC and PT using MedDRA version 17.1. Concomitant medications were coded to Anatomical Therapeutic Chemical class and preferred term using the WHO Dictionary (June 2011).

There are no issues concerning the submitted data quality or integrity that raise questions about the purported efficacy results.

Efficacy Results – Secondary and Other Relevant Endpoints

As with the review of Study CL002_168, not all the efficacy endpoints are discussed in this review of CL003_168. A summary of the renal assessments, health-related QoL measures, vasculitis damage index (VDI), and non-study supplied glucocorticoid use are reviewed.

Renal Assessments

Renal Response

Similar to Study CL002_168, renal response was defined as an improvement eGFR, hematuria, and albuminuria, without any specific parameters to define improvement. Numerically more patients achieved renal response in the avacopan 30 mg arm (n=5, 62.5%) compared to avacopan 10 mg (n=2, 40.0%) and placebo (n=1, 16.7%). Differences between groups were due

to small numbers of patients, and, as noted, there is uncertainty about how this assessment was determined to inform the clinical relevance.

eGFR

At the end of the 12-week treatment period, in patients with baseline renal disease, there was the mean increase in eGFR from baseline was greatest in the avacopan 30 mg arm (6.2 mL/min/1.73 m^2 [15.4%]), compared to the avacopan 10 mg arm (1.3 mL/min/1.73 m^2 [4.4%]), and the standard-of care arm (2.0 mL/min/1.73 m^2 [10.2%]).

Hematuria

The mean % change from baseline in urinary RBC count (as measured by geometric mean ratio of visit over baseline) in patients with hematuria at baseline was similar in all treatment arms but numerically greatest proportion in the avacopan 30 mg arm (0.03 [97%]), compared to avacopan 10 mg arm (0.06 [94%]), and standard-of-care arm (0.08 [92%]).

Albuminuria (UACR)

The first morning UACR decreased from baseline in all 3 treatment arms. The mean decrease from baseline was the greatest proportion in standard-of-care arm (0.27 [73%]), compared to avacopan 10 mg arm (0.49 [51%]) and avacopan 30 mg arm (0.32 [68%]).

Overall, the renal assessments including the protocol-defined renal response, increase in eGFR, and decrease in hematuria were greatest in the avacopan 30 mg arm. The decrease in albuminuria was greatest in the standard-of-care arm. Interpretation of these results is limited given the small sample size, the difficulty in characterizing the activity of renal vasculitis at baseline, and the clinical meaningfulness of the protocol-defined "renal response."

Rescue Glucocorticoids

No patients required rescue glucocorticoids in this study.

Vasculitis Damage Index (VDI)

The mean increase from baseline in VDI was numerically lower in the avacopan arms compared to the standard-of-care arm. The mean increase was 0.1 in both the avacopan + low dose prednisone arm and the avacopan 30 mg arm and 0.31 in the standard-of-care arm. Overall, change was small in each group. Like Study CL002_168, the study treatment duration was 12 weeks, and VDI is a measure of persistent disease activity (i.e., present for more than 3 months). Thus, its clinical meaningfulness in this short study is limited.

SF-36 and EQ-5D-5L

For hr-QoL measures, the Applicant evaluated both SF-36 and EQ-5D-5L. For SF-36, the Physical Component Summary score increased in all 3 treatment arms, greatest in the avacopan 10 mg arm (mean change from baseline through Day 85 was 13.7 in the avacopan 10 mg arm, 4.8 in the avacopan 30 mg arm, and 3.7 in the standard-of-care arm). The Mental Component Summary score increased in all arms, also greatest in the avacopan 10 mg arm (mean change from baseline through Day 85 was 8.8 in the avacopan 10 mg arm, 7.5 in the avacopan 30 mg arm, and 6.4 in the standard-of-care arm). The mean EQ-5D-5L VAS score also increased in all treatment arms, greatest in the standard-of-care arm. The mean EQ-5D-5L health scale index showed a minimal increase from baseline in all treatment arms, greatest in the avacopan 10 mg arm. Numerically there was greater improvement in the hr-QoL measures in the avacopan arms, but the differences between treatment arm were small. In addition, as previously discussed under Study CL010_168, there is insufficient evidence of content validity to ensure adequate interpretation of hr-QoL in the proposed context.

Dose/Dose Response

In Study CL003_168, a dose dependent treatment effect of avacopan was not demonstrated. As shown above, the greatest BVAS 50% response was observed in the avacopan 10 mg BID arm (91.7%), whereas the avacopan 30 mg arm had the lowest response (80.0%), which was lower than the placebo standard-of-care arm (84.6%). Similarly, the proportion of patients with a BVAS of 0 on Day 85 was greatest in the avacopan 10 mg arm. Avacopan 10 mg was not the dose studied in the pivotal trial. Rather, avacopan 30 mg was pursued based on PD markers that demonstrated dose regimens ≥30 mg twice daily provided at least 95% C5aR coverage on blood neutrophils continuously throughout the day.

Durability of Response

Early remission, defined as BVAS of 0 at Days 29 and 85, was assessed, as presented above. A similar number of patients had a BVAS of 0 at Days 29 and 85, n=1 (8.3%) in the avacopan 10 mg arm, n=3 (20.0%) in the avacopan 30 mg arm, and n=2 (15.4%) in the standard-of-care arm. The observed differences in proportions can be attributed to the small sample size. Thus, the durability of response based on BVAS of 0 at Days 29 and 85 was similar in all treatment arms.

Persistence of Effect

After the 12-week follow-up period (off study drug), BVAS 50% response was similar to the results at Week 12 and was similar across treatment arms, 11 out of 11 patients (100%) in the avacopan 10 mg arm vs. 13 of 14 patients (92.9%) in the avacopan 30 mg arm vs. 12 of 13 patients (92.3%) in the standard-of-care arm. Interestingly, BVAS remission was greater after

follow-up, 11 of 11 (100%) in the avacopan 10 mg arm vs. 11 of 14 (78.6%) in the avacopan 30 mg arm vs. 9 of 13 patients (69.2%) in the standard-of-care patients.

As noted above, no patients required rescue glucocorticoids in Study CL003_168, including the follow-up period.

Although avacopan was discontinued in the follow-up period, all these patients continued to receive standard-of-care, including prednisone (which was still being administered through Day 140). Therefore, the continued efficacy during the follow-up period and lack of need for rescue glucocorticoids may be more reflective of standard-of-care background therapy, rather than persistence of effect.

Efficacy Results – Secondary or Exploratory Clinical Outcome Assessment (PRO) Endpoints

Hr-QoL measures are described above.

8.1.4. Assessment of Efficacy Across Trials

The Applicant submitted one phase 3 trial (CL010_168) and two phase 2 trials (CL002_168 and CL003_168) to support the efficacy of avacopan in the treatment of AAV. However, these data cannot be pooled, as the phase 2 studies had differences in study design, doses (in Study CL003_168), and patient population. The number of patients is small with 67 patients in Study CL002_168 and 42 patients in Study CL003_168. In addition, in Study CL002_168, 26 patients were enrolled with active renal vasculitis based on renal biopsy or presence of hematuria and proteinuria. These criteria were not carried forward in clinical development, and the patients with baseline renal manifestations did not necessarily have the same level of active renal vasculitis. Both phase 2 studies were of shorter treatment duration (12 weeks) and evaluated a different primary endpoint than the phase 3 study. One of the difficulties with drawing conclusions from the data is the early timepoint of the efficacy assessment. The primary endpoints of both studies were assessed at Week 12. Whether a clinical response at Week 12 translates to long-term remission is unknown. Along with timing of endpoint assessment, the ability to interpret the clinical meaningfulness of the efficacy assessments in the phase 2 studies is limited. The primary endpoint in the studies was BVAS 50% response, defined as BVAS percent reduction from baseline of at least 50% plus no worsening in any body system component. The clinical meaningfulness of BVAS 50% response is unknown, whereas the BVAS remission or BVAS of 0, assessed as secondary endpoints, is more clinically interpretable. However, BVAS remission and BVAS of 0 in these studies were assessed while patients may have been receiving protocol-specified prednisone, which makes disentangling the treatment effect of avacopan from an effect of prednisone more complex.

Further, the results of the phase 2 studies do not confirm a treatment benefit of avacopan 30 mg BID in AAV, which is the proposed dose for the treatment indication. In CL002_168, BVAS

50% response was higher in the group that received avacopan plus low dose prednisone, compared to the avacopan plus no prednisone group or the standard-of-care group. Response based on BVAS remission (defined as BVAS of 0 and urinary RBCs <10/hpf) was highest in the control standard-of-care arm that did not receive avacopan. The efficacy based on BVAS 50% response, BVAS remission, and BVAS of 0, was greater in the group that received avacopan with low dose steroids than the avacopan without prednisone group. In CL003_168, the phase 2 dose-ranging study, no dose-response was observed for avacopan; the greatest BVAS response was reported in the avacopan 10 mg BID arm (91.7%), while lower response rates were reported in the avacopan 30 mg BID arm (80.0%) and control standard-of-care arm (84.6%). Similarly, BVAS of 0 at Week 12 was also lowest in the avacopan 30 mg BID plus standard-of-care group. Overall, the phase 2 data do not provide support for the efficacy of avacopan over standard of care nor support for avacopan as a steroid-sparing agent. Therefore, the evidence of effectiveness is based on the efficacy of a single trial, the phase 3 study CL010_168.

8.1.5. Integrated Assessment of Effectiveness

The efficacy results from Study CL010_168 are the primary source to support effectiveness of avacopan for the treatment of AAV. Study CL010_168 met its primary endpoints in that remission was achieved by 72.3% of patients in the avacopan group and 70.1% of patients in the prednisone group at Week 26 (treatment difference: 3.4%, 95% CI (-6.0%, 12.8%)). Superiority was not demonstrated in disease remission at Week 26. At Week 52, a significantly higher percentage of patients had sustained remission in the avacopan group (65.7%) compared to the prednisone group (54.9%).)

Conclusions on the Superiority Assessment of Sustained Remission at Week 52

There were discrepancies between the Investigator and Adjudication Committee assessments of BVAS. While superiority was met at Week 52 using the adjudicated BVAS score, superiority was not met using the Investigator assessed score. Differences between Adjudication Committee and Investigators were driven by assessment of persistent active disease, which was not scored in the modified version of the BVAS used in this study. Investigators tended to score persistent disease as “active,” which may reflect real-world use where “active inflammation” is treated, whether new or persistent.

Subgroup analyses showed a greater treatment difference in sustained remission in the RTX subgroup (71.0% in the avacopan arm vs. 56.1% in the prednisone arm) who did not receive standard of care maintenance therapy, while no treatment difference was observed in the CYC subgroup (55.9% in the avacopan arm vs. 52.6% in the prednisone arm). This inconsistency across background therapies and the larger effect in the population who did not receive standard-of-care maintenance immunosuppression therapy and may be considered

undertreated, raises questions about the clinical meaningfulness of the avacopan effect at Week 52.

The clinical meaningfulness of the superiority results at Week 52 are, therefore, unclear. There remain questions as to whether avacopan truly has a treatment benefit compared to standard of care on sustained remission in AAV.

Avacopan has been proposed as a steroid-sparing agent in AAV. However, the data from Study CL010_168 do not support its use as a replacement for glucocorticoids. As previously discussed, patients in both treatment arms received non-study supplied glucocorticoids, including for management of vasculitis. Use of glucocorticoids was similar between treatment groups after completion of the specified prednisone taper at Week 20.

Based on the literature, the ideal glucocorticoid regimen in the induction and maintenance treatment of AAV is evolving. It has been proposed that a reduced dose regimen or a rapid taper of steroids may be appropriate. Thus, since the prednisone taper was pre-specified in the prednisone arm, it is unknown whether a lower dose regimen may have also been effective in the comparator arm. Based on the study design, it cannot be determined whether the differences in use of glucocorticoids from Weeks 0 to 26 was due to a treatment effect of the avacopan or was due to the specified prednisone taper administered to the prednisone arm.

There is limited support of a treatment benefit of avacopan from the secondary endpoints. In addition, the secondary endpoints were not adjusted for multiplicity, and therefore nominal significance achieved by a secondary endpoint should be interpreted with caution. More relapses were observed in the prednisone arm compared to the avacopan arm through the study duration (20.1% in the prednisone arm compared to 9.6% in the avacopan arm). However, the study was not designed to assess time to relapse or proportion of relapses. The Applicant's analyses based on the subset of patients who achieved remission condition on post-randomization variables, i.e., having first achieved remission and the timing of achieving remission. As a result, the subset of patients included in this analysis and the time those patients are at risk for relapse can no longer be assumed to be similar across treatment arms. The advantages of randomization are eliminated because the treatment arms are no longer balanced with respect to possible confounders, leading to biased comparisons between treatment arms and limiting the interpretability of these results.

The Glucocorticoid Toxicity Index, intended to quantitatively capture glucocorticoid toxicity and the glucocorticoid-sparing ability of therapies, showed a greater improvement from baseline in the avacopan arm on GTI-CWS and GTI-AIS at Weeks 13 and 26. Differences in GTI between the treatment groups may reflect the study design which specified the prednisone doses to be used in the control group. GTI was not assessed at later time points to assess the effects of glucocorticoids after completion of the pre-specified prednisone taper. In Study CL010_168, where differences in glucocorticoid use were pre-specified in the protocol, the GTI does not

provide information beyond that of the cumulative glucocorticoid doses to further inform the effect of avacopan. In addition, the DCOA concluded that the Applicant did not support a conclusion that the GTI-derived endpoint is fit-for-purpose to measure glucocorticoid-related toxicities and glucocorticoid-sparing effects for the context of use in this drug development program.

Multiple renal endpoints were assessed as secondary endpoints. Mean improvement in eGFR from baseline to Week 52 for patients meeting BVAS criteria for renal disease at baseline was greater in the avacopan group compared to the prednisone group, however the difference between groups was small 3.3 mL/min/1.73 m^2 (95% CI: [-0.4, 6.9]), and was not sustained by 8 weeks post-treatment. Percent change in UACR at Week 52 was similar in the avacopan and prednisone arms and need for dialysis was also similar between groups.

A similar mean increase in Vasculitis Damage Index, an instrument intended to assess cumulative organ damage as a result of ANCA-associated vasculitis, was observed between treatment groups from baseline to Week 52.

Favorable trends toward improvement were observed in quality of life, based on the SF-36 and EQ-5D-5L, in the avacopan group compared to the prednisone group, however there was large variability around the point estimates, and these measures are not specific to vasculitis.

Clinical Meaningfulness and Interpretation of a Non-Inferiority Comparison of Avacopan to Prednisone for Remission at Week 26 and Sustained Remission at Week 52

As the Agency reiterated in pre-submission communications, a non-inferiority comparison is not sufficient to show that avacopan can replace glucocorticoids, as it would be difficult to determine whether the background CYC or RTX was driving the efficacy results in both treatment arms. In addition, there is a lack of relevant historical data for justification of an appropriate non-inferiority margin. The Applicant has not provided adequate data or information that would isolate the effect of prednisone to inform the margin of the non-inferiority comparison in this study.

Interpretation of the non-inferiority is further limited by the large number of patients who received glucocorticoids in the avacopan arm. Both treatment arms received non-study supplied glucocorticoids at the Investigator's discretion, including 145 patients in the avacopan arm (87.3%) and 149 patients in the prednisone arm (90.9%).

The mean cumulative total glucocorticoid use, including both protocol-specified prednisone and non-study supplied glucocorticoids, over 52 weeks was greater in the prednisone arm, as expected based on the study design (3654.5 mg in the prednisone arm and 1348.9 mg in the avacopan arm). However, comparing the mean cumulative non-study supplied glucocorticoid dose was much more similar, 1265.3 mg in the prednisone arm and 1348.9 mg in the avacopan

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

The clinical pharmacology program has identified avacopan as a CYP3A4 inhibitor that has the potential to increase exposures to systemic glucocorticoids which are CYP3A4 substrates, raising further uncertainties about the true difference in glucocorticoid exposures and its impact on the non-inferiority comparisons between the two groups at Week 26, and respectively the proposed role of avacopan as a steroid-sparing agent, as glucocorticoid exposures were not assessed in Study CL010_168. Thus, the non-inferiority comparison was not a comparison of avacopan versus glucocorticoids but is more accurately described as avacopan plus potentially lower doses of glucocorticoids compared to higher doses of glucocorticoids, in addition to background induction therapy (CYC or RTX) and maintenance therapy (only in the CYC arm). The clinical meaningfulness of this non-inferiority comparison is very difficult to interpret to support a treatment benefit of avacopan.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review focuses on the pivotal Study CL010_168. The phase 2 trials (CL002_168 and CL003_168) provide limited safety data, as they add few patients to the safety database. Additionally, in the phase 2 trials, patients received different doses of avacopan and varying concomitant therapy (e.g., different doses of a prednisone taper). Another difference is the clinical manifestations in Study CL002_168 Steps 1 and 2, which enrolled patients with renal vasculitis active renal vasculitis as defined by renal biopsy or the presence of hematuria or proteinuria. Patients with generalized AAV were enrolled in Step 3 of Study CL002_168 as well as the other phase 2 study and the pivotal trial. Therefore, pooling of safety data is not feasible. A summary of the phase 2 safety findings will be presented alongside the data from the pivotal trial. In a few sections of the review (e.g., review of SAEs), the phase 2 studies are presented together with all arms that received avacopan combined (i.e., avacopan + low dose prednisone and avacopan + no prednisone in Study CL002_168 as well as avacopan 10 mg BID and avacopan 30 mg BID in Study CL003_168) compared to all arms that did not receive avacopan combined (i.e., the standard-of-care arm with high dose prednisone).

During conduct of Study CL010_168, ChemoCentryx issued a Notification to Investigators after the DMC reviewed unblinded SAEs. The Notification identified a potential risk of liver toxicity to which all investigators and study coordinators needed to acknowledge, and all patients needed to be informed. The study protocol was also amended to increase clinical and laboratory monitoring for liver toxicity. Thus, potential hepatotoxicity was identified as a safety review issue. The Division of Hepatology and Nutrition (DHN) was consulted to assist with evaluating

for a potential liver safety signal. Based on the mechanism of action (i.e., C5aR inhibitor), infection and low WBC count were also adverse events of special interest (AESI). Other AESIs included hypersensitivity reactions and elevated creatine phosphokinase. Lastly, during clinical development, it was noted, in the phase 2 studies, disease flares were sometimes captured as a safety event. Therefore, "vasculitis" and other related preferred-terms were also considered "safety issues." For specific AEs of interest (e.g., hepatotoxicity and infections), additional analyses were conducted by the Agency.

8.2.2. Review of the Safety Database

Overall Exposure

The safety population included all patients who were randomized and received at least 1 dose of study drug. Therefore, in Study CL010_168, 166 patients in the avacopan arm and 164 patients in the prednisone were included in the safety population.

One hundred thirty-four patients (80.7%) received at least 184-365 days of avacopan. The mean exposure in the avacopan arm is 305.1 days, and the median exposure is 364.0 days. The active control arm received a pre-specified shorter prednisone taper; therefore, the mean exposure of prednisone to study drug in the prednisone arm is 129.2 days (median of 140.0 days).

An additional 73 patients received avacopan in the two phase 2 studies (n=44 in study CL002_168 and n=29 in study CL003_168). The treatment periods in these studies were much shorter at 12 weeks, so the contribution to the safety database is small. In both phase 2 studies, a total of 67 patients received at least 30-183 days of avacopan. Additional differences between the phase 2 studies and the pivotal trial include clinical manifestations and use of concomitant glucocorticoids in some of the avacopan arms.

Relevant Characteristics of the Safety Population

The baseline demographics and disease characteristics of patients in Study CL010_168 are described in Section 8.1.1.1 (specifically, Table 17 and Table 18). As already described, more patients are male (56.5%), between the ages of 51-75 years (67.7%), and White (84.3%). More patients had newly diagnosed AAV (69.4%), specifically, GPA (54.8%) with MPO positivity (57.0%) and IV RTX for induction (64.8%). The safety database reflects the general population of patients with AAV. Although the population is not very heterogeneous (particularly in terms of race), this reflects the demographics of patients who are diagnosed with AAV, i.e., more common in White and Asian population and less common in African American populations (Geetha and Jefferson 2020).

For the phase 2 studies, see the baseline demographics and disease characteristics in Sections 8.1.2.1 and study 8.1.3.1. Study CL002_168 included mostly male patients (70.1%) with a mean

age of 57.9 years. The majority of patients had newly diagnosed disease (73.1%) with numerically more patients diagnosed with GPA (49.3%) compared to MPA (41.8%). More patients (80.6%) received CYC as induction therapy. As previously described, Steps 1 and 2 required the presence of renal vasculitis, confirmed by renal biopsy or the presence of hematuria/albuminuria, and Step 3 opened the study to general AAV. Enrolled patients in Study CL003_168 were mostly women (54.8%) with a mean age of 57.7 years. More patients had newly diagnosed disease (64.3%) and a diagnosis of GPA (69.0%). Patients in Study CL003_168 had generalized AAV, not limited to renal vasculitis, with more receiving induction treatment with rituximab (92.9%).

Adequacy of the Safety Database

The safety population is relatively small (n=239, including the phase 2 studies), particularly for the adequate assessment of rare and latent adverse events. The population of in patients who received long term treatment with avacopan, up to approximately one year, is also small (n=166). ChemoCentryx has proposed avacopan for chronic treatment in AAV, including induction and maintenance phases of treatment; therefore, the potential duration of treatment may be quite long (e.g., 24 months or longer). However, the Agency recognizes that AAV is a rare disease. The sample size was appropriate for the population and objectives of the study, in the context of AAV as an orphan disease. The safety data are sufficient for the Agency to draw conclusions of the safety of avacopan in AAV, but it is not adequate to quantitate the risks of rare events such as hepatotoxicity. If approved, a PMR study would be required to better evaluate the risks.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The clinical reviewer did not identify any important issues regarding data quality or the quality of the overall submission that had an effect on the safety review. The DHN DILI team did note that there were missing data from the LB dataset, and the Applicant explained that the LB dataset only included results from a central laboratory. The Applicant subsequently provided the missing local laboratory data for Agency analysis.

Additionally, the Office of Computational Science provided a Core DataFitness (CoreDF) service to further assist with evaluation of data quality. There were no major issues identified.

Categorization of Adverse Events

Adverse events, medical/surgical history, physical examination data, and concomitant medications were coded by a coding specialist and reviewed by a medical monitor prior to the

study being unblinded. Adverse events and medical/surgical history were coded to SOC and PT using the MedDRA (version 19.1). Concomitant medications were coded to Anatomical Therapeutic Chemical class and PT using the WHO Drug Dictionary (June 2011).

The Applicant utilized standard definitions of adverse events and SAEs. 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 drug and were captured through the end of the 8-week follow-up period (i.e., Week 60 of Study CL010_168). The half-life of avacopan is 1.5 days; thus, 5 half-lives would be less than 1 week. The Applicant's definition of treatment-emergent adverse event (TEAE) is reasonable.

The Applicant also allowed Investigators to relate AEs to study medication, i.e., glucocorticoids, cyclophosphamide, rituximab, azathioprine, or mycophenolate use. The study was stratified by baseline induction therapy and was balanced across treatment arms. As avacopan is a new molecular entity, all AEs will be reviewed, regardless of relatedness to study medication or other concomitant standard-of-care medication.

Severity of each AE was determined by the Investigator using the following scale:

- Mild (Grade 1): no limitation of usual activities
- Moderate (Grade 2): some limitation of usual activities
- Severe (Grade 3): inability to carry out usual activities
- Life-threatening (Grade 4): an immediate risk of death
- Death (Grade 5)

As noted above, specified AESI included infection, hepatic abnormalities (including hepatobiliary disorders and liver-enzymes elevations), low WBC count, hypersensitivity reactions, and elevated creatine phosphokinase. The method for evaluating AESIs is described in more detail in the content of the review below.

The Applicant's approach to recording, coding, and categorizing AEs, as well as the approach to safety analyses, is generally reasonable and appropriate.

Routine Clinical Tests

Routine clinical testing was performed on Day 1 and Weeks 1, 2, 3, 4, 7, 10, 13, 16, 20, 23, 26, 29, 32, 35, 39, 42, 45, 48, 52, and 60. Laboratory testing included the following:

- Hematology: hemoglobin, hematocrit, RBC count, WBC count with differential, platelet count, mean cell hemoglobin, mean cell hemoglobin concentration, mean corpuscular volume
- Serum chemistry: liver panel (bilirubin, lactate dehydrogenase, AST, ALT), renal panel (blood urea nitrogen, creatinine), creatine phosphokinase, albumin, sodium, potassium,

magnesium, bicarbonate, chloride, calcium, inorganic phosphorus, glucose, total protein, alkaline phosphatase, total cholesterol, uric acid, serum amylase, serum lipase
- Hemoglobin A1c and LDL cholesterol (for use in the GTI)
- Urinalysis (performed at central laboratory): nitrite, blood, protein. If positive, microscopy will be performed.

Laboratory parameter results and changes from baseline were summarized by visit. The Applicant's summaries were limited to values assessed at the Central Laboratory. The proportion of patients with abnormal laboratory values (assessed by the Central Laboratory) of elevated hepatic enzymes (ALT, AST, or total bilirubin), elevated creatine phosphokinase, or low WBC (low neutrophils, low lymphocytes, low leukocytes) were summarized by treatment group and grade (defined by common terminology criteria for adverse events [CTCAE] Version 5).

In general, the safety assessment methods and time points in the protocol were reasonable and adequate for the pivotal trial CL010_168.

8.2.4. Safety Results

An overview of safety is presented in Table 46. Most patients in both arms experienced at least 1 TEAE (98.2% in the prednisone arm and 98.8% in the avacopan arm). Overall, a similar proportion of patients in both treatment arms experienced adverse events, including SAEs and adverse events leading to discontinuation. SAEs and AEs leading to discontinuation are described in more detail below.

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

Table 46. Overview of Treatment Emergent Adverse Events in Study CL010_168

Number of Patients With ≥1	Prednisone (N=164) n (%)	Avacopan (N=166) n (%)	Avacopan vs. Prednisone Diff (95% CI)
TEAEs	161 (98.2)	164 (98.8)	0.6% (-2.0, 3.3)
Deaths	4 (2.4)	2 (1.2)	-1.2% (-4.1, 1.7)
Serious TEAEs (SAEs)[1]	74 (45.1)	70 (42.2)	-3.0% (-13.7, 7.7)
Severe TEAEs	41 (25.0)	39 (23.5)	-1.5% (-10.8, 7.7)
TEAEs leading to treatment discontinuations[2]	28 (17.1)	27 (16.3)	-0.8% (-8.9, 7.2)

Source: CL010_168 CSR Table 22; ISS
[1] Two patients in the prednisone group had Grade 4 lymphopenia and 1 patient in the avacopan had Grade 4 neutrophil count decreased that were not considered to be SAEs by the Investigator. See below for description of these events.
[2] Note: Treatment discontinuations due to AEs are also described in Table 19 in this review, and there are some differences in the number of discontinues attr buted to AE. Table 19 presents 2 additional patients (one in each arm) who discontinued treatment due to AE were discontinuations due to death. In this table, 2 patients in the avacopan arm who discontinued treatment were attributed to "other" and "sponsor decision" in Table 19.
Abbreviations: CI, confidence interval; Diff, difference; N, number of patients randomized who received at least one dose of drug; n, number of subjects with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

An overview of Studies CL002_168 and CL003_168 are presented in Table 47 and Table 48, respectively. In Study CL002_168, the proportion of patients who experienced any AE were similar across treatment arms. SAEs were reported by a greater proportion of patients in the avacopan and no prednisone arm (36.4%), compared to the avacopan and low dose prednisone arm (13.6%) and standard-of-care arm (17.4%). In addition, a greater number of patients in the avacopan and no prednisone arm discontinued treatment due to AEs.

Table 47. Overview of Safety in Study CL002_168 (84-Day Treatment Period)

Number of Patients With ≥1	PBO + CYC/RTX + High Dose Prednisone (SOC) (N=23) n (%)	Avacopan + CYC/RTX + Low Dose Prednisone (N=22) n (%)	Avacopan + CYC/RTX + No Prednisone (N=22) n (%)
TEAEs	21 (91.3)	19 (86.4)	21 (95.5)
Deaths	0	0	0
Serious TEAEs (SAEs)	4 (17.4)	3 (13.6)	8 (36.4)
TEAEs leading to treatment discontinuations	2 (8.7)	1 (4.5)	3 (13.6)

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

As shown in Table 48, the proportion of patients in Study CL003_168 who experienced AEs, SAEs, and AEs leading to discontinuation was similar across treatment arms with differences due to small numbers of patients.

Table 48. Overview of Safety in Study CL003_168

Number of Patients With ≥1	PBO + CYC/RTX + Prednisone (N=13) n (%)	Avacopan 10 mg BID + CYC/RTX + Prednisone (N=13) n (%)	Avacopan 30 mg BID + CYC/RTX + Prednisone (N=16) n (%)
TEAEs	13 (100)	11 (84.6)	15 (93.8)
Deaths	0	0	0
Serious TEAEs (SAEs)	2 (15.4)	2 (15.4)	3 (18.8)
TEAEs leading to treatment discontinuations	2 (15.4)	1 (7.7)	3 (18.8)

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

Deaths

In Study CL010_168, the overall number of deaths was low and similar between treatment arms with 4 patients who died in the prednisone arm (fungal sepsis, pleural empyema, acute ST elevation myocardial infarction with cardiogenic shock, and a death from unknown cause) and 2 patients in the avacopan arm (worsening GPA and *Aspergillus* pneumonia). An additional death occurred in the screening period (myocardial infarction) prior to study drug administration.

The patients who died on avacopan are described in more detail below. Death from worsening GPA or AAV and infection is not unexpected in this patient population who has severe AAV and received treatment with potent immunosuppression.

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

to infection, pulmonary hemorrhage, and her underlying vasculitis; however, her death was attributed to "*Aspergillus* superinfection."

A brief description of the 4 patients who died in the prednisone arm is also described below. These causes of death are not unexpected in this patient population.

- A 61-year-old man with newly diagnosed, MPO-positive MPA received IV CYC for induction and died from a pleural empyema and pneumothorax on Day 108. The patient was taking prednisone 5 mg BID at the time of his death. Multiple AEs and SAEs were reported for this patient throughout the study; the SAEs included influenza B (Day 23), hydropic decompensation with shortness of breath requiring dialysis (Day 42), and cytomegalovirus (CMV) pneumonia (Day 88).
- A 38-year-old man with relapsed, PR3-positive GPA received rituximab for induction and died unexpectedly on Day 359. The patient was found by his parents the morning after his death and an autopsy was not performed. No death certificate was available. Therefore, no cause of death was identified.
- A 73-year-old woman with newly diagnosed, MPO-positive MPA received rituximab for induction and died on Day 34. She first experienced diarrhea and vomiting on Day 17, a generalized fungal infection (later confirmed to be Candida albicans and Aspergillus) on Day 24, and lastly septic shock on her day of death. She received IV methylprednisolone 125 mg with 3 rituximab infusions prior to onset of her adverse events. She also received IV hydrocortisone 300 mg on Day 21 (for fever), oral prednisone/prednisolone 30 mg on Days 23 to 25 (for AAV), IV hydrocortisone 50 mg 4 times a day on Day 25 and IV hydrocortisone 40 mg daily on Day 26 (for acute adrenal insufficiency).
- A 68-year-old man with newly diagnosed, MPO-positive MPA received rituximab for induction and died on Day 160 from an acute ST-elevation MI. He received methylprednisolone with his rituximab infusions. He also had a suspected relapse and was treated with IV methylprednisone 500 mg on Days 16 to 18. It is unclear what dose of prednisone he was taking at the time of his death, but his last dose of study medication was on Day 113. His medical history was significant for HTN. On Study Day 111, he was hospitalized for an acute ST-elevation myocardial infarction with cardiogenic shock. He was treated with a primary percutaneous coronary intervention with stent to his left anterior descending artery. He required an intra-aortic balloon pump due to cardiogenic shock. He was transferred to critical care, then step down, and then palliative care. He died on Study Day 160.

No deaths occurred in the phase 2 studies.

Serious Adverse Events

In Study CL010_168, 284 SAEs were reported in 145 patients. The proportion of patients with SAEs was similar in both treatment arms, 45.1% in the prednisone arm and 42.2% in the avacopan arm. There were numerically more events in the prednisone arm (n=166) compared to the avacopan arm (n=116). Table 49 presents the number of patients with SAEs that occurred in more than 1 patient in either treatment arm. The most common SOCs in which SAEs occurred were Infections and infestations (n=25 (15.2%) in the prednisone arm and 22 (13.3%) in the avacopan arm) and Immune system disorders (n=21 (12.8%) in the prednisone arm and 14 (8.4%) in the avacopan arm). Each SAE by PT occurred in a small number of patients. SAEs that occurred in more than 2 patients in the avacopan arm were ANCA-positive vasculitis (7.2% in the avacopan arm and 12.2% in the prednisone arm), pneumonia (4.8% in the avacopan arm and 3.7% in the prednisone arm), GPA (3.0% in the avacopan arm and 0.6% in the prednisone arm), acute kidney injury (1.2% in the avacopan arm and 0.6% in the prednisone arm), and urinary tract infection (UTI) (1.8% in the avacopan arm and 1.2% in the prednisone arm).

Table 49. Serious Adverse Events (SAEs) by Preferred Term (≥2 Patients in Either Treatment Group) in Study CL010_168

Number of Patients With ≥1 SAE	Prednisone N=164 n (%)	Avacopan N=166 n (%)
Any SAEs	74 (45.1)	70 (42.2)
ANCA antibody positive vasculitis	20 (12.2)	12 (7.2)
Pneumonia	6 (3.7)	8 (4.8)
Granulomatosis with polyangiitis	1 (0.6)	5 (3.0)
Acute kidney injury	1 (0.6)	3 (1.8)
Urinary tract infection	2 (1.2)	3 (1.8)
Angina pectoris	0	2 (1.2)
Cardiac failure	0	2 (1.2)
Device-related infection	0	2 (1.2)
Drug hypersensitivity	2 (1.2)	2 (1.2)
Hepatic enzyme increased	3 (1.8)	2 (1.2)
Hepatic function abnormal	0	2 (1.2)
Hyperglycemia	1 (0.6)	2 (1.2)
Influenza	1 (0.6)	2 (1.2)
Pyrexia	3 (1.8)	2 (1.2)
Acute myocardial infarction	2 (1.2)	1 (0.6)
Agranulocytosis	2 (1.2)	1 (0.6)
Blood creatinine increased	2 (1.2)	1 (0.6)
Lymphopenia	3 (1.8)	1 (0.6)
Pulmonary alveolar hemorrhage	2 (1.2)	1 (0.6)
Anemia	2 (1.2)	0
Dehydration	2 (1.2)	0
Diarrhea	3 (1.8)	0
Epistaxis	2 (1.2)	0
Glomerulonephritis	2 (1.2)	0

Number of Patients With ≥1 SAE	Prednisone N=164 n (%)	Avacopan N=166 n (%)
Herpes zoster	2 (1.2)	0
Infectious pleural effusion	2 (1.2)	0
Large intestine polyp	2 (1.2)	0
Microscopic polyangiitis	2 (1.2)	0
Mononeuropathy multiplex	2 (1.2)	0
Neutropenia	2 (1.2)	0
Pneumonia bacterial	2 (1.2)	0
Prostate cancer	2 (1.2)	0

Source: CL010_168 CSR, Table 25, pages 122-123.
Abbreviations: ANCA, anti-neutrophilic cytoplasmic ant body; N, number of patients randomized who received at least one dose of drug; n, number of subjects with at least one event.

The Applicant highlighted the SAEs that occurred more frequently in the avacopan-treated group. The SOC with the greatest difference in patients with SAEs (i.e., ≥2% difference) in the avacopan arm over the prednisone arm was Hepatobiliary disorders (3.6% in the avacopan arm and 0.6% in the prednisone arm). These patients are further discussed below under AESIs (hepatotoxicity). SAEs (by preferred term) that occurred in more patients in the avacopan arm (with a difference of >1% compared to patients in the prednisone arm) included pneumonia, GPA, acute kidney injury (AKI), angina pectoris, cardiac failure, device-related infection, and hepatic function abnormal. To explore these differences further, infection (which captures the PTs of pneumonia and device-related infection), hepatotoxicity (including hepatic function abnormal), and vasculitis (including GPA) are discussed below under AESIs. AKI and major adverse cardiac events (MACE) are discussed here.

Acute Kidney Injury

The SAE of AKI was reported in more patients in the avacopan arm (n=3 in the avacopan arm vs. n=1 in the prednisone arm). However, when combining AKI and blood creatinine increased, the number of patients with these renal-related SAEs appear more balanced (n=4 in the avacopan arm vs. n=3 in the prednisone arm). In the prednisone arm, none of the patients required study drug interruption, and all patients had resolution of the SAE. In the avacopan arm, one patient with the PT of "AKI" required study drug discontinuation from a hypersensitivity reaction (described below); the AKI required one session of dialysis. Two patients (PTs of "AKI") required study drug interruption, but avacopan was restarted without worsening in eGFR. One patient with the PT of "blood creatinine increased" was able to continue avacopan.

Based on the few observed events and the small safety database, it is difficult to draw conclusions regarding renal risk. Additionally, AKI may be a manifestation of the underlying disease. The SAEs of AKI resolved for all avacopan-treated patients with interruption/discontinuation of avacopan.

Major Adverse Cardiac Events (MACE)

Although there were more SAEs of angina pectoris (n=2) and cardiac failure (n=2) in the avacopan arm compared to the prednisone arm (no patients with either AE), the Applicant reported that there were more MACE in the prednisone arm (3 patients in the prednisone arm and 1 patient in the avacopan arm). MACE was defined by the Applicant as nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death. The specific AEs that were considered MACE included 2 patients with non-fatal myocardial infarctions (MIs) and 1 patient with a fatal MI in the prednisone group and 1 non-fatal MI in the avacopan group. The Applicant's assessment of MACE did not include PTs of cardiac failure or myocardial ischemia, nor did they include the PT of "cerebral infarct," despite it being part of their definition of MACE. When including these additional PTs, the number of patients with MACE were the same with 7 patients in both arms. In addition to the cases of myocardial infarction already described, there was 1 patient with a cerebral infarct in the prednisone group and 4 patients with cardiac failure and 1 patient with myocardial ischemia in the avacopan group.

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

Table 50 presents the SAEs that occurred in Study CL002_168 and Study CL003_168.

Table 50. Serious Adverse Events (SAEs) During the 84-day Treatment Period in the Phase 2 Studies (CL002_168 and CL003_168)

Study and Treatment Arms	Serious Adverse Events (Preferred Term)
CL002_168	
Avacopan 30 mg BID + low dose prednisone N=22	n=3 (13.6%) Vasculitis Musculoskeletal chest pain and hematuria Febrile infection (no source)
Avacopan 30 mg BID + no prednisone N=22	n=8 (36.4%) Renal impairment Increased hepatic enzymes and pancreatic enzymes MPA Rash Respiratory tract infection CRP increased Vasculitis Renal vasculitis
Control Arm (high dose prednisone) N=23	n=4 (17.4%) Pneumonia Dehydration Renal vasculitis Back pain and lumbar vertebral fracture

Study and Treatment Arms	Serious Adverse Events (Preferred Term)
CL003_168	
Avacopan 10 mg BID + high dose prednisone N=13	n=2 (15.4%) Neutropenia Cellulitis staphylococcal, abscess limb, perirectal abscess
Avacopan 30 mg BID + high dose prednisone N=16	n=3 (18.8%) Atrial fibrillation Sepsis Urinary tract infection
Control arm (high dose prednisone) N=13	n=2 (15.4%) Methemoglobinemia Gangrene

Source: CL002_168 CSR and CL003_168 CSR
Abbreviations: BID, twice daily; n, number of patients with SAEs; N, safety population.

In the phase 2 studies (combined), the SOCs with SAEs that were reported more frequently were Infections and infestations (n=3 [8.3%] in the SOC group vs. n=7 [9.6%] in the avacopan-treated groups), Renal and urinary disorders (n=2 [5.6%] in the SOC group vs. n=5 [6.8%] in the avacopan-treated groups), and Vascular disorders (n=1 [2.8%] in the SOC group vs. n=5 [6.8%] in the avacopan-treated groups). Thus, in this combined analysis of these 3 SOCs, more SAEs occurred in the avacopan-treated groups. Overall, the number of patients with SAEs was low in the combined phase 2 studies.

In Study CL002_168, more SAEs occurred in the avacopan + no prednisone arm. The SAEs that occurred most frequently were PTs that fell under the category of vasculitis: vasculitis (n=1 in the avacopan + low dose prednisone arm, n=1 in the avacopan + no prednisone arm), renal vasculitis (n=1 in the avacopan + no prednisone arm, n=1 in the standard-of-care arm), and MPA (n=1 in the avacopan + no prednisone arm). Therefore, more vasculitis events were observed in patients receiving avacopan + no prednisone. Serious infections were generally balanced across treatment arms and are further described under AESIs (Infections). There was also a patient with an SAE of increased hepatic enzymes and pancreatic enzymes, and this case was considered to be possibly related to avacopan. This patient will be further detailed below under hepatotoxicity.

In Study CL003_168, the number of patients with SAEs was even fewer, reflecting the smaller study size. Proportions of patients with SAEs were similar across treatment arms. The SOC of Infections and infestations had the greatest number of patients with SAEs (n=1 in the avacopan 10 mg arm, n=2 in the avacopan 30 mg arm, n=1 in the standard-of-care arm).

Conclusions regarding SAEs are limited by the relatively small size of the safety database. Overall, SAEs were generally balanced between the avacopan and the prednisone arm in Study CL010_168. SAEs within the Infections and Infestations SOC were reported most frequently and were generally balanced by arm. SAEs reported by more patients in the avacopan arm include SAEs within the hepatobiliary SOC, as well as pneumonia, AKI, GPA, angina pectoris, cardiac

failure, and device-related infection. As previously discussed, the phase 2 studies were significantly smaller studies, of shorter duration, and with different treatment arms. In the phase 2 study CL002_168, a greater proportion of patients had SAEs in the avacopan + no prednisone arm, including SAEs related to vasculitis, compared to avacopan + low dose prednisone or standard of care prednisone arm. In CL003_168, serious infections were reported by the greatest numbers of patients, balanced by treatment arm. Serious infections and hepatotoxicity are discussed further under AESI below.

Dropouts and/or Discontinuations Due to Adverse Effects

In Study CL010_168, the proportion of patients who discontinued study medication due to AEs was similar in both treatment arms (28 [17.1%] in the prednisone arm and 27 [16.3%] in the avacopan arm). The most common AEs leading to discontinuation were ANCA-antibody positive vasculitis (n=4 (2.4%) in the avacopan arm and n=8 (4.9%) in the prednisone arm), hepatic enzyme increased (n=1 (0.6%) avacopan, n=2 (1.2%) prednisone), hepatic function abnormal (n=3 (1.8%) avacopan), and lymphopenia (n=3 (1.8%) prednisone). Other AEs leading to discontinuation occurred in 2 or fewer patients.

In comparing the 2 treatment arms, only the SOC of hepatobiliary disorders showed ≥2% greater incidence of discontinuation due to AE in the avacopan arm relative to the prednisone arm. Five patients (3%) in the avacopan arm discontinued study drug due to an AE in the hepatobiliary disorders SOC compared to no patients in the prednisone arm. Overall AEs associated with liver enzyme-related abnormalities, including AEs from the Hepatobiliary SOC and Investigations SOC, led to drug discontinuation in 7 patients in the avacopan arm and 2 patients in the prednisone arm. Hepatotoxicity is further discussed below under the AESIs. In the prednisone arm, only the SOC of Blood and lymphatic disorders occurred in ≥2% greater incidence compared to the avacopan arm (n=6 (3.7%) prednisone, n=2 (1.2%) avacopan). This difference can be attributed to patients with PTs of anemia (n=1), leukopenia (n=1), lymphopenia (n=3), and thrombocytopenia (n=2) that occurred in the prednisone arm compared to patients with PTs of febrile neutropenia (n=1) and neutropenia (n=1) in the avacopan arm.

AEs leading to drug interruption occurred in 37 avacopan-treated patients (22.3%) and 22 prednisone-treated patients (13.4%), based on reviewer analysis. The most frequently reported AEs leading to drug interruption were acute kidney injury (n=3 (1.8%) avacopan, no prednisone), neutropenia (n=3 (1.8%) avacopan, no prednisone), pyrexia (n=2 (1.2%) avacopan, n=1 (0.6%) prednisone), lymphopenia (no avacopan, n=3 (1.8%) prednisone), and vomiting (n=2 (1.2%) avacopan, n=3 (1.8%) prednisone).

In Study CL002_168, the most common AE leading to discontinuation was vasculitis (specifically, vasculitis, MPA, and renal vasculitis) which occurred in arms with avacopan and arms with

standard of care. Specifically, 2 patients who received standard of care discontinued for vasculitis and renal vasculitis. One patient in the avacopan + low dose prednisone taper arm discontinued for vasculitis. In the avacopan + no prednisone arm, 3 patients discontinued study drug due to AEs. One patient discontinued for MPA; one patient discontinued for renal impairment; one patient discontinued for increased hepatic and pancreatic enzymes (i.e., same patient described above with the SAE of hepatotoxicity).

In Study CL003_168, more patients who received avacopan (n=3 in the avacopan 30 mg group and n=1 in the 10 mg group) discontinued medication due to AEs compared to the standard of care/placebo arm (n=1). The numbers were low, overall, and the AEs leading to discontinuation were single events by PT. The most common SOC leading to discontinuation in patients who received avacopan was Infections and infestations, which occurred in 1 patient in the avacopan 10 mg arm (2 events (perirectal abscess and abscess limb)) and 1 patient in the avacopan 30 mg arm (1 event (sepsis)). A patient in the standard-of-care arm also experienced a PT in the Infections and infestations SOC that led to discontinuation (gangrene). No AEs leading to discontinuation of vasculitis or hepatic AEs were reported.

In conclusion, overall AEs leading to discontinuation were generally balanced between treatment groups. Treatment discontinuation due to hepatic abnormalities, more frequently observed in the avacopan treatment arm, is a significant finding and will be further discussed under AESIs (hepatotoxicity) below.

Significant Adverse Events

All adverse events were assessed for severity as described above. Of the 3918 TEAEs in Study CL010_168, there were 165 severe TEAEs in 98 patients (n=44 (26.5%) in the avacopan arm, n=54 (32.9%) in the prednisone arm), based on reviewer analysis. Severe AEs by PTs that occurred in the greatest numbers of patients included ANCA positive vasculitis (n=13 (7.9%) in the prednisone arm and n=7 (4.2%) in the avacopan arm), lymphopenia (n=4 (2.4%) in the prednisone arm and n=1 (0.6%) in the avacopan arm), and pneumonia (n=2 (1.2%) in the prednisone arm and n=4 (2.4%) in the avacopan arm).

In addition, life threatening (Grade 4) AEs occurred in 8 (4.8%) avacopan-treated patients and 14 (8.5%) prednisone-treated patients.

- Eight patients in the avacopan arm experienced life-threatening AEs:
  - diabetic ketoacidosis
  - acute myocardial infarction
  - pulmonary alveolar hemorrhage,
  - pulmonary hemorrhage
  - granulomatosis with polyangiitis

  - neutrophil count decreased
  - pancreatic carcinoma
  - hepatitis B
  - –

- Fourteen patients in the prednisone group experienced life-threatening AEs:

  - neutropenia
  - anemia, small intestinal hemorrhage, thrombocytopenia
  - pulmonary hemorrhage
  - myocardial infarction
  - acute myocardial infarction
  - ANCA positive vasculitis (2 patients)
  - lymphopenia
  - hyperglycemia, agranulocytosis
  - lymphopenia
  - lymphopenia, neutropenia
  - lymphopenia, hepatocellular injury, bilateral pulmonary embolism
  - sepsis
  - bacteremia and meningitis

The life-threatening events of Grade 4 lymphopenia in one patient in the prednisone group and the event of decreased neutrophil count in the avacopan group were not considered SAEs by the Investigators. The most frequently reported life-threatening AEs included pulmonary hemorrhage in the avacopan group, and lymphopenia, neutropenia, and ANCA vasculitis in the prednisone group.

In Study CL002_168, during the 84-day treatment period, 6 patients had severe TEAEs, evenly distributed across treatment arms. Similarly, during the 84-day treatment period of Study CL003_168, 6 patients experienced severe TEAEs, evenly distributed across all 3 treatment arms.

Treatment Emergent Adverse Events and Adverse Reactions

In Study CL010_168, treatment emergent AEs were reported by the majority of patients, balanced by treatment group (avacopan 164 patients (98.8%), prednisone 161 patients (98.2%). The most common SOC in which TEAEs were reported in both treatment arms was Infections and infestations (n=113 [68.1%] in the avacopan arm and n=124 [75.6%] in the prednisone arm). Infections are discussed in detail in the AESI section below. TEAEs were reported by a greater proportion of patients in the avacopan arm in the following SOCs: Gastrointestinal disorders (avacopan 60.8%, prednisone 50.6%), Investigations (avacopan 41.6%, prednisone 40.9%), Cardiac disorders (avacopan 15.7%, prednisone 12.8%), Ear and labyrinth disorders

(avacopan 12.0%, prednisone 9.8%), Hepatobiliary disorders (avacopan 6.0%, prednisone 1.8%), Reproductive system and breast disorders (avacopan 4.8%, prednisone 3.7%), and Surgical and medical procedures (avacopan 0.6%, prednisone 0).

The most frequently reported TEAEs by PT in the avacopan arm were nausea (n=39 [23.5%], 54 events), peripheral edema (n=35 [21.1%], 39 events), headache (n=34 [20.5%], 43 events), arthralgia (n=31 [18.7%], 42 events), and hypertension (n=30 [18.1%], 36 events). The most frequently reported TEAEs in the prednisone arm were generally similar, including peripheral edema (n=40 [24.4%], 56 events), muscle spasms (n=37 [22.6%], 47 events), arthralgia (n=36 [22.0%], 48 events), ANCA-positive vasculitis (n=34 [20.7%], 46 events), and nausea (n=34 [20.7%], 46 events).

Table 51 presents all TEAEs that occurred in ≥2% in patients in the avacopan arm and that occurred in a greater proportion of patients than those in the prednisone arm. The TEAEs that occurred in ≥2% of patients in the avacopan arm and with the greatest difference from the prednisone arm included headache, rash, white blood cell count decreased, CRP increased, and blood CPK increased.

Table 51. Summary of TEAEs Reported in ≥2% of Patients in the Avacopan Arm and Greater than Prednisone Arm (CL010_168)

Adverse Event	Prednisone (N=164) n (%)	Avacopan (N=166) n (%)
Any TEAEs	161 (98.2)	164 (98.8)
Nausea	34 (20.7)	39 (23.5)
Headache	23 (14.0)	34 (20.5)
Hypertension	29 (17.7)	30 (18.1)
Diarrhea	24 (14.6)	25 (15.1)
Vomiting	21 (12.8)	25 (15.1)
Rash	13 (7.9)	19 (11.4)
Fatigue	15 (9.1)	17 (10.2)
Abdominal pain upper	10 (6.1)	11 (6.6)
Dizziness	10 (6.1)	11 (6.6)
Blood creatinine increased	8 (4.9)	10 (6.0)
Paresthesia	7 (4.3)	9 (5.4)
Decreased appetite	7 (4.3)	8 (4.8)
Mouth ulceration	4 (2.4)	8 (4.8)
Musculoskeletal pain	6 (3.7)	8 (4.8)
Purpura	7 (4.3)	8 (4.8)
White blood cell count decreased	2 (1.2)	8 (4.8)
C-reactive protein increased	1 (0.6)	7 (4.2)
Depression	5 (3.0)	7 (4.2)
Dysgeusia	5 (3.0)	7 (4.2)
Dyspnea exertional	5 (3.0)	7 (4.2)
Granulomatosis with polyangiitis	3 (1.8)	7 (4.2)
Hematuria	5 (3.0)	7 (4.2)
Myopathy	6 (3.7)	7 (4.2)

Adverse Event	Prednisone (N=164) n (%)	Avacopan (N=166) n (%)
Acute kidney injury	5 (3.0)	6 (3.6)
Blood creatine phosphokinase increased	1 (0.6)	6 (3.6)
Gastroesophageal reflux disease	3 (1.8)	6 (3.6)
Hyperglycemia	5 (3.0)	6 (3.6)
Iron deficiency anemia	3 (1.8)	6 (3.6)
Syncope	3 (1.8)	6 (3.8)
Vertigo	5 (3.0)	6 (3.6)
Anxiety	4 (2.4)	5 (3.0)
Arthritis	1 (0.6)	5 (3.0)
Dysuria	2 (1.2)	5 (3.0)
Gastroenteritis	1 (0.6)	5 (3.0)
Infusion related reaction	4 (2.4)	5 (3.0)
Lipase increased	1 (0.6)	5 (3.0)
Nephrogenic anemia	3 (1.8)	5 (3.0)
Rhinitis	2 (1.2)	5 (3.0)
Angina pectoris	2 (1.2)	4 (2.4)
Cardiac failure	0	4 (2.4)
Cellulitis	0	4 (2.4)
Chronic kidney disease	3 (1.8)	4 (2.4)
Dyslipidemia	1 (0.6)	4 (2.4)
Ear pain	0	4 (2.4)
Gout	2 (1.2)	4 (2.4)
Hypotension	1 (0.6)	4 (2.4)
Otitis media	1 (0.6)	4 (2.4)
Palpitations	1 (0.6)	4 (2.4)
Renal impairment	3 (1.8)	4 (2.4)
Tinnitus	2 (1.2)	4 (2.4)

Source: CL010_168 Week 52 Final Tables, Table 14.3.1.1.2
Abbreviations: n, number of patients with adverse event; TEAE, treatment-emergent adverse event

In the phase 2 studies, the most common TEAEs were generally consistent with what was reported in the pivotal trial. In Study CL002_168, the most frequently reported AEs by PT in the combined avacopan arms included nausea (n=10 [22.7%]), vomiting (n=8 [18.2%]), and nasopharyngitis and hypertension (each with n=7 [15.9%]). The most frequently reported AEs in the standard-of-care arm included nausea (n=6 [26.1%]), muscle spasms (n=5 [27.1%]), and constipation and peripheral edema (each with n=4 [17.4%]). In Study CL003_168, common TEAEs were reported in a low number of patients, reflecting the small study population. The most frequently reported TEAEs in the avacopan 10 mg arm were nausea and hypertension, each reported by 2 patients. In the avacopan 30 mg arm, the most frequently reported TEAEs were hypertension (n=4 [25.0%]); peripheral edema (n=3 [18.8%]); and ecchymosis, diarrhea, flatulence, and blood creatinine increased (each with n=2 [12.5%]). These most frequently reported TEAEs in the avacopan arms were generally similar to the standard-of-care arm, which included hypertension (n=4 [30.8%]); fatigue (n=3 [23.1%]), and scab, weight increased, headache, fall, epistaxis, and paranasal sinus discomfort (each with n=2 [15.4%]).

In conclusion, in the pivotal trial, the frequency and types of reported TEAEs were generally similar in both treatment arms. The more frequently reported TEAEs in the phase 2 studies were also generally similar to the types of TEAEs reported in the pivotal study.

Laboratory Findings

Laboratory values (hematology, chemistry, urinalysis) were monitored per protocol in the pivotal trial and the phase 2 studies.

Hematology

In the pivotal trial, leukocyte counts were elevated at baseline at essentially the same counts in both arms, a mean ± SEM leukocyte count of 12.2 ± 0.35 x 10^3/µL in the prednisone arm and 12.2 ± 0.38 x 10^3/µL in the avacopan arm. At Week 1, there was initially an increase in the prednisone arm and a decrease in the avacopan arm, which may be reflective of the differences in glucocorticoid therapy. From there, both arms showed a similar decrease in mean leukocyte count to 6.8 ± 0.22 x 10^3/µL in the prednisone arm (mean change: -5.5 ± 0.37 x 10^3/µL) and 6.5 ± 0.19 x 10^3/µL in the avacopan arm (mean change: -5.6 ± 0.40 x 10^3/µL).

Like the total leukocyte counts, neutrophil counts were similarly elevated at baseline in both arms with a mean ± SEM neutrophil count of 9.8 ± 0.34 x 10^3/µL in the prednisone arm and 9.8 ± 0.36 x 10^3/µL in the avacopan arm. At Week 1, there was also an initial increase in the prednisone arm but a decrease in the avacopan arm, after which there was a gradual decrease in both arms. By Week 52, the mean neutrophil count remained in the normal range at 5.0 ± 0.20 x 10^3/µL in the prednisone arm (mean change: -4.9 ± 0.36 x 10^3/µL) and 4.7 ± 0.18 x 10^3/µL in the avacopan arm (mean change: -5.0 ± 0.37 x 10^3/µL).

Lymphocyte counts were within the low normal range at baseline, 1.9 ± 0.09 x 10^3/µL in the prednisone arm and 2.0 ± 0.10 x 10^3/µL in the avacopan arm. Over the course of the study, lymphocyte counts remained in the low normal range, decreasing similarly from baseline in both arms, 1.2 ± 0.04 x 10^3/µL in the prednisone arm (mean change: -0.7 ± 0.09 x 10^3/µL) and 1.2 ± 0.05 x 10^3/µL in the avacopan arm (mean change: -0.8 ± 0.1 x 10^3/µL) at Week 52.

Baseline hemoglobin values were slightly low but similar in both treatment arms at baseline, 11.5 ± 0.15 g/dL in the prednisone arm and 11.6 ± 0.14 g/dL in the avacopan arm. There was general stability to a slight increase in hemoglobin over the course of treatment. At Week 52, the mean ± SEM hemoglobin was 12.8 ± 0.13 g/dL in the prednisone arm (mean change: 1.2 ± 0.13 g/dL) and 13.0 ± 0.12 g/dL in the avacopan arm (mean change: 1.3 ± 0.13 g/dL).

Chemistry

Lab values were reported for baseline and at Week 52. Important measurements to review include serum creatinine, liver enzymes (aminotransferases, alkaline phosphatase, bilirubin), lactate dehydrogenase (LDH), total and LDL cholesterol, and creatine phosphokinase (CPK).

Baseline serum creatinine (mean ± SEM) was elevated for both treatment arms at baseline, 1.6 ± 0.07 mg/dL in the prednisone arm and 1.7 ± 0.07 mg/dL in the avacopan arm. The Week 52 values showed a similar decrease in both arms, 1.4 ± 0.08 mg/dL with a mean decrease of 0.2 ± 0.06 mg/dL in the prednisone arm and 1.4 ± 0.05 mg/dL with a mean decrease of 0.2 ± 0.04 mg/dL in the avacopan arm.

The liver enzymes showed the following changes during the treatment period:

The baseline alanine aminotransferase (ALT) (mean ± SEM) was in the normal range for both treatment arms, 23.0 ± 1.48 U/L in the prednisone arm and 22.5 ± 1.60 U/L in the avacopan arm. At the end of treatment visit, ALT had a similar decrease in both treatment arms. At Week 52, the value was 15.3 ± 0.63 U/L in the prednisone arm with a mean decrease of 8.2 ± 1.48 U/L in the prednisone arm and 14.9 ± 0.73 U/L with a mean change of 7.2 ± 1.46 U/L in the avacopan arm.

The baseline aspartate aminotransferase (AST) (mean ± SEM) was in the normal range for both treatment arms, 16.8 ± 0.71 U/L in the prednisone arm and 15.1 ± 0.54 U/L in the avacopan arm. At the Week 52 visit, AST remained relatively stable in both treatment arms. The Week 52 value was 17.4 ± 0.46 U/L in the prednisone arm with a mean change of 0.5 ± 0.81 U/L in the prednisone arm and 17.2 ± 0.48 U/L with a mean change of 2.0 ± 0.69 U/L in the avacopan arm.

Baseline alkaline phosphatase (mean ± SEM) began at the same values within normal range, 65.1 ± 1.72 U/L in the prednisone arm and 66.0 ± 2.24 U/L in the avacopan arm. Alkaline phosphatase decreased initially in the prednisone arm with the greatest decreases at Weeks 7 and Week 13, a mean change of 12.8 ± 1.71 U/L and 12.4 ± 1.91 U/L, respectively. The decrease in alkaline phosphatase persisted through approximately Week 23. A similar trend was not seen in the avacopan arm. However, by Week 52, both values were close to baseline with a slightly greater decrease in the avacopan arm, 65.2 ± 1.61 U/L in the prednisone arm (mean change: 0.8 ± 1.77 U/L) and 62.1 ± 1.71 U/L in the avacopan arm (mean change: -4.0 ± 2.34 U/L).

The baseline total bilirubin value (mean ± SEM) was in the normal range for both treatment arms, 0.4 ± 0.01 mg/dL in the prednisone arm and 0.5 ± 0.02 mg/dL in the avacopan arm. At the end of treatment visit, bilirubin remained relatively stable in both treatment arms. The Week 52 value was 0.5 ± 0.02 mg/dL in the prednisone arm with a mean change of 0.05 ± 0.02 mg/dL in the prednisone arm and 0.5 ± 0.02 mg/dL with a mean change of 0.06 ± 0.02 mg/dL in the avacopan arm.

Baseline lactate dehydrogenase (LDH) (mean ± SEM) began at the same values within normal range, 182.3 ± 5.29 U/L in the prednisone arm and 182.5 ± 4.11 U/L in the avacopan arm. LDH increased through Week 16 in the prednisone arm, 206.4 ± 5.23 U/L with a mean change of 24.0 ± 6.45 U/L in the prednisone arm and 179.4 ± 3.36 U/L with a mean change of -3.1 ± 5.11 U/L in the avacopan arm. However, both values decreased by Week 52, 174.5 ± 3.26 U/L with a mean change of -8.6 ± 5.33 U/L in the prednisone arm and 172.0 ± 2.65 U/L with a mean change of -10.7 ± 4.80 U/L in the avacopan arm.

Total and LDL cholesterol increased over the treatment period in a greater amount in the prednisone arm. The baseline total cholesterol value (mean ± SEM) was in the normal range for both treatment arms, 201.0 ± 3.45 mg/dL in the prednisone arm and 205.5 ± 3.96 mg/dL in the avacopan arm. Total cholesterol increased in both treatment arms with the greatest increase in the first 20 weeks of study. By Week 52, total cholesterol values were 214.3 ± 3.78 mg/dL in the prednisone arm with a mean change of 13.8 ± 4.28 mg/dL in the prednisone arm and 212.1 ± 4.21 mg/dL with a mean change of 9.3 ± 4.05 mg/dL in the avacopan arm. The baseline LDL cholesterol value (mean ± SEM LDL cholesterol) was in the normal range for both treatment arms, 115.0 ± 2.87 mg/dL in the prednisone arm and 117.7 ± 3.26 mg/dL in the avacopan arm. LDL cholesterol increase was greater in the prednisone arm. The end of treatment value was 136.5 ± 3.51 mg/dL in the prednisone arm with a mean change of 21.7 ± 3.48 mg/dL in the prednisone arm and 128.9 ± 3.72 mg/dL with a mean change of 11.9 ± 3.41 mg/dL in the avacopan arm. (Week 52 values were not provided.)

The baseline CPK (mean ± SEM) was in the normal range for both treatment arms, 53.2 ± 4.42 U/L in the prednisone arm and 47.2 ± 3.46 U/L in the avacopan arm. At the Week 52 visit, CPK increased in both arms but with a greater increase in the avacopan arm. The Week 52 value was 110.2 ± 5.44 U/L in the prednisone arm with a mean change of 57.6 ± 5.67 U/L in the prednisone arm and 125.4 ± 10.58 U/L with a mean change of 76.3 ± 9.68 U/L in the avacopan arm.

The phase 2 studies showed similar changes in neutrophil count, lymphocyte count, LDH, and CPK. Otherwise, laboratory values stayed relatively stable through the treatment period.

The total WBC count (mean ± SEM) in Study CL002_168 was elevated at baseline, 11.4 ± 0.97 x 10^9/L in the standard-of-care arm, 11.4 ± 0.97 x 10^9/L in the avacopan + low dose prednisone arm, and 9.96 ± 0.68 x 10^9/L in the avacopan + no prednisone arm. The total WBC decreased in all treatment arms through the study. Day 85 values showed a numerically greater decrease in the avacopan + low dose prednisone arm with values of 6.2 ± 0.58 x 10^9/L with a mean decrease of 5.1 ± 1.08 x 10^9/L compared to 8.8 ± 0.63 x 10^9/L with a mean decrease of 2.4 ± 0.92 x 10^9/L in the standard-of-care arm and 6.3 ± 0.62 x 10^9/L with a mean decrease of 3.4 ± 0.58 x 10^9/L in the avacopan + no prednisone arm.

Specifically, for the absolute neutrophil count, there was a decrease in all treatment arms that was greatest in the avacopan + low dose prednisone arm. On Day 85, the mean change ± SEM was -4.5 ± 1.16 x 10^9/L in the avacopan + low dose prednisone arm compared to -2.4 ± 0.96 x 10^9/L in the standard-of-care-arm and -2.6 ± 0.48 x 10^9/L in the avacopan + no prednisone arm.

In Study CL003_168, the total WBC count (leukocytes) was also elevated at baseline and decreased in the study in all treatment arms, with a numerically greater change in the avacopan 10 mg arm. The baseline WBC count (mean ± SEM) was 11.4 ± 1.56 x 10^9/L in the standard-of-care arm, 11.7 ± 1.41 x 10^9/L in the avacopan + low dose prednisone arm, and 11.6 ± 1.03 x 10^9/L in the avacopan + no prednisone arm. Day 85 values were 7.5 ± 0.47 x 10^9/L with a mean decrease of 4.2 ± 1.32 x 10^9/L in the avacopan 10 mg arm and 8.62 ± 0.67 x 10^9/L with a mean decrease of 3.0 ± 1.08 x 10^9/L in the avacopan 30 mg arm compared to 8.7 ± 1.06 x 10^9/L with a mean decrease of 2.7 ± 1.49 x 10^9/L in the standard-of-care arm.

Neutrophil counts, however, decreased in a similar amount in all treatment arms and may reflect that glucocorticoids were administered in all treatment arms. On Day 85, the mean change ± SEM was a mean decrease of 2.4 ± 1.25 x 10^9/L in the standard-of-care-arm and 3.2 ± 1.10 x 10^9/L in the avacopan 10 mg arm and 2.7 ± 0.98 x 10^9/L in the avacopan 30 mg arm.

Changes in liver enzymes were generally unremarkable in the phase 2 studies and did not show consistent trends. In Study CL002_168, ALT decreased in all treatment arms with a mean decrease on Day 85 of 2.0 ± 2.69 U/L in the standard-of care arm and 8.6 ± 5.37 U/L in the avacopan + low dose prednisone arm and 1.3 ± 5.37 U/L in the avacopan + no prednisone arm. AST stayed relatively stable in the standard-of-care arm and avacopan + low dose prednisone arm but showed a small increase in the avacopan + no prednisone arm. On Day 85, there was a mean decrease of 0.4 ± 1.79 U/L in the standard-of care arm and 1.1 ± 3.25 U/L in the avacopan + low dose prednisone arm compared to a mean increase of 4.4 ± 1.64 U/L in the avacopan + no prednisone arm.

In Study CL003_168, ALT values showed a mean decrease in the standard-of-care and avacopan 10 mg arms but a small increase in the avacopan 30 mg arm. On Day 85, there was a mean decrease of 1.3 ± 1.63 U/L in the standard-of care arm and 6.9 ± 3.99 U/L in the avacopan 10 mg arm compared to a mean increase of 2.8 ± 4.36 U/L in the avacopan 30 mg arm. AST values were generally stable in the standard-of-care arm with a small decrease in the avacopan 10 mg arm and a small increase in the avacopan 30 mg arm. The mean change at the on Day 85 was a mean increase of 0.2 ± 0.80 U/L in the standard-of care arm and 2.4 ± 2.63 U/L in the avacopan 30 mg arm compared to a mean decrease of 3.6 ± 2.58 U/L in the avacopan 10 mg arm.

CPK elevations were seen in the avacopan arms in the phase 2 studies. On Day 85, in Study CL002_168, the mean increase was 33.7 ± 11.71 U/L in avacopan + low dose prednisone arm and 121.5 ± 36.36 U/L in the avacopan + no prednisone arm compared to a mean decrease of 9.8 ± 24.92 U/L in the standard-of care arm. In Study CL003_168, there was CPK elevation in all

treatment arms, but the increase was numerically greater in the arms receiving avacopan with an apparent dose response. The mean change on Day 85 was a mean increase of 11.5 ± 8.18 U/L in the standard-of care arm compared to 33.3 ± 22.91 U/L in the avacopan 10 mg arm and 64.1 ± 54.47 U/L in the avacopan 30 mg arm.

In this review, the significant laboratory abnormalities (elevated liver enzymes, low WBC count, and elevated CPK) reported as AEs are discussed under the AESIs below.

Vital Signs

No clinically meaningful changes in vital signs (e.g., blood pressure, pulse rate, temperature) were noted and changes were similar across treatment arms. Additionally, weight and BMI were noted by the Applicant to be a reflection in glucocorticoid toxicity. Both measures increased in both treatment arms without a significant difference in change from baseline. The change in mean weight from baseline to Week 52 was 3.48 kg in the prednisone arm and 3.37 kg in the avacopan arm. The change in mean BMI from baseline to Week 52 was 1.23 kg/m2 in the prednisone arm and 1.02 kg/m2 in the avacopan arm.

No clinically meaningful changes in vital signs were noted in the phase 2 studies.

Electrocardiograms

In Study CL010_168, 20 patients had an abnormal electrocardiogram (ECG) considered clinically significant during the study. Three patients (1 in the prednisone arm and 2 in the avacopan arm) had an abnormal ECG at baseline. For the other 17 patients (n=7 in the prednisone group and n=10 in the avacopan group), the following ECG abnormalities were reported as AEs:

- T wave abnormalities (n=2 in the prednisone group and n=1 in the avacopan group)
- QT prolongation (n=1 in the prednisone group and n=2 in the avacopan group)
- AV or bifascicular block (n=3 in the prednisone group and n=2 in the avacopan group)
- Bradycardia (n=1 in the prednisone group and n=2 in the avacopan group)
- Tachycardia (none in the prednisone group and n=1 in the avacopan group)
- Atrial fibrillation (none in the prednisone group and n=1 in the avacopan group)
- Ventricular extrasystole (none in the prednisone group and n=1 in the avacopan group)

Of these patients, three also had cardiac SAEs. In the prednisone arm, one of the patients with the ECG finding of T-wave inversion subsequently had a non-fatal MI. Two patients had cardiac SAEs in the avacopan arm. One patient with the ECG finding of tachycardia was later diagnosed with a non-fatal MI and thrombosis. The other patient in the avacopan arm had an SAE of a first-degree AV block.

The phase 2 studies also noted few ECG abnormalities, also greater in the avacopan groups.

In Study CL002_168, 19 patients were reported to have abnormal ECGs. Of these, Investigators deemed five of them to be "clinically significant." Four of the five clinically significant ECG findings occurred in patients in the avacopan and no prednisone arm. These included completed left bundle branch block, atrial fibrillation, right bundle branch block/bradycardia/left ventricular hypertrophy, and tachycardia. One patient in the standard-of-care arm had atrial fibrillation.

In Study CL003_168, 32 patients were reported to have abnormal ECGs. Of these, Investigators deemed three of them to be "clinically significant." Two patients were in the avacopan 30 mg arm and had ECG findings of atrial fibrillation and "normal sinus rhythm with sinus arrhythmia, anterior infarct (age undetermined)." One patient in the standard-of-care arm had QT lengthening/premature ventricular complexes.

The proportion of patients with ECG findings and AEs of abnormal ECG findings was greater in the avacopan arm compared to the prednisone arm. However, the overall numbers are low, without clustering by type of abnormality. Few patients had ECG abnormalities associated with a cardiac SAE. Given the small numbers of events, conclusions are limited on the effect of avacopan on ECGs.

QT

A thorough QT study, Study CL014_168, a randomized, double-blind, placebo- and active-controlled, parallel group study was conducted in healthy subjects. The study was reviewed by the Interdisciplinary Review Team (IRT) for Cardiac Safety Studies who determined that no significant QTc prolongation effect of avacopan was detected in the QT assessment. See QT Study Review by Dr. Girish Bende for additional details of the IRT review.

Immunogenicity

Not applicable

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant identified the following AESIs in Study CL010_168: infections, hepatotoxicity (hepatic abnormalities including hepatobiliary disorders and liver-enzyme elevations), low WBC count, and hypersensitivity/angioedema. Additionally, the following AEs are described in more detail as AESIs: elevated CPK, vasculitis, and AEs associated with glucocorticoid use. In the phase 2 studies, AEs associated with glucocorticoid use and infections were not pre-specified as AESIs but are discussed below. Malignancy was not an AESI but is a potential risk with immunosuppression and is described further below. The methods by which the Applicant defined these AESIs are described under each AE.

8.2.5.1. Infections

In Study CL010_168, infections occurred in similar proportions of patients in both treatment arms, as displayed in Table 52. The difference in overall treatment-emergent infections was 7.5%, with a greater proportion of patients in the prednisone arm with infections. An exposure-adjusted incidence rate was also similar across treatment arms but numerically greater in the prednisone arm, 155.7/100 patient-years in the prednisone arm and 133.3/100 patient-years in the avacopan arm. The proportion of patients with infections leading to study drug discontinuation, severe and life-threatening infections, and infections leading to death was similar across treatment arms. Serious infections are further discussed below.

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

Infection Type	Prednisone (N=164) n (%)	Avacopan (N=166) n (%)	Avacopan vs. Prednisone Diff (95% CI)
Any treatment-emergent infections	124 (75.6)	113 (68.1)	-7.5% (17.2, 2.1)
Any serious treatment-emergent infections	25 (15.2)	22 (13.3)	-2.0% (-9.5, 5.6)
Any severe treatment-emergent infections	10 (6.1)	12 (7.2)	1.1% (-4.2, 6.5)
Any treatment-emergent infection leading to study drug discontinuation	5 (3.0)	4 (2.4)	-0.6% (-4.2, 2.9)
Any treatment-emergent life-threatening infection	2 (1.2)	1 (0.6)	-0.6% (-2.7, 1.4)
Any treatment-emergent infection leading to death	2 (1.2)	1 (0.6)	-0.6% (-2.7, 1.4)

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

The most common infections were nasopharyngitis (n=25 [15.1%] in the avacopan arm and n=30 [18.3%] in the prednisone arm), upper respiratory tract infection (n=24 [14.5%] in the avacopan arm and n=24 [14.6%] in the prednisone arm), urinary tract infection (n=12 [7.2%] in the avacopan arm and n=23 [14.0%] in the prednisone arm), pneumonia (n=11 [6.6%] in the avacopan arm and n=11 [6.7%] in the prednisone arm), and sinusitis (n=10 [6.0%] in the avacopan arm and n=12 [7.3%] in the prednisone arm). Of the common infections, only gastroenteritis (n=5 [3.0%] in the avacopan arm vs. n=1 [0.6%] in the prednisone arm) and rhinitis (n=5 [3.0%] in the avacopan arm vs. n=2 [1.2%] in the prednisone arm) occurred in a greater proportion of patients in the avacopan arm compared to the prednisone arm. The other common treatment-emergent infections reported occurred in similar proportions or were higher in the prednisone arm.

The proportion of patients with serious infections for the duration of the study period was similar between treatment arms (n=22 [13.3%, 25 events] in the avacopan arm and n=25 [15.2%, 31 events] in the prednisone arm). While on-treatment, there were 20 patients in the avacopan arm and 19 patients in the prednisone who experienced a serious infection. The exposure-adjusted incidence rates of serious infections while on-treatment was similar in both treatment arms, 15.7/100 patient-years in the avacopan arm and 14.1/100 patient-years in the

prednisone arm. Table 53 presents the number of patients in the pivotal trial who reported serious infections. The most common serious infection by PT was pneumonia occurring in 4.8% (n=8) in the avacopan arm and 3.7% (n=6) in the prednisone arm. Four serious infections occurred in more than 1 patient in the avacopan arm; these included pneumonia, urinary tract infection (n=3 [1.8%] in the avacopan arm and n=2 [1.2%] in the prednisone arm), device-related infection (n=2 [1.2%] in the avacopan arm and none in the prednisone arm), and influenza (n=2 [1.2%] in the avacopan arm and n=1 [0.6%] in the prednisone arm). In the avacopan arm, there were 4 patients with serious infections related to sepsis (one patient each with neutropenic sepsis, post-procedural sepsis, sepsis, and urosepsis), compared to 1 prednisone treated patient with sepsis. Other reported serious infections include single avacopan-treated patients with bronchitis, *Campylobacter* gastroenteritis, hepatitis B, pneumonia haemophilus, infective exacerbation of chronic obstructive airways disease. In the prednisone arm, there were 2 patients with herpes zoster (n=2 herpes zoster), 2 patients with respiratory syncytial virus (RSV) infection, and 2 patients with infectious pleural effusion. In addition, there were also single patients with the following serious infections: *Aspergillus* infection, *Cryptococcus*, fungal infection, meningitis, CMV pneumonia, bacterial pneumonia, parainfluenzae virus infection, bacteremia, bronchitis, subcutaneous abscess, lower respiratory tract infection, *Staphylococcal* infection, and ophthalmic herpes simplex.

Table 53. Serious Infections in Study CL010 168 (Safety Population)

Preferred Terms	Prednisone N=164 n (%)	Avacopan N=166 n (%)
Any Serious Infection	25 (15.2)	22 (13.3)
Pneumonia	6 (3.7)	8 (4.8)
Urinary tract infection	2 (1.2)	3 (1.8)
Device related infection	0	2 (1.2)
Influenza	1 (0.6)	2 (1.2)
Bronchitis	1 (0.6)	1 (0.6)
Campylobacter gastroenteritis	0	1 (0.6)
Hepatitis B	0	1 (0.6)
Infective exacerbation of chronic obstructive airways disease	0	1 (0.6)
Neutropenic sepsis	0	1 (0.6)
Pneumonia haemophilus	0	1 (0.6)
Post procedural sepsis	0	1 (0.6)
Sepsis	1 (0.6)	1 (0.6)
Urosepsis	0	1 (0.6)
Aspergillus infection	1 (0.6)	0
Bacteraemia	1 (0.6)	0
Cryptococcus	1 (0.6)	0
Fungal infection	1 (0.6)	0
Herpes zoster	2 (1.2)	0
Infectious pleural effusion	2 (1.2)	0
Lower respiratory tract infection	1 (0.6)	0

Preferred Terms	Prednisone N=164 n (%)	Avacopan N=166 n (%)
Meningitis	1 (0.6)	0
Ophthalmic herpes simplex	1 (0.6)	0
Parainfluenzae virus infection	1 (0.6)	0
Pneumonia bacterial	2 (1.2)	0
Pneumonia cytomegaloviral	1 (0.6)	0
Respiratory syncytial virus infection	2 (1.2)	0
Respiratory tract infection viral	1 (0.6)	0
Staphylococcal infection	1 (0.6)	0
Subcutaneous abscess	1 (0.6)	0

Source: CL010_168 CSR, Table 14.3.1.3.1, pages 1916-1917.
Abbreviations: N, number of patients randomized who received at least one dose of drug; n, number of subjects with at least one event.

The Applicant defined serious opportunistic infections as those secondary to the following organisms: tuberculosis, *Candida*, *Aspergillus*, *Cryptococcus*, herpes, CMV, *Clostridium difficile* and *Clostridium jejuni*, respiratory syncytial virus, *Ehrlichia*, hepatitis B reactivation, *Pseudomonas* UTI, and metapneumovirus respiratory tract infection. More cases of serious opportunistic infections were reported in the prednisone arm (n=11, 6.7%) compared to the avacopan arm (n=6, 3.6%). The opportunistic infections in the avacopan arm included the following:

- Chlamydia pneumonia and sepsis
- Two cases of Aspergillus pneumonia, one which led to death as already described above
- "Infective COPD" with RSV on nasopharyngeal swab
- Campylobacter gastroenteritis
- Hepatitis B virus (HBV) reactivation – this case was described as life-threatening but resolved. The event occurred 27 days after the last day of avacopan. Patient 9xx-xx1 is described in more detail in Table 134 (in the Appendix) which describes SAEs of elevated liver enzymes, as the HBV reactivation was associated with Grade 3/4 aminotransaminase elevations.
    - This patient was a 79-year-old man who received avacopan and rituximab on Day 1. Avacopan was dosed twice daily. Rituximab was dosed on Days 21, 29, 36, 225, and 239. On Day 50, he had mild hepatic enzyme elevations that resolved by study day 71 without any changes in his medication. On Day 391, he experienced elevated ALT and AST (ALT 90 U/L and AST 90 U/L), determined to be an SAE of HBV reactivation. Subsequently, liver enzymes continued to increase with a peak in ALT on Day 448. Avacopan was discontinued on Day 364, and rituximab was not re-dosed after Day 239. The Investigator described this case as life-threatening and possibly related to avacopan. The DHN DILI team reviewed this case and noted that the INR was elevated (up to 1.48) with normal

bilirubin after Day 421. DHN generally agreed with the Investigator's assessment although HBV reactivation secondary to rituximab could not be excluded.

- In addition, there was another case of non-life-threatening HBV reactivation. This case is described below in the Hepatotoxicity Section (Section 8.2.5.2) as one of the cases of probable drug-induced liver injury due to avacopan. This case is also described in Table 134 (in the Appendix).

In general, these opportunistic infections were similar to the cases observed in the prednisone arm, which included two cases of *Aspergillus*, two cases of RSV, two cases of *Cryptococcus* (one pneumonia, one meningitis), two cases of serious herpes zoster, and single cases of Metapneumovirus respiratory infection, CMV pneumonia, and ophthalmic herpes simplex. In addition, non-serious herpes zoster was reported by six patients in the prednisone arm and four patients in the avacopan arm. There were two cases of latent tuberculosis in the avacopan arm during screening, and these patients had early withdrawal of study medication (by Day 7). No other cases of latent or active TB were reported in the pivotal study.

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

In the phase 2 studies, patients with reported treatment-emergent infections were generally balanced across avacopan-treated groups (52.1%) and the standard-of-care group (41.7%). In Study CL002_168, the proportion of patients with AEs in the SOC of Infections and infestations was numerically greater in the arms that received avacopan (54.5% in the avacopan + no prednisone group vs. 45.5% in the avacopan + low dose prednisone group vs. 39.1% in the standard-of-care group). Serious infections generally occurred evenly across treatment arms with 1 patient in the avacopan + low dose prednisone arm (PT of febrile infection), two patients in the avacopan + no prednisone arm (PTs of respiratory tract infection and CRP increased [likely infectious source based on narrative]), and one patient in the standard-of-care arm (PT of pneumonia). In Study CL003_168, the proportion of patients with AEs in the SOC of Infections and infestations was numerically greatest in patients who were treated with avacopan 30 mg (31.3%) compared to both the avacopan 10 mg group (15.4%) and the standard-of-care group (15.4%). Only four serious infections occurred in the entire study and were balanced across treatment arms. These comprised one patient with *Staphylococcal* cellulitis, abscess limb, and perirectal abscess in the avacopan 10 mg arm; two patients, one with sepsis and one with a UTI, in the avacopan 30 mg arm; one patient with gangrene (likely related to infection with underlying osteomyelitis) in the standard-of-care arm. All patients, except the one with the UTI, discontinued study treatment.

In summary, based on the larger pivotal trial, infections, including treatment-emergent and serious infections, were generally similar between treatment groups. Serious opportunistic infections were observed in a greater number of prednisone-treated patients, although

differences between groups were due to a small number of patients. The types of serious opportunistic infections were generally similar between treatment groups. In the phase 2 studies, a numerically greater proportion of patients on avacopan developed an infection. Serious infections were balanced across treatment arms, but the number of patients with serious infections was low.

8.2.5.2. Hepatotoxicity

Hepatotoxicity was a specified adverse event of interest based on cases of liver enzyme elevation (specifically, AST and ALT) in the clinical development program. The Applicant evaluated any "TEAEs associated with hepatic abnormalities," which included PTs in the SOCs of Investigations (hepatic enzymes increased, alanine aminotransferase increased, blood bilirubin increased, liver function test increased, aspartate aminotransferase increased, transaminases increased, liver function test abnormal) and Hepatobiliary Disorders (hepatic function abnormal, drug-induced liver injury, hepatitis cholestatic, hepatocellular injury). As presented in Table 54, 22 patients (13.3%) in the avacopan arm and 19 patients (11.6%) in the prednisone arm had AEs associated with hepatic abnormalities. In the avacopan arm, this included 16 patients who had the defined AEs in the Investigations SOC and 6 who had AEs in the Hepatobiliary Disorders SOC; in the prednisone arm, this included 18 patients who had AEs in the Investigations SOC and 1 who had AEs in the Hepatobiliary Disorders SOC. AEs associated with hepatic abnormalities led to drug discontinuation in 7 patients in the avacopan arm and 2 patients in the prednisone arm. Specifically, 5 patients in the avacopan arm and no patients in the prednisone arm discontinued due to an AE in the Hepatobiliary Disorder SOC, whereas 2 patients in each arm discontinued study drug due to an AE in the Investigations SOC.

Table 54. TEAEs Associated with Hepatic Abnormalities in Study CL010_168 (Safety Population)

System Organ Class Preferred Term	Prednisone N=164 n (%)	Avacopan N=166 n (%)
Any TEAE associated with hepatic abnormalities	19 (11.6)	22 (13.3)
Investigations	18 (11.0)	16 (9.6)
Hepatic enzyme increased	7 (4.3)	5 (3.0)
Alanine aminotransferase increased	6 (3.7)	3 (1.8)
Blood bilirubin increased	0	3 (1.8)
Liver function test increased	1 (0.6)	3 (1.8)
Aspartate aminotransferase increased	4 (2.4)	2 (1.2)
Transaminases increased	3 (1.8)	2 (1.2)
Liver function test abnormal	2 (1.2)	0
Hepatobiliary disorders	1 (0.6)	6 (3.6)
Hepatic function abnormal	0	3 (1.8)
Drug-induced liver injury	0	1 (0.6)
Hepatitis cholestatic	0	1 (0.6)
Hepatocellular injury	1 (0.6)	1 (0.6)

Source: CL010_168 CSR, Table 29, page 134.
Abbreviations: N, number of patients randomized who received at least one dose of drug; n, number of subjects with at least one event.

These "TEAEs associated with hepatic abnormalities" are not inclusive of all AEs in the Hepatobiliary or Investigations (liver-related) SOC that occurred in this trial, as not all PTs were identified by the Applicant as a "TEAE associated with hepatic abnormalities." If all PTs within the Hepatobiliary SOC are assessed, the total number of patients with AEs are greater in both arms with a total of 10 patients in the avacopan arm (additional PTs of cholelithiasis (n=2, 1.2%), cholestasis (n=2, 1.2%), hepatitis (n=2, 1.2%), biliary dilatation (n=1, 0.6%)) and 3 patients in the prednisone arm (additional PTs of cholelithiasis (n=1, 0.6%) and hepatic steatosis (n=1, 0.6%)). If all "liver-related" PTs within the Investigations SOC are assessed, there were 2 additional patients (1.2%) in each treatment arm with the PT of gamma-glutamyltransferase increased. This would make a total of 20 patients in the prednisone arm and 18 patients in the avacopan arm with a liver-related PT in the Investigations SOC.

The proportion of patients with SAEs within the Hepatobiliary system organ class were greater in the avacopan group (3.6%) as compared to the prednisone group (0.6%). Nine patients (5.4%) in the avacopan arm and 6 patients (3.7%) in the prednisone arm experienced SAEs associated with hepatic abnormalities.

Evaluation of hepatotoxicity also included a review of the liver enzymes by CTCAE grade, as shown in Table 55. This table shows the results from the central laboratory.

Table 55. Liver Enzyme Elevations by CTCAE Grade in Study CL010_168

Parameter (Normal Range) CTCAE Grade	Avacopan (N=166) n (%)	Prednisone (N=164) n (%)
Alanine aminotransferase (U/L) normal range: 6-41		
Grade 1	35 (21.1)	28 (17.1)
Grade 2	6 (3.6)	4 (2.4)
Grade 3	4 (2.4)	3 (1.8)
Grade 4	0	1 (0.6)
Aspartate aminotransferase (U/L) normal range: 9-34		
Grade 1	28 (16.9)	29 (17.7)
Grade 2	3 (1.8)	0
Grade 3	5 (3.0)	4 (2.4)
Grade 4	0	0
Bilirubin (mg/dL) normal range: 0.1-1.1		
Grade 1	12 (7.2)	8 (4.9)
Grade 2	2 (1.2)	1 (0.6)
Grade 3	1 (0.6)	0
Grade 4	0	0
Alkaline phosphatase (U/L) normal range: 37-116		
Grade 1	24 (14.5)	16 (9.8)
Grade 2	3 (1.8)	1 (0.6)
Grade 3	0	1 (0.6)
Grade 4	0	0

Source: CL010_168 CSR, Table 31, page 137.
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

Alkaline Phosphatase:
- 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

Abbreviations: CTCAE, common terminology criteria for adverse events; ULN, upper limit of normal.

For both treatment arms, the majority of elevations in these values was low (Grade 1). All the patients with Grade 3 or 4 elevations were captured in the SAEs associated with hepatic abnormalities or as the event of HBV reactivation (described below and in Table 134). However, it may also be helpful to consider the extent of elevation (i.e., higher grades of 3 or 4), which was low in both treatment arms.

The DHN DILI team reviewed the avacopan program for hepatotoxicity and provided an analysis of each SAE in the phase 3 trial (n=9) and the additional SAE in the phase 2 study CL002_168 for potential DILI. In summary, the DILI team noted the following findings:

- One patient had peak transaminases over 3 times ULN with concurrent jaundice and only modest alkaline phosphatase elevation (Hy's Law criteria3). The case was determined to be highly likely DILI, but there was a plausible competing medication (specifically, simvastatin) making it impossible to implicate avacopan with confidence. It is noteworthy that simvastatin is metabolized via CYP3A4, and avacopan is a weak inhibitor of CYP3A4. Thus, a potential drug-drug interaction between simvastatin and avacopan should also be considered.
- Of the 10 SAEs, 3 cases were considered unlikely due to avacopan hepatotoxicity due to alternate causes being much more likely (i.e., azathioprine liver injury, bile duct obstruction, and gallstone disease). Three cases were determined to be possible DILI due to avacopan; 3 cases were determined to be probably DILI due to avacopan; 1 case was determined to be highly likely DILI due to avacopan. Of these 4 cases that are more clearly due to avacopan, no patients became jaundiced, and all cases improved back to baseline without stopping avacopan.

Highly likely DILI

- Severe hepatocellular injury: An 80-year-old woman with MPO+ MPA developed elevated liver enzymes (ALT 300 U/L and AST 150 U/L) on Day 37. She had received avacopan and rituximab on Day 1. After liver enzymes elevation, avacopan and sulfamethoxazole-trimethoprim (Sulfa-TMP) were both held. A work-up for liver etiology was negative. Liver enzymes decreased on Day 43. Avacopan was re-started and followed by an increase in liver enzymes after which avacopan was permanently discontinued. Liver enzymes then return to baseline. The Investigator considered this case to be possibly related to study drug. With the positive re-challenge and complete washout to baseline after stopping avacopan permanently, DHN determined this case to be highly likely DILI from avacopan.

Probable DILI

- Moderately severe hepatitis and hepatitis cholestatic: A 54-year-old woman with MPO+ MPA developed elevated transaminases without jaundice 13 weeks after avacopan start and while still on avacopan. This patient's background immunosuppressive therapy

[3] Hy's Law is a means of identifying DILI cases that have a mortality risk of approximately 10%. The criteria have been used in drug development to identify drugs that may have significant or unacceptable risk of severe liver injury. Components of Hy's Law include the following criteria: (1) Evidence of hepatocellular injury by any elevated aminotransferase of >3x ULN; (2) Evidence of liver dysfunction by an increase in bilirubin ≥ 2x ULN and without evidence of cholestasis by alkaline phosphatase <2x ULN; (3) No other cause such as viral hepatitis, pre-existing or acute liver disease, or another drug capable of causing the observed injury.

included IV CYC on Day 1 which was then transitioned to AZA on Day 107. She had normal liver enzymes at baseline but then developed a modest elevation on Day 70. Without a change in avacopan dosing, AST and ALT further increased to 229 U/L and 380 U/L on Day 92, respectively. Avacopan was discontinued on Day 97 after which liver enzymes decreased. No other etiology of liver disease was diagnosed. The Investigator considered this case to be possibly related to avacopan, whereas DHN determined this case to be probable DILI attributed to avacopan due to the latency being acceptable and rapid washout after stopping avacopan.

- Moderately severe hepatic enzyme increased: A 79-year-old woman with MPO+ MPA developed elevated liver enzymes without jaundice 6-7 weeks after avacopan start and while still on drug. On Day 1, the patient had a mild elevation in AST and ALT (35 U/L and 88 U/L, respectively). Liver enzymes fell to normal and remained within normal range until Day 49 when they increased substantially (ALT 336 U/L, AST 224 U/L, Alkaline phosphatase 190 U/L). Sulfa-TMP and avacopan were held, and liver tests fell. Avacopan was restarted on Day 70, and Sulfa-TMP was restarted on Day 83. Liver enzymes then increased again on Day 103. Sulfa-TMP was held, and liver enzymes continued to rise. Avacopan was held, and liver enzymes returned to normal. The Investigator considered this case to be possibly related to avacopan. DHN determined this case to be probable DILI due to avacopan. Although there was a positive re-challenge with avacopan, sulfa-TMP also competes as a possible etiology. Additionally, no other tests to evaluate for an alternate liver etiology were conducted.

- Severe hepatic function abnormal: 81-year-old Asian woman with MPO+ MPA developed cholestatic liver injury 4 weeks after starting avacopan and while still on study drug. Background immunosuppressive therapy was IV CYC. Liver enzymes were normal at baseline. The patient is presumed to have had prior exposure to HBV, although HBV DNA was negative while on avacopan. No serologies were provided. She developed an elevation in alkaline phosphatase on Day 29, which increased to 1503 U/L on Day 44. AST and ALT were also increased by Day 43, but only 3x to 5x ULN. Both avacopan and sulfa-TMP were stopped. Sulfa-TMP was subsequently restarted, whereas avacopan was not. The investigator considered this case to be possibly related to study drug or IV CYC. DHN determined this to be probably related to avacopan, as no other cause competed well. No other etiology of liver disease was determined (negative imaging). Sulfa-TMP was restarted, and liver enzymes continued to improve. CYC liver injury is not typically associated with alkaline phosphatase elevation. HBV DNA remained negative through Day 29 when injury began. HBV DNA was noted to be persistently positive at low titer only after enzymes were declining (Day 50). Thus, DHN did not feel that the clinical course was consistent with acute HBV infection based on

liver injury pattern and timing of HBV DNA appearance. Patient did not receive rituximab until Day 71, well after HBV DNA appeared. Therefore, DHN considered the events to be most consistent with HBV reactivation unrelated to the liver injury but potentially due to avacopan.

- Because there is not clear attribution of the Hy's Law case to avacopan, if approved, the DILI team recommended close monitoring of liver tests should be described in the label.

These patients are summarized in greater detail in Table 134 in the Appendix. Additional details and analyses are in the review by Dr. Paul Hayashi (DHN DILI team leader).

8.2.5.3. Neutropenia/lymphopenia

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

The Applicant also assessed decreased leukocytes, lymphocytes, and neutrophil count by CTCAE grade in the laboratory database. Grade 3 and 4 decreased leukocyte and neutrophil counts occurred in a small number of patients, generally balanced by treatment group. Decreased lymphocyte counts were most frequently Grade 2 or 3, generally balanced by treatment arm. Grade 4 decreased lymphocyte count occurred more frequently in the prednisone arm (n=13 patients) than in the avacopan arm (n=4 patients). No Grade 4 decreased leukocyte counts were reported in either treatment arm, but two Grade 4 decreased neutrophil counts were reported in the prednisone arm. As previously described, there was one Grade 4 event of lymphopenia in the prednisone group and one Grade 4 event of decreased neutrophil count in the avacopan group that were not considered SAEs by the Investigator. Additionally, a patient in the prednisone group developed Grade 4 lymphopenia in the setting of an SAE of systemic inflammatory response syndrome; therefore, the Investigator did not consider the lymphopenia to be a separate SAE.

Few adverse events of low WBC count occurred in the phase 2 studies. In Study CL002_168, 1 AE associated with low WBC each occurred in the standard of care arm (WBC count decreased) and avacopan + high dose prednisone arm (lymphocyte count decreased). In Study CL003_168,

1 AE associated with low WBC each (specifically, the PT of neutropenia) occurred in the 2 avacopan arms (avacopan 10 mg and 30 mg).

Overall, neutropenia/lymphopenia (including but not limited to PTs of decreased WBC count, absolute granulocytes, neutrophils, and lymphocytes) occurred in both treatment arms and in small numbers, generally balanced by treatment group.

8.2.5.4. Hypersensitivity/Angioedema

Hypersensitivity was assessed utilizing preferred terms from the Standardized MedDRA Query (SMQ) for hypersensitivity. Sixty-eight patients in the avacopan arm (41.0%) and 70 patients in the prednisone arm (42.7%) had an AE of hypersensitivity.

Two patients had angioedema in the avacopan arm (one of which was an SAE), whereas no patients in the prednisone arm had angioedema. The patient with the SAE of angioedema had resolution of the angioedema after discontinuation of avacopan but was not rechallenged. The non-serious event of angioedema also resolved after study medication interruption; however, this patient did restart study drug and did not have a recurrence of angioedema.

Along with the SAE of angioedema in the avacopan arm, the SAEs under the hypersensitivity SMQ were reviewed. There were 5 additional SAEs in the avacopan arm and 3 SAEs in the prednisone arm. After review of the case narratives, of these SAEs, 2 in the avacopan arm and none in the prednisone arm seemed possibly related to study drug hypersensitivity by the Investigator. One of the SAEs was the patient with angioedema described above. The additional patient in the avacopan arm with an SAE developed rash and fevers in the setting of waxing-waning eosinophilia between study days 18 to 59 that resolved a day after avacopan was discontinued.

In the phase 2 studies combined, the Applicant noted that, under the SMQ for hypersensitivity, there were AEs reported in 19 patients (26.0%) in all avacopan-treated groups and 7 patients (19.4%) in the standard-of-care groups. There were no SAEs related to hypersensitivity during the treatment period. No AEs of angioedema (serious or non-serious) were reported.

Hypersensitivity reactions were few in the study and occurred in both treatment arms. Two SAEs of hypersensitivity observed in the pivotal trial, as described above, could possibly be related to avacopan as determined by the Investigator. One of these SAEs was angioedema, and there was an additional non-serious case of angioedema. There were no SAEs or AEs of angioedema in the prednisone arm.

8.2.5.5. Elevated Creatine Phosphokinase

In the Investigations SOC, more patients in the avacopan arm (n=6, 3.6%) experienced an elevated CPK compared to patients in the prednisone arm (n=1, 0.6%). None of these AEs in

either treatment was an SAE. In the avacopan arm, one patient (with 2 AEs of elevated CPK) interrupted the drug on both occasions; another patient discontinued study drug due to Grade 3 CPK elevations. Investigators attributed 3 of the AEs in the avacopan and the single AE in the prednisone arm as possibly related to study drug treatment. The other 3 events in the avacopan arm were determined to be probably not related, according to the Investigator.

There was an increase in CPK in both treatment arms, and the magnitude of increase was greater in the avacopan arm at multiple visits. However, by Week 52, the mean CPK levels were similar (although numerically higher in the avacopan arm) and below the ULN, 125.4±10.58 UL in the avacopan arm and 110.2±5.44 U/L in the prednisone arm. Grade 3 CPK elevations were reported in 3 avacopan treated patients, while 1 prednisone treated patient had Grade 4 CPK elevations.

Additionally, there was no major difference in AEs of myalgias (n=16 [9.6%] in the avacopan arm vs. n=22 [13.4%] in the prednisone arm) or myopathies (n=7 [4.2%] in the avacopan arm vs. n=6 [3.7%] in the prednisone arm) in the study.

Three patients had a TEAE of elevated CPK in the phase 2 studies: 2 patients in Study CL002_168 (n=1 in the avacopan + low dose prednisone arm and n=1 in the avacopan + no prednisone arm) and 1 patient in the avacopan 10 mg arm in Study CL003_168. No AEs of elevated CPK led to study drug interruption or discontinuation. In Study CL002_168, myalgia was reported in 1 patient in the avacopan + no prednisone arm. In Study CL003_168, there were 2 AEs of myalgia (both in the avacopan 30 mg arm) and 2 AEs of myopathy (1 in the standard-of-care arm and 1 in the avacopan 30 mg arm).

In summary, elevated CPK was reported in more patients in the avacopan arm compared to patients in the prednisone arm. However, the numbers are low. AEs of muscular symptoms (e.g., myalgia and myopathy) were generally comparable across treatment arms.

8.2.5.6. Vasculitis

"Vasculitis" was reported as an adverse event in both treatment arms in Study CL010_168. However, in this study, a measure of vasculitis may also inform the efficacy. As shown in Table 49, AAV and GPA were amongst the most common SAEs reported by PT in Study CL010_168.

An Agency assessment of all PTs for TEAEs that could be attributed to active vasculitis is summarized in Table 56. This analysis shows than reports of AAV occurred in 20.7% of the prednisone arm and 15.7% of the avacopan arm; other AEs consistent with active vasculitis occurred in low numbers. Only AAV, GPA, and pulmonary hemorrhage were reported in more than 2 patients in either treatment arm. There were more patients with AEs of AAV in the prednisone arm, difference of 5.1%, while GPA was reported more frequently in the avacopan arm (difference of 2.4%). Pulmonary alveolar hemorrhage and pulmonary hemorrhage occurred

in a similar number of patients in both treatment arms. Other TEAEs consistent with active vasculitis were generally similar by PT.

Table 56. TEAEs Consistent With Active Vasculitis by Preferred Term (PT) in Study CL010_168

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

Source: Statistical Reviewer
Abbreviations: ANCA, anti-neutrophilic cytoplasmic ant body; CI, confidence interval; GPA; granulomatosis with polyangiitis; MPA, microscopic polyangiitis; N, number of patients randomized who received at least one dose of drug; n, number of subjects with at least one event; TEAE, treatment-emergent adverse event.

Although vasculitis was documented as a safety finding, these AEs are more likely reflective of underlying disease activity. Table 27, which shows the number of patients who required non-study supplied glucocorticoids for active vasculitis, provides additional information about the number of patients with active vasculitis in the pivotal trial. This is further discussed in Section 8.1.1 Glucocorticoid Use.

In the phase 2 studies, specifically Study CL002_168, it is notable that, during the 12-week treatment period, the most frequently reported SAE was vasculitis. As shown in Table 50, more SAEs of vasculitis (specifically, the PTs of vasculitis, renal vasculitis, and MPA) occurred in the avacopan-treated arms (1 SAE of vasculitis in the avacopan + low dose prednisone arm and 3 SAEs of vasculitis in the avacopan + no prednisone arm) compared to the standard-of-care arm (1 SAE of vasculitis). Vasculitis was not reported as an SAE in Study CL003_168. As noted, these events are likely more reflective of efficacy than safety and are consistent with the efficacy results that did not show greater "remission" in the patients on avacopan and no prednisone arm. (See efficacy results in Sections 8.1.2.1 and 8.1.3.1 above.)

8.2.5.7. Adverse Events Associated With Glucocorticoid Use

Adverse events related to glucocorticoids was an area of interest for the Applicant. As previously reviewed, the GTI was a secondary efficacy endpoint that attempted to evaluate for toxicities associated with glucocorticoids.

Additionally, as a safety assessment, the Applicant utilized EULAR-recommended search terms to assess "AEs potentially associated with glucocorticoid use." These included the PTs listed in Table 135 in the Appendix and cover a very broad range of PTs. In utilizing these EULAR-recommended search terms, there was a greater proportion of AEs in the prednisone arm (80.5%) compared to that in the avacopan arm (66.3%). The Applicant separately assessed the TEAEs that the Investigator attributed to being possibly related to glucocorticoid use (both the prespecified prednisone taper and non-study supplied glucocorticoids). This assessment showed that there were more TEAEs in the prednisone arm (79.9%) compared to the avacopan arm (64.5%). The greatest number of AEs for both treatment arms was in the Infections and infestations SOC (40.2% in the prednisone arm and 30.1% in the avacopan arm). A greater proportion of patients in the avacopan arm had AEs related to glucocorticoid use in the following SOCs: Gastrointestinal disorders (13.4% in the prednisone arm and 20.5% in the avacopan arm), Nervous system disorders (10.4% in the prednisone arm and 12.0% in the avacopan arm), Respiratory, thoracic and mediastinal disorders (6.1% in the prednisone arm and 7.2% in the avacopan arm), Injury, poisoning and procedural complications (4.3% in the prednisone arm and 5.4% in the avacopan arm), Ear and labyrinth disorders (0.6% in the prednisone arm and 2.4% in the avacopan arm), Renal and urinary disorders (1.8% in the prednisone arm and 2.4% in the avacopan arm), Immune system disorders (0.6% in the prednisone arm and 1.8% in the avacopan arm), and Cardiac disorders (0.6% in the prednisone arm and 1.2% in the avacopan arm). A greater proportion of patients in the prednisone arm had AEs related to glucocorticoid use in the following SOCs: Infections and infestations (as already described, 40.2% in the prednisone arm and 30.1% in the avacopan arm), Musculoskeletal and connective tissue disorders (18.9% in the prednisone arm and 16.3% in the avacopan arm), Metabolism and nutrition disorders (18.3% in the prednisone arm and 12.7% in the avacopan arm), Skin and subcutaneous tissue disorders (23.8% in the prednisone arm and 12.0% in the avacopan arm), General disorders and administration site conditions (12.2% in the prednisone arm and 10.2% in the avacopan arm), Investigations (18.3% in the prednisone arm and 10.2% in the avacopan arm), Psychiatric disorders (20.7% in the prednisone arm and 9.6% in the avacopan arm), Vascular disorders (11.6% in the prednisone arm and 7.2% in the avacopan arm), Blood and lymphatic system disorders (14.6% in the prednisone arm and 6.0% in the avacopan arm), Eye disorders (9.1% in the prednisone arm and 3.6% in the avacopan arm), Endocrine disorders (8.5% in the prednisone arm and 2.4% in the avacopan arm), Neoplasm benign, malignant, and unspecified (1.8% in the prednisone arm and 1.2% in the avacopan

arm), and Reproductive system and breast disorders (1.2% in the prednisone arm and none in the avacopan arm).

In several communications with the Applicant, the Agency conveyed that the pivotal trial would not be sufficient to support a safety comparison that avacopan is less toxic than standard-of-care glucocorticoids. Given the small safety database and the limited duration of exposure, the conclusions are limited from this analysis. Additionally, as described in the discussion of GTI, the safety findings of AEs associated with glucocorticoid use may reflect the study design where the control arm received a pre-specified prednisone taper and, thus, more glucocorticoids. Also of importance, an assessment for only toxicities associated with the control treatment (i.e., glucocorticoids), in the absence of inclusion of assessment of toxicities of the investigational product, is biased as an assessment of overall safety.

In the phase 2 studies, a similar analysis was conducted. Study CL003_168 included pre-specified prednisone use in all treatment arms, so the comparisons are limited. In Study CL002_168, the Applicant identified TEAEs "associated with glucocorticoid use," including categories of new-onset/worsening HTN, psychiatric disorders, serious infections, new-onset/worsening diabetes mellitus/hyperglycemia, weight gain more than 10 kg, bone fracture, and cataracts. Although more patients experienced AEs in the standard-of-care arm (n=15 [65.2%]), the next greatest proportion of patients was in the arm with no pre-specified prednisone (n=11 [50.0%]), and the fewest patients were in the avacopan + low dose prednisone arm (n=4 [18.2%]). The phase 2 studies similarly did not assess for the toxicities associated with the investigational product, and therefore, a safety assessment based only on toxicities associated with GC use may be biased. Thus, the assessment of AEs associated with glucocorticoids in the phase 2 studies does not provide added support to the findings of the pivotal trial.

8.2.5.8. Malignancy

Malignancy was not an AESI in the pivotal trial, but risk of malignancy may be associated with immunosuppressive agents. Therefore, the Agency conducted an analysis of malignancies that occurred in Study CL010_168. More malignancies occurred in the prednisone arm (n=8, 4.9%) compared to the avacopan arm (n=3, 1.8%). The only malignancy that occurred in more than 1 patient was prostate cancer (n=2 (1.2%) in the prednisone arm and n=1 (0.6%) in the avacopan arm). The types of malignancies reported in the avacopan arm included basal cell carcinoma, prostate cancer (as already described), and metastatic pancreatic cancer. In the prednisone arm, reported malignancies included carcinoma in situ of skin, squamous cell carcinoma of skin, transitional cell carcinoma, and prostate cancer (as already described). In addition, ear neoplasm and hepatic neoplasm were reported in the prednisone group. Overall, the numbers of malignancies observed were small, numerically lower in the avacopan group, and without clustering by type of malignancy in the avacopan group.

No malignancies were reported in the avacopan arms during the 12-week treatment period in either of the phase 2 studies. However, malignancies were observed in the follow-up periods in both phase 2 studies. In Study CL002_168, there was 1 patient (4.5%) in the avacopan + no prednisone arm with melanocytic nevus. In Study CL003_168, there was 1 patient (7.7%) in the avacopan 10 mg arm with skin papilloma and 2 patients in the standard-of-care arm with reported malignancies (n=1 (7.7%) with basal cell carcinoma and n=1 (7.7%) with hemangioma of liver). The phase 2 findings were limited due to the short duration but generally supportive of the pivotal trial.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Glucocorticoid Toxicity Instrument is an instrument designed to assess toxicities associated with glucocorticoids. Multiple categories of clinical manifestations were scored and weighted to quantitatively assess glucocorticoid toxicity. This instrument was reviewed by DCOA as discussed in Section 8.1.1.1.

8.2.7. Safety Analyses by Demographic Subgroups

Safety analyses were conducted by demographics (gender, age, race) and by disease characteristics (baseline renal function, background immunosuppressive therapy, ANCA status, newly diagnosed/relapsed disease, baseline liver function.

The safety analyses by demographic variables were generally similar to the overall safety population. Infections and infestations was the most common SOC for both genders (numerically greater in females) in both treatment arms. There was a slight increase in AEs with age in several SOCs (e.g., Infections and infestations; Metabolism and nutrition disorders; Injury, poisoning, and procedural complications; Hepatobiliary disorders). Due to the limited number of non-White patients (n=52), the analysis of race only comprised of a comparison of "White vs. non-White," which are very broad categories with limited interpretability. Generally, the safety findings were similar across race groups. Interestingly, in the avacopan arm, hepatic enzyme increased occurred in none of the White patients but in 17.0% of non-White patients, and, in the prednisone arm, it occurred in 2.9% of White patients and 12.5% of non-White patients.

By baseline disease characteristics, the following safety findings were most notable:

- For several SOCs, there was a trend toward a greater proportion of patients with TEAEs with decreasing renal function (eGFR) in both treatment arms. This trend was seen in the SOCs of General disorders and administration, Metabolism and nutrition disorders, Blood and lymphatic, Renal and urinary disorders. For the SOC of Nervous system disorders, a similar trend was seen only in the avacopan arm. These safety findings are reflective of the underlying disease with baseline impaired renal function.

- Based on induction immunosuppression therapy (cyclophosphamide vs. rituximab), generally many SOCs were numerically greater in the CYC arm compared to the RTX arm in the avacopan treatment group. Of interest, in the Hepatobiliary disorders SOC (already discussed), there were numerically more patients in the CYC-treated patients (n=6, 10.2%) compared to the RTX-treated patients (n=4, 3.7%). AEs within that SOC appeared to occur generally evenly and as single events. The only PT that occurred in more than 1 patient was "hepatic function abnormal" (n=2 in the CYC-treated group and n=3 in the RTX-treated group). In the prednisone-treated arm, both AEs in the Hepatobiliary disorder SOC occurred in patients with background RTX.
- The analysis by ANCA antibody (MPO vs. PR3), baseline disease status (newly diagnosed vs. relapsing), and type of vasculitis (GPA vs. MPA) was generally consistent with the overall population.

In conclusion, by demographic variables, the safety assessment was generally similar to the overall safety population. By baseline disease characteristics, there were numerically greater AEs in patients who received background CYC therapy. Otherwise, the safety assessments were similar to the overall study population.

8.2.8. Specific Safety Studies/Clinical Trials

No specific studies were conducted to evaluate a specific safety concern.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No additional safety explorations were submitted on human carcinogenicity or tumor development. A discussion of malignancies that occurred in the clinical program is described in Section 8.2.5.8.

Human Reproduction and Pregnancy

There are no data on use of avacopan during pregnancy or lactation. There were no pregnancies reported in Study CL010_168 or in the phase 2 studies.

Pediatrics and Assessment of Effects on Growth

Three adolescents were enrolled in Study CL010_168. Heights were recorded at all visits. Two patients (ages 13 and 16) had no change in height and one patient (age 15) had 1 cm loss in height between baseline and end of treatment. There are inadequate data to draw conclusions about effects on growth.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No studies were conducted specifically to evaluate the abuse and dependence potential of avacopan, as it has limited distribution to the CNS. No evidence of CNS-related side effects was reported in the safety pharmacology or toxicology studies. Avacopan and its M1 metabolite were tested against a panel of chemotactic receptors, unrelated receptors, and membrane-associated proteins. For M1, weak activity was detected against cannabinoid receptor type 1, as well as a sodium channel, and a GABA-gated chloride channel at a concentration 50-fold greater than the M1 Cmax from clinical subjects that received avacopan at 30 mg BID. The parent drug, Avacopan, had little or no activity against cannabinoid receptor type 1 and a GABA-gated chloride channel. Both avacopan and its M1 metabolite had weak activity against a sodium channel at a concentration 12-fold greater than the summed Cmax of avacopan and M1 from clinical subjects that received avacopan at 30 mg BID.

The pivotal study CL010_168 included an 8-week follow-up period during which patients were monitored off study drug. During that time, there did not appear to be evidence of withdrawal or rebound.

Similar proportions of patients experienced a defined relapse in both treatment arms, n=6 (3.8%) in the avacopan arm and n=7 (4.5%) in the prednisone arm.

Numerically more patients in the prednisone arm experienced worsening in BVAS although the difference was small, n=12 (7.6%) in the prednisone arm and n=9 (5.7%) in the avacopan arm.

Numerically more patients in the prednisone arm required extra glucocorticoids (n=49 [29.5%] in the avacopan arm and n=57 [34.8%] in the prednisone arm) and extra immunosuppressants, including but not limited to rituximab, azathioprine, cyclophosphamide, and mycophenolate (n=20 [12.0%] in the avacopan arm and n=26 [15.9%] in the prednisone arm).

Other efficacy endpoints were also assessed during this period, including hr-QoL measures and renal endpoints. There was a loss of treatment difference in the renal endpoints, as already discussed in Section 8.1.1.1. There was also a loss of treatment difference in EQ-5D-5L although the mean SF-36 PCS was similar at Weeks 52 and 60.

Additionally, both phase 2 studies had a 12-week follow-up period. There did not appear to be evidence of rebound or withdrawal nor an increase of more than 3 patients with adverse events following discontinuation of avacopan. However, there did appear to be a loss of efficacy after discontinuation of medication, as discussed above in Section 8.1.2.1.

Study CL002_168

The proportion of patients with at least 1 TEAE through the follow-up period was similar to what was seen in treatment period (95.5% in the avacopan + low-dose prednisone arm, 95.5% in the avacopan + no prednisone arm, and 91.3% in the standard-of-care prednisone arm).

Study CL003_168

The proportion of patients with at least 1 TEAE through the follow-up period was essentially the same as that in the treatment period (92.3% in the avacopan 10 mg arm, 93.8% in the avacopan 30 mg arm, and 100% in the placebo standard-of-care arm).

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Avacopan is not approved for use for any indication anywhere in the world. Therefore, there is no post marketing experience with avacopan.

Expectations on Safety in the Postmarket Setting

No risk evaluation and mitigation strategy (REMS) for the purposes of evaluating safety has been recommended. A postmarketing required study will be issued to further evaluate the potential risk of hepatotoxicity and angioedema.

8.2.11. Integrated Assessment of Safety

Based on the clinical development program of avacopan for the treatment of AAV, a total of 239 patients with AAV have been exposed to avacopan. As already described above, the data from the phase 2 studies cannot be pooled with the safety data from the pivotal trial, given the different doses of avacopan and concomitant therapy in treatment arms. However, the safety from the phase 2 studies reflects a much shorter duration of exposure (12 weeks) and fewer number of patients (n=73) but was generally consistent with that of the pivotal trial. Thus, conclusions from safety are primarily drawn from the relatively small safety database of the phase 3 trial, Study CL010_168, including 166 patients exposed to at least 1 dose of avacopan and 134 patients who received study drug for >6 months. The proportions of patients with TEAEs were similar across treatment arms or nominally lower in the avacopan arm, including deaths, serious adverse events, and AEs leading to discontinuation. AEs of special interest included infections, AEs due to hepatic abnormalities, neutropenia, and hypersensitivity/angioedema. The proportion of patients with serious infections was low and similar across treatment arms (13.3% in the avacopan arm and 15.2% in the prednisone arm).

More cases of serious opportunistic infections occurred in the prednisone arm (6.7%) compared to the avacopan arm (3.6%). No cases of *Neisseria meningitides* occurred in the avacopan arm.

More patients in the avacopan arm experienced AEs related to hepatic abnormalities (including hepatobiliary and liver enzyme-related AEs), CPK elevations, and hypersensitivity events. The proportion of patients with hepatobiliary AEs and SAEs were greater in the avacopan group (6.0% and 3.6%, respectively) as compared to the prednisone group (1.8% and 0.6%, respectively). Hepatobiliary SAEs included one patient with a liver biopsy consistent with drug induced liver injury and one patient with increased liver enzymes upon positive rechallenge with avacopan, suggesting potential hepatotoxicity. AEs associated with hepatic abnormalities led to drug discontinuation in 7 patients in the avacopan arm and 2 patients in the prednisone arm. As for hypersensitivity, 2 patients in the avacopan arm experienced angioedema, and no patients in the prednisone arm experienced angioedema. There was an additional case of rash and fever in the avacopan arm that resolved after discontinuation of avacopan. Although the database is small, there is a greater incidence of hepatotoxicity, hypersensitivity, and CPK elevation with avacopan. The consideration as to whether the safety database is adequate is made as part of the assessment of benefit-risk and is described in detail in Section 1 and 8.4 of this review.

8.3. Statistical Issues

There are several statistical issues with Study CL010_168, beginning with the Applicant's proposed method to derive the non-inferiority margin. First, there are no historical placebo-controlled trials evaluating the efficacy of glucocorticoids as an add-on therapy to CYC or RTX. Thus, the Applicant relied on single arm results from various different studies. Second, the relevance of many of the historical studies cited for the setting of the proposed NI study is questionable because of potential differences in important factors such as the patient population (e.g., several studies included patients with necrotizing crescentic glomerulonephritis, polyarteritis nodosa), standard of medical care, and treatment regimen (e.g., rate and amount of glucocorticoid tapering). Even the definition of 'remission' and the time point of endpoint assessment were not consistent. Third, the determination of the extent of the contribution of glucocorticoids to the historical estimated remission rate on glucocorticoids + CYC or RTX is based on key, implausible, and unverifiable assumptions; it is unlikely that the efficacy of glucocorticoids alone is similar to that of glucocorticoids when added on to CYC or RTX. Therefore, with the proposed NI margin of -20%, it would be very difficult to determine if a finding of similar remission rates on the proposed comparator arms was due to the efficacy of avacopan or to the fact that the remission rates on both arms were primarily driven by the induction treatment with cyclophosphamide or rituximab (with little to no benefit provided from avacopan).

Interpretation of the non-inferiority at Week 26 is further limited by the large number of patients in the avacopan arm (86%) who received non-study supplied glucocorticoids from Week 0 to 26. While the mean cumulative glucocorticoid dose per patient over Week 0 to 26 was lower in the avacopan-treated patients compared to the mean cumulative dose in the prednisone-treated patients, the non-inferiority assessment is not a comparison of avacopan vs. prednisone, but instead avacopan plus lower dose glucocorticoids vs. higher dose glucocorticoids. At this time, it is not clear how much reduction in glucocorticoids may have clinically meaningful impact on efficacy outcome and if the protocol-specified higher dose of glucocorticoids is required for control of disease activity. Therefore, the interpretability and meaningfulness of this comparison is challenging.

In terms of the superiority comparison, there were also several statistical issues, though the overall treatment effect was statistically significant. At Week 52, there was a disparity in observed treatment effects between the subgroups that received rituximab and cyclophosphamide (IV and oral) induction treatment. The estimated difference in remission rates at Week 52 was 15.0% (95% CI: [2.2%, 27.7%]) in the subgroup receiving induction with rituximab and 3.3% (95% CI: [-14.8%, 21.4%]) in the cyclophosphamide plus maintenance azathioprine subgroup. Other subgroups, such as relapsing vs. newly diagnosed patients, also reflected differential treatment effects. These differences raise questions about the consistency of the treatment effect across patient groups and/or across background therapies.

There were also differences between the assessments performed by the Investigator and the Adjudication Committee, most frequently related to the attribution of persistent vasculitis which was not captured in the modified BVAS administered in the study. Discrepancies between the Investigator and Adjudication Committee occurred in 17 patients at Week 52. Statistical analyses of the primary endpoint using the Investigator assessment of BVAS remission resulted in more conservative estimates of treatment effect, e.g., statistical significance for superiority would no longer be demonstrated with these scores.

In the Study CL010_168, secondary endpoints were not adjusted for the multiplicity. Hence, a nominal significance achieved by a secondary endpoint should be interpreted with caution.

8.4. Conclusions and Recommendations

ChemoCentryx has submitted an NDA for avacopan, a new molecular entity C5a receptor antagonist, for treatment of adult patients with ANCA-associated vasculitis (GPA and MPA). The proposed dosing regimen is 30 mg twice daily orally. To support the application, the Applicant submitted a single phase 3 study, CL010_168, and two phase 2 studies, CL002_168 and CL003_168. Study CL010_168 was a randomized, double-blind, active controlled study to evaluate the safety and efficacy of avacopan compared to a protocol-specified 20-week prednisone taper in 331 patients with newly diagnosed or relapsed ANCA-associated vasculitis.

All patients received induction treatment with cyclophosphamide or rituximab. Patients who received cyclophosphamide received maintenance therapy with azathioprine, while patients who received rituximab induction did not receive maintenance treatment. The primary endpoints of Study CL010_168 were remission at Week 26 and sustained remission at Week 52, each evaluated for both non-inferiority and superiority.

Based on the multiple testing procedure of these endpoints, Study CL010_168 met its primary endpoint, demonstrating superiority for sustained remission at Week 52 (avacopan vs. prednisone treatment difference 12.5%). However, in the evaluation of the subgroups by background therapy, the treatment effect was observed in the RTX induction subgroup (15%) that did not receive maintenance standard of care, whereas no meaningful treatment effect was observed in the cyclophosphamide induction subgroup that received maintenance treatment with AZA (3%). While subgroup analyses must be interpreted with caution as there is often low precision and considerable uncertainty around these estimates, this inconsistency raises concerns regarding the persuasiveness of the evidence of effectiveness and how avacopan may fit into the treatment armamentarium of ANCA-associated vasculitis. In addition, the analysis based on the Investigator BVAS Assessment did not support superiority. Differences between the Investigator Assessment and the pre-specified analysis based on the Adjudication Committee were due to differences in attribution of persistent vasculitis. These discrepancies in remission status between the Investigator and the Adjudication Committee were relatively balanced by treatment arm but underscore the lack of robustness of the superiority assessment.

Noninferiority but not superiority was demonstrated for remission at Week 26 (avacopan vs. prednisone treatment difference 3.4%). However, because both treatment arms received background therapy in the form of cyclophosphamide or rituximab and the benefit of glucocorticoids on top of cyclophosphamide or rituximab is not well-understood, it cannot be determined if similar remission rates observed on both arms can support a conclusion that avacopan is effective or if similarities can be primarily attributed to both arms receiving rituximab or cyclophosphamide. Further, while only the prednisone group was intended to receive the protocol-specified prednisone taper, 87% of patients in the avacopan treatment group also received glucocorticoids during the study for vasculitis and other clinical conditions. Thus, the assessment of non-inferiority is a comparison of avacopan and lower dose glucocorticoids versus higher dose glucocorticoids.

Finally, the increased glucocorticoid use in the prednisone arm compared to the avacopan arm was limited to the period of the first 20 weeks of the study. Differences in the glucocorticoid doses used from Week 0 to 26 between the prednisone and avacopan arms may therefore be an artifact of the study design rather than a reflection of better control of disease activity in the avacopan arm.

Secondary endpoints were not adjusted for multiplicity, and, therefore, these results are considered exploratory. While decreases in relapses were observed in the avacopan group, other measures of increased disease activity (i.e., maintenance of remission, worsening vasculitis, and persistent vasculitis) were similar between the avacopan and prednisone treatment groups. Additionally, the analysis of relapse is limited, as it depends on post-randomization variables, i.e., having first achieved remission and the timing of the remission. The overwhelming majority of patients in both arms achieved remission; however, numerically a greater number of patients in the prednisone group achieved remission at an earlier time point and, therefore, were at risk for relapse for a longer duration. Urine albumin: creatinine ratio improved in both arms and more quickly in the avacopan arm by Week 4; however, improvement was similar between treatment arms after this early time point. Differences in eGFR were small and not sustained, thus, raising questions about the clinical importance of this finding. There were no differences in long-term renal outcomes, such as dialysis. There were no differences in Vasculitis Damage Index. Overall, the secondary endpoints provide limited support of a clinically meaningful benefit of avacopan treatment. In addition, the phase 2 studies, which included different doses of avacopan and varying concomitant prednisone tapers, shorter treatment duration, small patient populations, and different efficacy assessments, do not provide additional support for the treatment benefit of avacopan 30 mg BID when administered without GCs.

The overall safety database is relatively small (n=239), including 166 patients exposed to avacopan for up to 52 weeks in CL010_168. The differences in study designs and treatment arms in the phase 2 studies preclude pooling with the safety data of CL010_168 but were generally consistent with that of the pivotal study. In Study CL010_168, a greater proportion of avacopan-treated patients had hepatobiliary adverse events, SAEs, and AEs leading to discontinuation. There were 9 SAEs due to hepatic abnormalities (hepatobiliary and elevated liver enzymes) in the avacopan arm in the pivotal trial, of which 4 cases were probable or highly likely DILI due to avacopan. In addition, there was one SAE due to hepatic abnormalities in the avacopan arm in the phase 2 study CL002_168 and was felt to be possible DILI due to avacopan. Imbalances in angioedema and CPK elevations were also observed. Other events including deaths, SAEs, AEs leading to discontinuation, TEAEs, infections, and serious infections (including serious opportunistic infections) generally occurred in similar or fewer numbers of patients in the avacopan arm compared to the prednisone arm. Given the small safety database, conclusions regarding rare and latent toxicities, which are more relevant for chronic immunosuppressants like avacopan, are limited; however, imbalances in hepatotoxicity and angioedema were observed despite the small sample size.

In summary, the review team feels the Applicant has not provided confirmatory evidence to support the reliance on a single study to provide substantial evidence of effectiveness. Although Study CL010_168 demonstrated superiority of avacopan on sustained remission at

Week 52 and non-inferiority on remission at Week 26, the clinical meaningfulness of these results is unclear, as described above. In addition, while the Applicant has asserted that avacopan spares or reduces the need for glucocorticoid treatment in AAV, the use of glucocorticoids in both treatment arms, as well as the use of protocol-specified glucocorticoids in the prednisone arm, preclude a determination that differences in glucocorticoid use are due to a treatment effect of avacopan, rather than the design of the study. In addition, there are safety concerns related to hepatotoxicity and angioedema that have not been fully characterized in the small available safety database. Given these concerns, the context of use is uncertain and the benefit-risk of avacopan in AAV cannot be determined. Therefore, the review team recommends a Complete Response for NDA 214487 for avacopan for adult patients with ANCA-associated vasculitis (GPA and MPA), based on the currently available data. The review team recognizes the importance of wanting to decrease glucocorticoid use and its toxicities, particularly if the steroid-sparing occurs in the context of a treatment that effectively controls disease activity. To support the results of the single pivotal trial, conducting a second confirmatory study could provide additional evidence for the effectiveness of avacopan, better define the population in which the benefit-risk is favorable, and provide additional safety data to characterize the risks of hepatotoxicity and angioedema.

As summarized in Section 9 below, an Advisory Committee meeting was held to present the Agency and Applicant's discussion and analyses of the data to support the use of avacopan as a treatment for AAV and as a possible replacement for glucocorticoids in a public forum. The Committee members were generally split as to whether the application included sufficient efficacy or safety data to support approval and whether the benefit-risk profile sufficiently supported the use of avacopan for the treatment of AAV. Subsequent to the Arthritis Advisory Committee (AAC) meeting, discussions between the Agency and Applicant were initiated to discuss the impacts of the AAC on the proposed indication and labeling with a telephone conference (t-con) that occurred on June 2, 2021. During the t-con, the Agency advised the Applicant to address the discussion at the AAC and the Agency's expressed concerns. Specifically, the Agency recommended that ChemoCentryx consider revisions to the proposed indication with regard to the treatment population and background therapy, as supported by the data from the pivotal trial. Additionally, the Agency reiterated that the pivotal study did not support the use of avacopan to reduce or eliminate glucocorticoid use. The Agency and Applicant also discussed how the Applicant may be able to address safety concerns that emerged from the clinical trial, namely, the increased numbers of patients in the avacopan arm who developed hepatobiliary disorders and elevated liver enzymes. This included a case of a patient on avacopan who met Hy's law laboratory criteria. Typically, 1 or 2 Hy's Law cases attributed to the study medication in large registry trials (i.e., N=1000 to 2000) is enough to raise concerns that drug may be unsafe for wider market use. The Applicant understood the Agency's concerns regarding safety but stated that it would be unable to conduct another pre-

approval study. Rather, ChemoCentryx stated that the Agency's concerns, particularly, the safety concerns, could be addressed in a postmarketing study.

The Applicant submitted a clinical information amendment on June 18, 2021, which included the Applicant's revised indication statement along with an attempt to address the Agency's concerns related to efficacy and safety with the available data from the pivotal trial as well as a proposal for post-approval study/ies. This information was determined to be a major amendment. Thus, the PDUFA goal date was extended to accommodate its review.

In summary, the amendment included the following:

- Revised indication statement

  (b) (4)

  ChemoCentryx proposed this indication (b) (4) The Applicant, however, agreed that avacopan did not eliminate all glucocorticoid use in the pivotal trial.

- The Applicant attempted to address the concerns that were laid out in the Agency's AAC background material. These included the need for additional safety data, the study design of the phase 3 trial, relevance of the Week 26 remission results, the discrepancy in the BVAS results at Week 52 based on Investigator vs. Adjudicator, differences in response based on background immunosuppression (rituximab vs. cyclophosphamide/azathioprine), glucocorticoid use in both treatment arms, differences in glucocorticoid toxicity, and limitations in interpretation of the secondary endpoints. The Applicant did not submit any new data. Rather, the Applicant re-summarized the data to address these particular areas of concern.

- Additional post-approval studies

  To obtain long-term efficacy and safety of avacopan in AAV, ChemoCentryx proposed a post-approval study (b) (4)

(b) (4)

Along with this post-approval study, the Applicant proposed (b) (4)

The Agency did not agree that the revised indication adequately addressed the Agency's and the Arthritis Advisory Committee concerns. Rather, the Agency recommended the indication clearly state that avacopan be considered as adjunctive treatment of AAV and that avacopan did not eliminate glucocorticoid use. Additionally, the Agency presented what data from the pivotal study would be appropriate for inclusion in the USPI. The Agency's proposed indication and description of the data are detailed below in Section 11. The Agency sent an IR (dated July 1, 2021) with these recommendations to which the Applicant agreed on July 13, 2021.

The proposed post-approval study would neither sufficiently address the need for additional safety information nor inform the appropriate role for avacopan in the treatment of AAV. (b) (4)

With these limitations in mind, the Agency proposed a study design that would both address the postmarketing requirement (PMR) for additional safety data and postmarketing commitment (PMC) for additional efficacy data. (b) (4)

(b) (4) This study is further described below in Section 13. The Applicant confirmed their agreement with the PMR study design.

The agreed upon postmarketing requirement study is designed to provide comparative safety data to better define the risks of hepatotoxicity and serious hypersensitivity reactions and other rare and latent safety events that may be observed with a larger safety database and longer duration follow-up time. In addition, the team agrees that the PMR/PMC study may provide the additional efficacy evidence necessary to determine a favorable benefit-risk profile and better define how avacopan should be used in AAV. Based on the currently available data, the review team maintains that the Applicant has not provided confirmatory data to meet the usual standard of substantial evidence of effectiveness. The review team further notes the input provided by the Medical Policy and Program Review Council and the Arthritis Advisory Committee, and the divided recommendations offered by each. The review team acknowledges the unmet need for new therapies for patients with AAV who do not respond to currently available therapies or who subsequently relapse, as well as the need for alternative therapeutic options with fewer toxicities. The review team further acknowledges that the more narrowed indication and the proposed postmarketing study will mitigate many of the uncertainties about the available evidence. Finally, the review team acknowledges the potential need for additional flexibility when determining whether the avacopan development program has provided substantial evidence of effectiveness, and the use of this additional flexibility by Division leadership in the approval of avacopan 30 mg twice daily as an adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with standard therapy including glucocorticoids. Avacopan does not eliminate glucocorticoid use.

9. Advisory Committee Meeting and Other External Consultations

The benefit-risk of avacopan for the treatment of adult patients with AAV (GPA and MPA) was discussed at an Arthritis Advisory Committee meeting on May 6, 2021, that included relevant rheumatology, nephrology, statistical, and clinical pharmacology experts. The following is a summary of the committee discussion:

1. DISCUSSION: Discuss whether the results at Week 26 support a clinically meaningful benefit of avacopan. Include discussion of the following:

    a. Appropriateness of a primary non-inferiority (NI) comparison

    Committee Discussion*: The committee did not come to an agreement regarding the appropriateness of a primary non-inferiority (NI) comparison. Some committee members stated that they did not have concerns with an NI study design and agreed that there were enough data supporting a clinically meaningful benefit of avacopan at Week 26. The committee members who disagreed expressed concerns that there were not adequate available data to determine an appropriate NI margin in order to draw conclusions based on the NI comparison. Other committee members added that there are too many uncertainties in the NI comparison and, thus, did not find the NI at Week 26 compelling.*

    b. Use of additional non-study supplied glucocorticoids in the avacopan group

    Committee Discussion*: The committee expressed difficulty interpreting the data regarding the use of additional non-study supplied glucocorticoids (GCs) in the avacopan group. Committee members noted that the use of GC in the avacopan arm makes the interpretation of the non-inferiority assessment at Week 26 difficult; concerns were raised that participants who received significant amounts of GC may be counted as responders, resulting in difficulty determining the true effects of avacopan vs. prednisone.*

    c. Lack of statistically significant superiority at Week 26

    Committee Discussion*: Several committee members expressed that the lack of statistically significant superiority of avacopan vs. the comparator group at Week 26 was not concerning or unexpected due to the fact that patients in both groups received background treatment with GCs and cyclophosphamide/azathioprine or RTX and the outcomes at week 26 are likely representing the effects of induction treatment.*

2. DISCUSSION: Discuss whether the results at Week 52 support a clinically meaningful benefit of avacopan. Include discussion of the following:

    a. Impact of the lack of maintenance therapy in the rituximab (RTX) subgroup

    ***Committee Discussion**: Overall, the committee members agreed that data from this single subgroup is difficult to interpret, as the trial was not designed to respond to this specific question. Committee members noted that there is ambiguity in how this drug should be used. Some committee members added that one would need a new trial where there is a separation in induction and maintenance therapy in order to evaluate if avacopan can be appropriately used as maintenance therapy as suggested by the effect observed in the RTX subgroup. Other committee members expressed challenges in differentiating the effects of treatment related to background medication, adding that the RTX subgroup was relatively small in sample size and use of CYC vs RTX as background therapy was not randomized.*

    b. Discrepancies in Birmingham Vasculitis Activity Score remission responses as determined by Adjudication Committee vs. Investigators

    ***Committee Discussion**: The committee members discussed the differences in how the site Investigators and Adjudication Committee may have scored the BVAS, how the Applicant provided data to the Adjudication Committee, and how the Adjudication Committee may have changed the scores. Some committee members noted that there was a loss of significance in the statistical analysis based on the Investigator assessment and that it may impact the strength of the evidence at Week 52. Other committee members noted difficulties in scoring the BVAS instrument including the determination of whether symptoms are due to persistent disease activity or damage. Several committee members noted that the Adjudication Committee BVAS assessment was a pre-specified analysis, thus is the analysis that should be used, and did not have specific concerns about the discrepancies.*

3. DISCUSSION: Discuss whether the data support the use of avacopan as a steroid-sparing agent in ANCA-associated vasculitis. Include discussion of the following:

    a. Use of additional non-study supplied GCs in the avacopan group
    b. Impact of a potential increase in GC exposures due to CYP3A4 inhibition by avacopan

    ***Committee Discussion:** Regarding the use of additional non-study supplied GCs in the avacopan group, the committee noted that avacopan may not eliminate the use of steroids, but some members felt the data support decreased steroid use with avacopan treatment, while others stated differences in GC use observed in the first half of the study were a result of the nature of the design and questioned the clinical relevance of the observed differences. The committee didn't express much concern*

on the impact of a potential increase in GC exposure due to CYP34A inhibition by avacopan based on prior experience with coadministration of GCs with known strong CYP3A4 inhibitors, as well as the results of the Glucocorticoid Toxicity Index which showed lower scores in the avacopan arm.

4. DISCUSSION: Based on the data from the clinical program, discuss how avacopan, if approved, should be used in the treatment of AAV.

   Committee Discussion*: Some committee members agreed that this was a difficult question to answer, particularly because the study, as designed and conducted, doesn't directly assess the role of avacopan for induction vs. maintenance therapy. Other committee members noted avacopan treatment may be considered in the following: 1) use as induction therapy consistent with the pivotal study; 2) use in patients with the highest risk for harm due to complications from high dose steroids; and 3) use in patients at risk for relapse or patients not responding to current therapy. One committee member expressed additional concerns that, given the limited experience with avacopan, it would be more appropriate for use in relapsing or refractory patients. However, if approved, avacopan use may be more widespread in an attempt to decrease GC use and may rapidly become first line treatment rather than rescue therapy.*

5. VOTE: Do the efficacy data support approval of avacopan for the treatment of adult patients with AAV (GPA and MPA)?

   If you voted "No", what data are needed?

   Vote Result: Yes: 9 No: 9 Abstain: 0

   Committee Discussion*: The committee members were split on whether the efficacy data support approval of avacopan for the treatment of adult patients with AAV (granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)). The committee members who voted "No" agreed that there is not enough substantial clinical and statistical evidence from a single trial to support approval of avacopan for the proposed broad indication. Some committee members stated the need for confirmatory evidence from another study, and some suggested that the drug may be better positioned as a maintenance therapy and recommended a study designed to evaluate this. One committee member noted the acceptability for a noninferiority trial to be considered if an effect on lowering steroid doses and BVAS remission were confirmed. The committee members who voted "Yes" agreed that, although the results did not demonstrate complete replacement of steroids, the sparing effect was sufficient enough to warrant approval of this drug, and also cited the difficulty of conducting studies in this rare disease.*

6. VOTE: Is the safety profile of avacopan adequate to support approval of avacopan for the treatment of adult patients with AAV (GPA and MPA)?

   If you voted "No", what data are needed?

   Vote Result: Yes: 10 No: 8 Abstain: 0

   Committee Discussion*: The majority of the committee members agreed that the safety profile of avacopan is adequate to support approval of avacopan for the treatment of adult patients with AAV (GPA and MPA). The committee members who voted "Yes" also provided recommendations for postmarketing surveillance. The committee members who voted "No" expressed concerns with the following: 1) small sample size; 2) shorter term safety database (as compared to knowledge of long-term safety of steroids); 3) risks of angioedema and hepatotoxicity; and 4) lack of data in minority groups.*

7. VOTE: Is the benefit-risk profile adequate to support approval of avacopan at the proposed dose of 30 mg twice daily for the treatment of adult patients with AAV (GPA and MPA)?

   If you voted "No", what further data are needed?

   Vote Result: Yes: 10 No: 8 Abstain: 0

   Committee Discussion*: A slight majority of the committee members voted that the benefit-risk profile is adequate to support approval of avacopan at the proposed dose of 30 mg twice daily for the treatment of adult patients with AAV (GPA and MPA). One committee member who voted "Yes" explained how they interpreted this question in a hypothetical sense but stated that they do not think the data that is needed is available yet. Therefore, the committee members were evenly split on whether the benefit-risk profile based on the data currently available are adequate to support approval of avacopan. The committee members who voted "Yes" advised on the judicious use of avacopan and guidance regarding the appropriate patient group for whom this medication should be reserved. The committee members who voted "No" stated concerns about the issues with the efficacy trial design as well as concerns with the safety data. In terms of what further data are needed, one committee member noted that there were uncertainties about the effects of the GC and recommended a specified steroid taper in the experimental and comparator arms, and then a study evaluating efficacy in induction with re-randomization to evaluate maintenance of remission.*

Please see the tran*script for details of the Committee's discussion.*

10. Pediatrics

As avacopan was granted orphan drug designation for the treatment of anti-neutrophil cytoplasmic autoantibodies associated vasculitides (granulomatosis with polyangiitis or Wegener's granulomatosis), microscopic polyangiitis, and Churg-Strauss syndrome (EGPA), a pediatric assessment was not required.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

The originally proposed prescribing information was not submitted according to format requirements under 21 CFR 201.57. Thus, the Applicant submitted an initial set of revisions to address these formatting comments on March 18, 2021. A high-level summary of subsequent labeling revisions is presented below in Table 65.

Table 57. Summary of Labeling Discussions and Revisions

Section	Labeling Discussions
1 Indications and Usage	Wording of the indication was discussed with the Applicant over the review on multiple occasions. In the Clinical Information Amendment (dated June 18, 2021), the Applicant revised the proposed indication in accordance with the Advisory Committee meeting and discussions with the Agency. However, the Agency continued to have concerns with the revisions, particularly in describing avacopan (b) (4) See the discussion under Section 8.4. Subsequently, in an IR and its response (dated July 13, 2021), the Applicant agreed to the wording of the indication below. *[Tradename] is indicated as adjunctive treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with standard therapy including glucocorticoids. [Tradename] does not eliminate glucocorticoid use.* Because of uncertainties with the clinical program, the Agency further recommended that the treatment population be narrowed to adult patients with **severe** AAV. This was accepted by the Applicant. Due to safety concerns for hepatotoxicity, a limitation of use was considered so that avacopan would not be recommended for patients with active, untreated and/or uncontrolled chronic liver disease (e.g., chronic active hepatitis B, untreated hepatitis C, uncontrolled autoimmune hepatitis) and cirrhosis. The Applicant instead proposed that the wording of the limitations of use be placed under Section 5 (Warning and Precautions). The Agency agreed that this was acceptable on September 30, 2021.

Section	Labeling Discussions
2 Dosage and Administration	Section 2.1 Recommended Evaluations Prior to Treatment Initiation The Agency added testing for liver function tests and HBV serology prior to initiation of avacopan. Section 2.2 Recommended Dosage and Administration The Agency agreed with the recommended dose as supported by the clinical trial of avacopan 30 mg (three 10 mg capsules) twice daily with food. Section 2.3 Dosage Modifications Due to CYP3A4 Inhibitors The Agency recommended that the dose of avacopan be reduced to once daily when used concomitantly with strong CYP3A4 inhibitors, and the Applicant agreed.
5 Warnings and Precautions	Section 5 was edited by the Agency to clearly reflect the safety findings in Study CL010_168 with appropriate monitoring and modifications to therapy. 5.1 Hepatotoxicity The wording of the hepatotoxicity section was revised by the Agency to be consistent with current labeling practices and to reflect that serious and life-threatening cases of hepatic injury occurred in the pivotal trial. Laboratory monitoring at initiation and during treatment, as well as recommendations for monitoring and treatment discontinuation for elevations in AST or ALT, were added by the Agency. 5.2 Hypersensitivity Reactions The description of cases of angioedema was expanded. Recommendations for medical care if angioedema should develop were also added by the Agency. 5.3 Hepatitis B Virus (HBV) Reactivation Because 2 cases of HBV reaction occurred, including life threatening hepatitis B, the Agency recommended inclusion of HBV reactivation as a separate warning and precaution. The Agency provided language for screening and monitoring as well for referral to a specialist if HBV reactivation occurs. The Applicant did not agree that HBV reactivation should be included in the PI, as the Applicant believed there was only 1 case that satisfied the criteria of HBV reactivation with HBsAg negative and anti-HBc positive. Given the small safety database, the Agency noted that any observed safety signal would be concerning. Therefore, HBV reactivation should remain as a separate warning. 5.4 Serious Infections The Agency recommended inclusion of a section on serious infections in Section 5, as there were fatal events of serious infections in the avacopan arm. Although there were more serious infections in the prednisone arm, the Agency again reiterated that, because the safety data were limited from Study CL010_168, any safety signals observed are concerning. Therefore, this section should remain with the Agency's recommended language.

Section	Labeling Discussions
6.1 Clinical Trials Experience under ADVERSE REACTIONS	The Agency recommended revisions in Section 6 to focus on Study CL010_168. As described in the review, the safety data from the phase 2 studies were not pooled with the safety from the pivotal trial, rather the data were supportive. Thus, a more detailed description with cumulative exposure of the pivotal trial was recommended. Additionally, the Agency recommended language to describe serious adverse reactions, adverse reactions leading to discontinuation, and the most common adverse reactions that occurred in ≥ 5% of patients and higher in the avacopan group. *The most frequent serious adverse reactions reported more frequently in patients treated with TAVNEOS than with placebo were pneumonia (4.8% TAVNEOS vs. 3.7% prednisone), GPA (3.0% avacopan vs. 0.6% prednisone), acute kidney injury (TAVNEOS 1.8% vs. 0.6% prednisone), and urinary tract infection (1.8% TAVNEOS vs. 1.2% prednisone). Within 52 weeks, 4 patients in the prednisone treatment group (2.4%) and 2 patients in the TAVNEOS group (1.2%) died. There were no deaths in the phase 2 trials.* *In the phase 3 trial, seven patients (4.2%) in the TAVNEOS treatment group and 2 patients (1.2%) in the prednisone treatment group discontinued treatment due to hepatic-related adverse reactions, including hepatobiliary adverse reactions and liver enzymes abnormalities. The most frequent adverse reactions that led to drug discontinuation reported by > 1 patient and more frequently reported in patients treated with TAVNEOS was hepatic function abnormal (1.8%).* The most common adverse reactions that occurred in ≥ 5% of patients and higher in the avacopan group included the following: nausea, headache, hypertension, diarrhea, vomiting, rash, fatigue, upper abdominal pain, dizziness, blood creatinine increased, paresthesia. These are presented in the Table 1 in the final PI.
7 Drug Interactions	The Agency recommended language for drug interactions with CYP3A4 inducers and CYP3A4 inhibitors. Additionally, the Agency recommended inclusion of language for CYP3A4 substrates.
8 Use in Specific Populations	The Agency recommended language for pregnancy (Section 8.1) and lactation (Section 8.2) based on animal data. The Agency recommended removal of (b) (4) in these sections, (b) (4) The Agency also recommended removal of the section (b) (4) (b) (4) The Agency recommended language in Section 8.5 regarding geriatric use with description of the geriatric population in Study CL010_168. The sections on patients with renal impairment (Section 8.6) and hepatic impairment (Section 8.7) were revised to the following: *Section 8.6 Patients with Renal Impairment* *No dose adjustment is required for patients with mild, moderate, or severe renal impairment. [TRADENAME] has not been studied in patients with ANCA-associated vasculitis who are on dialysis.* *Section 8.7 Patients with Hepatic Impairment* *No dosage adjustment is recommended for patients with mild or moderate (as indicated by Child-Pugh method) hepatic impairment. [TRADENAME] has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).*

Section	Labeling Discussions
12 Clinical Pharmacology	The Agency noted that the data submitted was insufficient to support the Applicant's description of the mechanism of action. The Agency recommended the following language: *Avacopan is a complement 5a receptor (C5aR) antagonist that inhibits the interaction between C5aR and the anaphylatoxin C5a. The mechanism by which avacopan exerts a therapeutic effect in patients with ANCA-associated vasculitis is unknown.* The Agency recommended removal (b) (4) but added a statement on cardiac electrophysiology. Additionally, the Agency provided multiple revisions to the PK section as well as requesting revisions from the Applicant based on the completed PK studies.
13 Nonclinical Toxicology	The Agency made several revisions to the nonclinical data for clarity and brevity of the information included in the PI.

14 CLINICAL STUDIES

Based on the data, the Agency recommended in an IR dated July 1, 2021, that the primary endpoint be presented as follows:
Remission at Week 26 and Sustained Remission at Week 52
Remission was achieved by 72.3% of patients in the TRADENAME] group and 70.1% of patients in the prednisone group at Week 26 (treatment difference: 3.4%, 95% CI (-6.0%, 12.8%)). At Week 52, a significantly higher percentage of patients had sustained remission in [TRADENAME] group (65.7%) compared to the prednisone group (54.9%), as presented in Table 58*.*

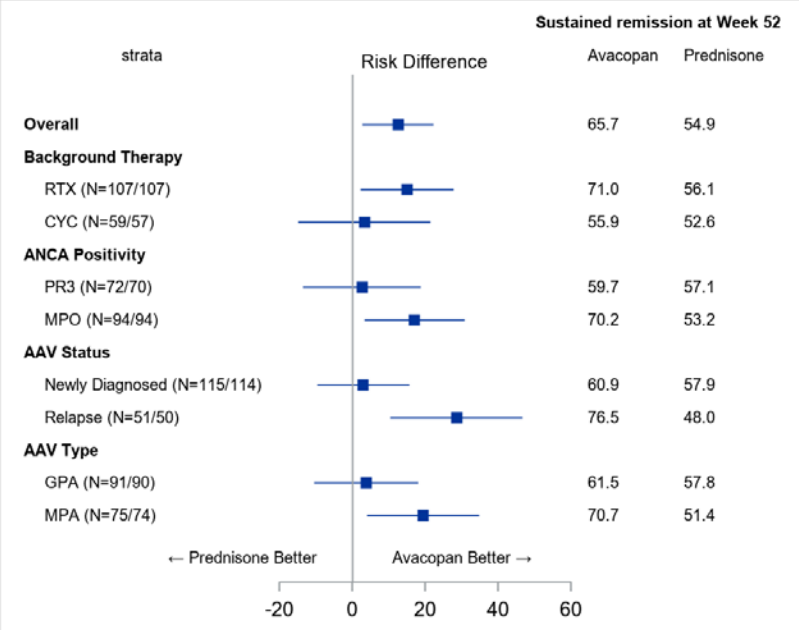
Table 58. Sustained Remission at Week 52 in the Trial #1 (Intent-to-Treat Population)

Parameter	Prednisone (N=164) n (%)	[TRADENAME] (N=166) n (%)	Estimate of Treatment Difference	P-Value
Sustained remission at Week 52	90 (54.9%)	109 (65.7%)	12.5%	0.013
95% CI	(46.9, 62.6)	(57.9, 72.8)	(2.6, 22.3)	

Abbreviations: 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

In pre-specified subgroup efficacy analyses, sustained remission at 52 weeks in patients was examined based on stratification factors, and GPA/MPA disease. The results are displayed in Figure 20 *below.*

Figure 20. Forest Plot of Sustained Remission at Week 52 Based on Disease-Related Variables



The notation N=XXX/YYY indicates the number of patients randomized who received at least one dose of drug in avacopan arm and prednisone arm, respectively. Subgroup findings should be interpreted with caution due to small sample sizes and overlapping subgroups.

Section	Labeling Discussions
	In terms of the [redacted] (b) (4) the Agency did not agree [redacted] (b) (4) [redacted] The Applicant agreed with the Agency's recommendations for clinical data presentation in Section 14. Subsequent discussions between the Agency and the Applicant led to some additional revisions in the description of the clinical study in Section 14 with a more detailed description of the treatment arms, standard-of-care background therapy, and the use of glucocorticoids. Additionally, the forest plot was revised slightly to show "response difference" rather than "risk difference." Avacopan was changed to TAVNEOS, and "relapse" was changed to "relapsed."

Source: Clinical Reviewer

Other Prescription Drug Labeling

The Applicant proposed [redacted] (b) (4) However, given the safety concerns, particularly for hepatotoxicity, the Agency recommended that the Applicant amend [redacted] (b) (4) [redacted] (b) (4) Medication Guide. The Agency offered several revisions to align the information with the Prescribing Information, to reduce redundancy, to make the patient information more consistent and concise, and to include the information necessary for patients to safely take their medications.

Labeling consultants, including DMEPA, OPDP, and DMPP, have reviewed the submitted labeling and their recommendations which pertain primarily to internal consistency, improving readability and clarity of the labeling and the Medication Guide, have been considered and conveyed to the Applicant. All labeling changes were agreed upon with the Applicant.

12. Risk Evaluation and Mitigation Strategies

No REMS were submitted nor required for this application. The risks of avacopan can be adequately managed in the postmarketing setting through labeling.

13. Postmarketing Requirements and Commitment

The Agency and the Applicant agreed to a postmarketing trial that would address the postmarketing requirement (PMR) for additional safety data and postmarketing commitment (PMC) for additional efficacy data.

Patient population: Newly-diagnosed or relapsing ANCA-associated vasculitis (GPA or MPA)

Background therapy: All patients should be treated with standard-of-care immunosuppressive background therapy, that is, rituximab or cyclophosphamide/azathioprine plus glucocorticoids. All patients should also receive maintenance therapy after induction treatment according to current treatment guidelines.

Study duration: 5 years (minimum)

(b) (4)

The primary objective of this trial is to provide a controlled assessment of safety. There are multiple safety comparisons possible with this design, as described in Table 59. (b) (4)

Applicant will include specific monitoring for hepatotoxicity, hypersensitivity, and infections. A minimum study duration of 5 years would allow for a reasonable precision of estimates for these rare safety outcomes of interest.

Details of the postmarketing trial will be finalized with the Agency after approval.

The following FDAAA PMR and PMC was conveyed to the Applicant:

PMR-1: Conduct a randomized controlled clinical trial of at least five years duration in patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis to evaluate safety outcomes, including hepatotoxicity and drug-induced liver injury, and serious hypersensitivity reactions, including angioedema and anaphylaxis.

Draft Protocol Submission Date: 01/31/2022
Final Protocol Submission Date: 05/30/2022
Interim Report Date: 05/15/2030
Trial Completion Date: 12/31/2030
Final Report Submission Date: 09/30/2031

PMC-1: Conduct a randomized controlled clinical trial of at least five years duration in patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis to evaluate efficacy outcomes with long-term avacopan treatment.

Draft Protocol Submission Date: 01/31/2022
Final Protocol Submission Date: 05/30/2022
Interim Report Date: 05/15/2030
Trial Completion Date: 12/31/2030
Final Report Submission Date: 09/30/2031

The Agency will also issue a PMR for assessment of the impact of avacopan at steady state under fed condition on CYP3A4 substrates. When a single dose of 30 mg avacopan was administered with a high-fat, high-calorie meal, avacopan AUC and Cmax increased by approximately 72% and 8%, respectively, as compared to fasted condition. Following 30 mg avacopan twice daily administration, the steady state of avacopan was reached by 13 weeks with approximately 4-fold accumulation. Avacopan showed time-dependent inhibition of CYP3A4. After 30 mg avacopan twice daily administration under fasted condition for 10 days, the AUC and Cmax of midazolam (a sensitive CYP3A4 substrate) increased by 81% and 55%, respectively. The impact of avacopan at steady state under fed condition on CYP3A4 substrates could be higher as compared to fasted condition but has not been studied in the clinical program to support the approval.

A clinical drug interaction study is required to evaluate the effect of repeat doses of avacopan 30 mg twice daily with food at steady state on the pharmacokinetics of a sensitive substrate of CYP3A4 (e.g., simvastatin) to inform appropriate dosing strategies for coadministration of avacopan with CYP3A4 substrates. The agreed-upon study will (b) (4)

The following FDAAA PMR was conveyed to the Applicant:

PMR- 2: Conduct a clinical drug interaction study to evaluate the effect of repeated doses of avacopan 30 mg twice daily with food at steady state on the pharmacokinetics of a sensitive substrate of CYP3A4 (e.g., simvastatin) to inform appropriate dosing strategies for coadministration of avacopan with CYP3A4 substrates.

Draft Protocol Submission Date: 01/2022
Final Protocol Submission Date: 04/2022
Trial Completion Date: 09/2022
Final Report Submission Date: 02/2023

14. Division Director (OB) Comments

The statistical concerns are clearly articulated in the review. The review captures the concerns and recommendations of the Division of Biometrics III review team. The OND Division and Office Directors acknowledged and considered the clinical and statistical review teams' concerns. Fundamentally the distinction is what is or is not considered a compelling efficacy finding. The OB Division Director does not consider the findings statistically very persuasive.

15. Division Director (Clinical) Comments

While the clinical and statistical review teams agree that the primary efficacy comparisons in Study CL010_168 were statistically significant and valid, they have identified several areas of concern which have led them to recommend a Complete Response and the conduct of a second study to better characterize the treatment benefit and benefit-risk balance of avacopan. These concerns include the following:

- Although the Week 26 primary comparison of noninferiority in the proportion of patients in remission was confirmed, superiority of avacopan was not demonstrated.
- Although the Week 52 primary comparison of superiority in sustained remission was confirmed for the overall population, there was lack of treatment effect in the cyclophosphamide induction subgroup, who received azathioprine maintenance therapy.
- The treatment effect for the primary endpoint at Week 52 was primarily observed in the rituximab induction subgroup, which did not receive maintenance standard of care.
- Discrepancy between BVAS assessment results when scored by Investigator vs. pre-specified Adjudication Committee analyses (due to differences in attribution of persistent vasculitis).
- Exploratory analyses (due to lack of multiplicity adjustments) across multiple secondary endpoints did not provide clear and consistent evidence of a treatment benefit for avacopan.
- Limited support from phase 2 studies necessitating reliance on the efficacy results of Study CL010_168 alone.
- A limited safety database which, nonetheless, showed imbalances which were greater with avacopan treatment with respect to hepatobiliary AEs and SAEs, liver enzyme elevations, hepatobiliary AEs leading to discontinuation, CPK elevation, and angioedema.

Overall, the review team has concluded that the above concerns show lack of robustness of efficacy and result in lack of clarity regarding the context of use and associated benefit-risk of avacopan.

The Division Director's recommendation of approval takes into consideration the clinical-statistical review team's recommendations and concerns but believes additional considerations ameliorate and outweigh those concerns, based on the following:

- The superiority analysis of Week 26 remission endpoint did not demonstrate superiority; however, this does not preclude a conclusion that avacopan has a beneficial treatment effect:

  - Because of the design features of Study CL010_168, in which the control group received 60 mg prednisone daily, tapered over 20 weeks, in addition to induction with rituximab or cyclophosphamide, an expectation that the avacopan group demonstrates statistically significant superiority to the control group would be a very high bar, as steroids + rituximab or CYC are associated with high remission rates at 6 months.
  - I agree with the review team that there was a question about whether the non-inferiority margin for the pre-specified primary endpoint at Week 26 was scientifically justified, and it may be difficult to characterize the exact contribution of avacopan to remission rates at Week 26 because of the evolving understanding of the contribution of systemic glucocorticoids (Walsh et al. 2020), the use of non-study-supplied glucocorticoids, and the potential drug-drug interactions. However, the point estimate of the results for the avacopan group was very similar to that of the prednisone control group (72.3% vs 70.1%, respectively), suggesting that avacopan had some level of treatment benefit toward remission rates at Week 26, albeit difficult to quantify.

- The pre-specified Week 52 primary endpoint of superiority in sustained remission was met. However, the subgroup results suggested most of this treatment effect was being driven by the rituximab subgroup and there was little effect in the cyclophosphamide subgroup. This concern is mitigated by the following considerations:

  - The rituximab induction subgroup, where the treatment effect was observed at Week 52, did not receive maintenance standard of care during the second half of the study, resulting in “de facto” placebo comparison in the rituximab induction stratum. This design feature allows for the clear demonstration of avacopan’s clinical activity in this patient population.
  - Further, superiority for avacopan at Week 52 was not due to non-study-supplied glucocorticoid use, which in Week 26 to Week 52 occurred in a lower proportion of avacopan patients (27%) compared to the control group (39%).
  - Additional consideration includes that the subgroup analyses should be interpreted with caution as there is considerable uncertainty around the estimates. Further, induction with rituximab or cyclophosphamide was at the discretion of the investigators and not a randomization variable.

- The discrepancy between Investigator BVAS and pre-specified Adjudication Committee BVAS due to differences in attribution of “persistent vasculitis.” The fact that the pre-specified analysis, by the Adjudication Committee, showed a statistically significant result in favor of avacopan, but the Investigator-assessed BVAS only trended in favor of avacopan, does not undermine the reliability of the pre-specified analysis.

  - As with outcome measures in other complex systemic diseases, i.e., Systemic Lupus Erythematosus (SLE), instruments to assess outcome domains in vasculitis are also complicated and have undergone multiple revisions. The Birmingham Vasculitis Activity Score is the most frequently used instrument in trials of ANCA-associated vasculitis and has also been associated with a tremendous variety of slightly different definitions of response, relapse, and remission (Monti et al. 2020).4 Given the complexity and heterogeneity in its application, inter- and intra-rater variability is likely to be high, and use of a well- and uniformly-trained Adjudication Committee would be reasonable as a preferred approach. Additionally, as noted by the review team, discrepancies between the Investigator and Adjudication Committee results were relatively well balanced by treatment arm.

- Exploratory analyses across multiple secondary endpoints were not consistently favorable. However, results for the clinically important endpoint of rates of relapse did favor avacopan. Based on the review team's analysis, Table 60, the proportion of patients who never achieved remission or achieved remission but had a relapse was larger in the prednisone group (24.4% vs 14.5%, difference: -9.9% with 95% CI: [-18.4%, -1.5%]). These differences do not appear to be driven by the lack of maintenance therapy in the rituximab induction stratum as they were observed even during the first half of the study, between Weeks 0 and 26 (9.1% in the comparator group vs 1.8% in the avacopan group), when the active comparator group was treated with standard of care. Notwithstanding the exploratory nature of these analyses, these results clearly support the clinical activity of avacopan beyond that demonstrated by the primary endpoint analyses. While several other secondary endpoints, e.g., related to glucocorticoid use, GTI, quality-of-life measures, and renal function measurement, also appeared supportive of avacopan's efficacy, their interpretation was confounded by the study design and conduct and other limitations, as detailed by the team. The heterogeneity of results among the secondary endpoints is expected in conditions where patients experience a wide range of manifestations and severity, such as SLE or AAV, as there would only be a subgroup of patients with a given manifestation or symptom. These results may not add clarity to the characterization of avacopan's treatment benefits, but they also do not preclude a conclusion of benefit.

[4] Monti S et al., Tables 3 and 4.

Table 60. Proportion of Patients Who Did Not Achieve Remission (BVAS =0) or Relapsed after Remission (BVAS =0)

BVAS Outcome	Prednisone (N=164) n (%)	Avacopan (N=166) n (%)
Did not achieve BVAS =0	7 (4.3)	8 (4.8)
Achieved BVAS =0	157 (95.7)	158 (95.2)
Relapse	33 (20.1)	16 (9.6)
Between Week 0-Week 26[1]	16 (9.1)	3 (1.8)
Between Week 27-Week 52[2]	17 (11.0)	13 (7.8)
Did not achieve BVAS =0 OR Relapsed	40 (24.4)	24 (14.5)
Difference (95% CI)	-9.9% (-18.4%, -1.5%)	

Source: Statistical Reviewer.
[1] Day 1 to Day 183
[2] Day 184 to End of treatment
Point estimate and 95% confidence interval using normal approximation were reported.
Counts and percentages relative to N.
Abbreviations: BVAS, Birmingham Vasculitis Activity Score; CI, confidence interval; Diff, difference; N, the number of patients randomized who received at least one dose of drug.

- Limited support from the phase 2 studies. Study CL002_168 ("CLEAR") was a small study of 67 patients, which included 26 patients with renal-limited AAV, and CL003_168 ("CLASSIC") was a small study in 42 patients with AAV. Both of these studies differed from Study CL010_168 in that treatment duration was only for 12 weeks, utilized a different primary endpoint (BVAS 50% response), and included different doses and concomitant medication regimens.
  - The Division Director's perspective is in agreement with the team that these two small studies are difficult to interpret and do not provide clear support for the single phase 3 study; however, they also do not conflict with a finding of efficacy in the phase 3 study.
- There is a limited safety database that is derived mainly from Study CL010_168. However, overall, TEAEs, deaths, SAEs, severe TEAEs, and TEAEs leading to treatment discontinuation were balanced between treatment groups. Signals of drug-induced liver injury and elevations in CPK were noted earlier in development and recurred in Study CL010_168. There were two cases of angioedema (one SAE) in the avacopan arm vs. none in the prednisone arm.
  - The Division Director's perspective is in agreement with the team that this is a limited safety database. However, the safety signals that were seen were consistent with early development.
  - To further characterize the safety of avacopan, an additional postmarketing study is warranted.
- AAV is a serious, potentially organ- and life-threatening rare disease with a limited therapeutic armamentarium. With a prevalence of 2.3 to 146 cases per million persons

for GPA and a prevalence of 9.0 to 94 cases per million persons for MPA (Kitching et al. 2020) and a compelling need to treat to remission when patients present with serious manifestations, requiring a second phase 3 study may delay access while not providing the desired additional clarity with respect to avacopan's ultimate role in the therapeutic armamentarium.

In summary, the Division Director's perspective is that sufficient information has been provided in this application to conclude that the benefit-risk profile is favorable for avacopan and sufficient evidence exists to support avacopan's approval for the treatment of AAV.

My recommendations are informed by my thorough review of the data submitted, the team's assessment, and input from the Medical Policy and Program Review Council meeting on March 17, 2021, the Arthritis Advisory Committee and the Open Public Hearing on May 6, 2021.

16. Office Director Comments

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a rare, potentially life-threatening condition. Therapeutic advances have increased the likelihood of induction and maintenance of remission however, disease relapse continues to pose a burden to patients. Morbidity related to disease-related organ damage and adverse effects of therapies to manage the disease negatively impact quality of life. Current challenges include improving measures of disease activity and risk of relapse, uncertainty about optimal therapy duration and a need for targeted therapies with fewer adverse effects.

Avacopan, a new molecular entity, is an antagonist of complement 5a receptor (C5aR) and blocks C5a-mediated neutrophil activation and migration. It therefore has the potential to impact important aspects of the pathogenesis of ANCA-associated vasculitis. Study CL010_168, a multicenter, randomized, double-blind and active-controlled trial in 330 newly diagnosed or relapsed patients with ANCA-associated vasculitis, provides the primary evidence for avacopan efficacy. The study met the pre-specified primary endpoints of non-inferiority (NI) in disease remission at Week 26 and superiority in sustained disease remission at Week 52, defined by Birmingham Vasculitis Activity Score (BVAS) remission, an established clinical endpoint. In addition, exploratory analyses suggest that fewer avacopan-treated patients relapsed after remission as compared to patients on the comparator arm. Data also suggest decreased glucocorticoid use in avacopan-treated patients but not elimination of glucocorticoid use. Supportive evidence of avacopan efficacy is derived from mechanistic considerations, from nonclinical studies (e.g., involving C5a-induced neutropenic cynomolgus monkeys, and a transgenic mouse ANCA disease model). The data from two 12-week phase 2 clinical studies do not conflict with the treatment effects seen in Study CL010_168.

As has been discussed in this review and at the Arthritis Advisory Committee Meeting held on May 6, 2021, there were insufficient data to determine an appropriate NI margin for the Week 26 remission endpoint, and superiority was not demonstrated for avacopan for this endpoint. While I acknowledge the limitations around the NI assessment, in my view, the lack of superiority of avacopan relative to the comparator arm at Week 26 is neither concerning nor unexpected due to the fact that patients in both arms received background treatment with standard induction regimens.

I believe the superiority finding for Week 52 sustained remission for the overall study population is a compelling efficacy finding despite the fact that the result appears to be primarily driven by assignment to rituximab induction but no maintenance standard of care. I acknowledge that residual questions remain regarding the role of avacopan as induction or maintenance therapy that should be explored further. In the meantime, avacopan approval would provide access to a novel mechanism of action drug that could be used as therapy

consistent with its use in Study CL010_168. Other clinical considerations could include use in patients at risk for relapse, in patients not responding to currently available therapy, or in patients at risk for/experiencing complications from chronic high dose glucocorticoid use.

The assessment of avacopan safety is derived primarily from Study CL010_168. Hepatic-related adverse reactions, including hepatobiliary adverse reactions and transaminase elevations, occurred in 13.3% and 11.6% of patients on the avacopan and comparator arms, respectively. Serious hepatic-related adverse reactions occurred in 5.4% and 3.7% of patients in these arms, respectively. Two cases of angioedema occurred in avacopan-treated patients, one of which resulted in hospitalization. Serious infections, some fatal, have occurred with avacopan use, consistent with other immunosuppressants. These events will be described in product labeling, in a Medication Guide, and further explored in a required long-term postmarket safety study.

In conclusion, I concur with the recommendation of the Director of the Division of Rheumatology and Transplant Medicine to approve NDA 214487 for avacopan as an adjunctive treatment of adult patients with severe active ANCA-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with standard therapy including glucocorticoids. Avacopan does not eliminate glucocorticoid use. Avacopan is not recommended for patients with active, untreated and/or uncontrolled chronic liver disease and cirrhosis. The recommended dosing regimen is 30 mg twice daily orally.

17. Appendices

17.1. References

Literature

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Guidances for Industry

Draft Guidance for Industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)

17.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): CL010_168

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: **238 Principal Investigators (PI)**		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): **0**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **3**		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: **3** Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Study Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) **0**		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

17.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

17.3.1. Clinical Pharmacology Individual Study Review

Note – In this review, early development names CCX168 is also used to refer to avacopan. All clinical pharmacology studies listed in Table 15 were reviewed in this section. Refer to the QT Study Review by Dr. Girish Bende dated October 13, 2020 for Study CL014_168 assessment.

17.3.1.1. In Vitro Studies

The brief summary of in vitro studies was listed in Table 61.

Table 61. Avacopan and Its Major Metabolites In Vitro Studies Using Human Biomaterials

ADME	Conclusions	Study/Report
Absorption	CCX168 showed high permeability across the Caco-2 cell monolayer (Papp values of ~25×10^{-6} and 27.3×10^{-6} cm/s for A→B and B→A directions, respectively) with no evidence of efflux.	PC0361_168_a
Distribution	CCX168 and metabolite M1 have limited penetration into red blood cells.	PC0364_168_a
	Both CCX168 and M1 were found to be highly protein bound (>99.9%) at the concentrations of 2.5, 10 and 50 µM.	PC0632_168
	CCX168 and M1 was found to be bound to human α1-acid glycoprotein (AAG) at >99.9% and 99%, respectively, at 5 µM and 10 µM.	PC0685_168
	Both CCX168 and metabolite CCX168-M1 at 5 µM and 10 µM were found to be bound to human albumin at 99.9% or greater.	PC0681_168

ADME	Conclusions	Study/Report
Metabolism	*In-vitro* stability study indicated that when incubated with cryogenically preserved hepatocytes using verapamil as a reference compound, avacopan showed low to moderate intrinsic clearance: average CLint values are 20.6, 45.3, 36.0, 33.4 10.9 µL/10^6 cells/min for mice, rats, dogs, monkeys and humans, respectively.	PC0370_168
	Only one metabolite (M1) was observed after incubation of CCX168 with human or cynomolgus monkey cryo-preserved hepatocytes. M1 was also observed in dog hepatocyte incubation, but not in rat hepatocyte incubation, which was found to contain several other metabolites.	PC0369_168
	The *in vitro* metabolite profiles of CCX168 were investigated through incubation of [^{3}H]CCX168 with liver microsomes (rat, hamster, rabbit, monkey and human) and hepatocytes (rat, rabbit, monkey and human). CCX168 was extensively metabolized in the liver microsomal incubations and was modestly metabolized in the hepatocyte incubations. M1, a mono-oxidation metabolite, was the major metabolite observed in the liver microsomal incubations of all five species (>10% of total radioactivity), but M1 and other metabolites were minor in the hepatocyte incubations (<10% of total radioactivity). There was no species difference observed.	PC0623_168_a
	CYP3A4 is the most likely CYP450 isoform responsible for the metabolic clearance of CCX168, while CYP1A2 and CYP2B6 may play some minor roles. The in vitro formation of M1 is largely attributed to CYP3A4, and to a lesser degree, CYP2C19 and CYP2D6.	PC0373_168
	CCX168 is rapidly metabolized when incubated with Aroclor-1254 induced rat liver S9, and metabolites CCX168-M1 and CCX168-M6 are also formed rapidly, reaching maximum levels at 30 minutes.	PC0488_168
	The human metabolic pathways of CCX168 and M1, including the CYP450 isozymes that are responsible for metabolic transformation, are characterized using recombinant CYP450 enzyme systems and pooled human liver microsomes. Results indicated that CYP3A4/5 was the primary isozyme involved in the in vitro metabolism of CCX168 and M1, which was also confirmed by using two other independent approaches (enzyme activity correlation analysis and chemical inhibition). Other isozymes (CYP2D6, CYP2C19, CYP2C8, CYP2C9 and CYP2B6) played minor roles.	PC0711_168
DDI potential-CYP inhibition	CCX168 does not inhibit CYP450 isoforms significantly with the IC50 values ≥30 µM for CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4.	PC0360_168
	CCX168 has no effect on the free fraction of prednisone or prednisolone in human plasma.	PC0466_168
	Neither CCX168 nor M1 inhibit the 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) and 11β-HSD2 activities significantly.	PC0469_168
	M1 does not inhibit CYPs 1A2, 2B6, 2C8, 2C19, 2D6 and 3A4 significantly with the IC50 values ≥10 µM, and moderately inhibits CYP2C9 with IC50 of 4.7±1.4 µM.	PC0489_168

ADME	Conclusions	Study/Report
	CCX168 showed time-dependent inhibition of CYP3A4, with the remaining activity decreasing by 51% (atorvastatin), 68% (midazolam) and 47% (Nifedipine) at 1µM. The maximal rate constant (K_{Inact}) and the concentration of CCX168 required to achieve half-maximal inactivation (K_I) of CYP3A4 were 0.0659 min^{-1} and 4.47 µM.	PC0622_168
	M1 showed no significant time-dependent inhibition of CYP2C9, but it inhibited CYP3A4 at 3 µM and 10 µM by 26% and 50%, respectively. The CYP3A4 inactivation constants of M1 were found to be K_I =11.7 µM and K_{Inact} =0.0402 min^{-1}.	PC0634_168
DDI potential-CYP induction	M1 does not have any significant induction potential for CYPs 3A4,1A2 and 2B6 in human hepatocytes.	PC0491_168
	In vitro study in human hepatocytes for CYP450 enzyme induction potential of CCX168 showed negligible induction of CYP1A2 and CYP2B6 mRNA levels (<4% and <23% of the positive control, respectively) and modest induction of CYP3A4 (up to 7.5-fold increase in mRNA level; 30-40% of the positive control rifampin).	PC0635_168_a
DDI potential-Transporter	CCX168 weakly inhibited OAT1 and OATP1B1 at 20 µM, by 21% and 25%, respectively. CCX168 is not an inhibitor of MATE1, MATE2-K, OAT3, OATP1B3 and OCT2 uptake and BCRP and P-gp. CCX168 is not a substrate of BCRP and P-gp efflux and OATP1B1 and OATP1B3 uptake transporters. M1 is a substrate of P-gp. M1 is not an inhibitor of MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3 and OCT2 uptake or BCRP and P-gp up to 2 µM. M1 is not a substrate of BCRP efflux and OATP1B1 and OATP1B3 uptake transporters.	PC0712_168

Source: reviewer summary
Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome P450 enzyme; DDI, drug-drug interaction; K_I, inhibition constant; $K_{Inactive}$, rate of enzyme inactivation; MATE, multidrug and toxin extrusion; OATP, organic anion transporting polypeptides; P-gp, P-glycoprotein.

17.3.1.2. Pharmacokinetics

17.3.1.2.1. SAD and MAD PK study

Study # CL001_168

Title: 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

Study period: 21 December 2009- 29 September 2010

Objective:

- Safety, tolerability
- Pharmacokinetic (PK), relationship between PK and C5aR-dependent CD11b upregulation

Study design: This was a double-blind, placebo-controlled, single, and multiple ascending dose study in 40 healthy subjects. Subjects were randomly assigned to receive single oral doses of CCX168 or placebo. The doses administered in the cohorts were

- Cohort 1: 1 mg CCX168 in Period 1 and 1 mg CCX168 once daily (QD) for 7 days in Period 2
- Cohort 2: 3 mg CCX168 in Period 1 and 3 mg CCX168 QD for 7 days in Period 2
- Cohort 3: 10 mg CCX168 in Period 1 and 10 mg CCX168 QD for 7 days in Period 2
- Cohort 4: 30 mg CCX168 in Period 1 and 30 mg CCX168 twice daily (BID) 7 days in Period 2
- Cohort 5: 100 mg CCX168 in Period 1 and 50 mg CCX168 BID for 7 days in Period 2

Test drug: CCX168 was administered as a solution for all dose cohorts in Period 1, and to the first three cohorts in Period 2. Cohorts 4 and 5 received study medication as gelatin capsules in Period 2. One of the capsule formulations contained Cremophor RH40 in (b) (4) gelatin capsules and the other contained (b) (4) Cremophor RH40 and (b) (4) PEG4000 also in (b) (4) gelatin capsules.

PK Samples:

- Period 1: predose and at Hours 0.08, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 10, 12, 18 and 24 postdose, and Days 3, 4, 8
- Period 2:
  - Predose and at Hours 0.08, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 10, and 12 after administration of the first dose of study medication for the first three dose cohorts, and at Time 0 and at Hours 0.25, 0.5, 1, 2, 3, 4, 6, 10, 12, 12.25, 12.5, 13, 14, 15, and 16 after administration of the first dose of study medication for the twice daily dosing cohorts
  - At Hours 18, 22 (for twice daily cohorts only), and 24 (Day 2), Hour 48 (Day 3), Hour 72 (Day 4), Hour 96 (Day 5), and Hour 120 (Day 6) after administration of the first dose of study medication
  - At Hours 144, 144.08, 144.25, 144.5, 145, 145.5, 146, 147, 148, 150, 154, and 156 (Day 7), and Hours 162 and 168 (Day 8) after the first dose of study medication for the first three dose cohorts, and at Hours 144, 144.25, 144.5, 145, 146, 147, 148, 150, 154, 156, 156.25, 156.5, 157, 158, 159, and 160 (Day 7), and Hours 162, 166, and 168 (Day 8) after administration of the first dose of study medication for the twice daily dosing cohorts
  - And Days 9, 10, 15

Results: The PK results were summarized as below.

Table 62. Summary Statistics by Formulation for Pharmacokinetic Estimates After a Single Oral Administration of Avacopan (Study CL001_168)

PK Parameter		Target CCX168 Dose (mg)									
		1		3		10		30		100	
		A*	B	A	B	A	B	A	B	A	B
C_{max} (ng/mL)	Mean	2.56	1.36	10.6	7.70	27.6	23.0	48.8	109	102	293
	SD	1.20	0.0737	1.80	0.281	4.61	6.67	12.8	17.6	34.0	181
	Min	1.71	1.30	8.73	7.38	22.8	18.0	34.5	98.2	81.2	84.4
	Median	2.56	1.33	10.9	7.84	28.0	20.5	52.7	98.9	83.1	378
	Max	3.40	1.44	12.3	7.89	32.0	30.6	59.1	129	141	416
	CV%	46.8	5.43	16.9	3.65	16.7	29.0	26.2	16.2	33.4	62.0
	Geometric Mean	2.41	1.36	10.5	7.70	27.3	22.4	47.5	108	98.4	237
	95% CI (Lower Mean)	-8.18	1.17	6.17	7.00	16.1	6.46	17.1	65.0	17.3	-158
	95% CI (Upper Mean)	13.3	1.54	15.1	8.40	39.1	39.6	80.5	152	186	744
	N	2	3	3	3	3	3	3	3	3	3
T_{max} (hr)	Mean	1.0	1.2	1.2	1.2	1.5	1.8	1.7	1.7	1.3	3.7
	SD	0.0	0.29	0.29	0.29	0.0	0.29	0.29	0.58	0.29	2.1
	Min	1.0	1.0	1.0	1.0	1.5	1.5	1.5	1.0	1.0	2.0
	Median	1.0	1.0	1.0	1.0	1.5	2.0	1.5	2.0	1.5	3.0
	Max	1.0	1.5	1.5	1.5	1.5	2.0	2.0	2.0	1.5	6.0
	CV%	0.0	25	25	25	0.0	16	17	35	22	57
	Geometric Mean	1.0	1.1	1.1	1.1	1.5	1.8	1.7	1.6	1.3	3.3
	95% CI (Lower Mean)	1.0	0.45	0.45	0.45	1.5	1.1	0.95	0.23	0.62	-1.5
	95% CI (Upper Mean)	1.0	1.9	1.9	1.9	1.5	2.6	2.4	3.1	2.1	8.8
	N	2	3	3	3	3	3	3	3	3	3
λ_z (hr^{-1})	Mean	0.275	0.431	0.434	0.442	0.0295	0.0389	0.0116	0.0139	0.0153	0.00879
	SD	0.0885	0.0518	0.218	0.171	0.00381	0.0229	0.00523	0.0124	0.00382	0.00151
	Min	0.213	0.392	0.195	0.245	0.0251	0.0212	0.00827	0.00665	0.0112	0.00712
	Median	0.275	0.412	0.488	0.537	0.0315	0.0307	0.00892	0.00686	0.0162	0.00919
	Max	0.338	0.490	0.620	0.545	0.0319	0.0648	0.0176	0.0282	0.0187	0.0101
	CV%	32.1	12.0	50.2	38.7	12.9	58.9	45.0	89.1	24.9	17.2
	Geometric Mean	0.268	0.429	0.389	0.415	0.0293	0.0348	0.0109	0.0109	0.0150	0.00870
	95% CI (Lower Mean)	-0.520	0.303	-0.107	0.0172	0.0200	-0.0180	-0.00137	-0.0169	0.00585	0.00503
	95% CI (Upper Mean)	1.07	0.560	0.976	0.867	0.0390	0.0958	0.0246	0.0447	0.0248	0.0125
	N	2	3	3	3	3	3	3	3	3	3

*Formulation A: PEG- (b) (4) liquid; Formulation B: PEG (b) (4) liquid

PK Parameter		Target CCX168 Dose (mg)									
		1		3		10		30		100	
		A	B	A	B	A	B	A	B	A	B
$t_{1/2}$ (hr)	Mean	2.66	1.62	2.03	1.80	23.8	22.0	66.9	76.6	47.3	80.6
	SD	0.853	0.184	1.33	0.896	3.32	11.0	24.1	45.1	13.1	14.9
	Min	2.05	1.41	1.12	1.27	21.8	10.7	39.3	24.6	37.1	68.9
	Median	2.66	1.68	1.42	1.29	22.0	22.6	77.7	101	42.8	75.5
	Max	3.26	1.77	3.56	2.83	27.6	32.6	83.8	104	62.1	97.4
	CV%	32.1	11.4	65.5	49.8	14.0	50.0	36.0	58.9	27.6	18.5
	Geometric Mean	2.59	1.61	1.78	1.67	23.6	19.9	63.5	63.7	46.2	79.7
	95% CI (Lower Mean)	-5.01	1.16	-1.28	-0.427	15.5	-5.31	7.03	-35.5	14.8	43.5
	95% CI (Upper Mean)	10.3	2.08	5.35	4.02	32.0	49.3	127	189	79.8	118
	N	2	3	3	3	3	3	3	3	3	3
CL/F (L/hr)	Mean	144	228	112	151	66.3	108	62.2	41.1	83.2	41.7
	SD	80.9	71.9	44.4	24.2	10.1	52.6	9.17	11.8	34.3	20.3
	Min	87.0	147	70.0	123	56.3	74.3	52.3	33.1	63.4	28.3
	Median	144	253	106	164	66.1	80.6	63.8	35.7	63.4	31.7
	Max	201	285	158	165	76.6	168	70.4	54.7	123	65.1
	CV%	56.1	31.5	39.8	16.0	15.3	48.8	14.8	28.6	41.2	48.8
	Geometric Mean	132	220	106	149	65.8	100	61.7	40.1	79.0	38.7
	95% CI (Lower Mean)	-583	49.6	1.22	90.7	41.1	-22.9	39.4	11.9	-2.04	-8.88
	95% CI (Upper Mean)	871	407	222	211	91.5	238	84.9	70.4	168	92.2
	N	2	3	3	3	3	3	3	3	3	3
Vz/F (L)	Mean	503	528	278	370	2310	2940	5940	4040	5390	5130
	SD	132	158	73.4	114	667	746	2160	1840	1360	3490
	Min	409	376	218	301	1770	2420	3620	1940	3910	2810
	Median	503	515	255	308	2100	2600	6320	4830	5680	3450
	Max	596	691	360	502	3050	3790	7890	5360	6580	9140
	CV%	26.3	29.9	26.4	30.8	29.0	25.4	36.3	45.6	25.2	68.0
	Geometric Mean	494	512	271	360	2240	2880	5650	3690	5270	4460
	95% CI (Lower Mean)	-686	135	95.2	86.9	647	1080	581	-538	2020	-3530
	95% CI (Upper Mean)	1690	920	460	654	3960	4790	11300	8620	8760	13800
	N	2	3	3	3	3	3	3	3	3	3
$AUC_{0\text{-}t}$ (ng*hr/mL)	Mean	7.29	3.72	27.4	19.4	145	98.1	451	662	1250	2520
	SD	4.35	1.40	11.4	3.64	24.8	37.5	71.6	130	406	1060
	Min	4.21	2.65	16.6	17.2	121	55.3	379	519	785	1300
	Median	7.29	3.19	26.4	17.3	145	114	453	694	1460	2940
	Max	10.4	5.31	39.3	23.6	170	125	522	773	1510	3300
	CV%	59.7	37.8	41.4	18.8	17.1	38.2	15.9	19.7	32.4	42.3
	Geometric Mean	6.61	3.56	25.8	19.1	144	92.3	448	653	1200	2330
	95% CI (Lower Mean)	-31.8	0.230	-0.798	10.3	83.6	4.99	274	338	244	-129
	95% CI (Upper Mean)	46.4	7.20	55.7	28.4	207	191	629	986	2260	5160
	N	2	3	3	3	3	3	3	3	3	3
$AUC_{0\text{-}inf}$ (ng*hr/mL)	Mean	8.23	4.75	30.0	20.3	153	106	490	765	1320	2750
	SD	4.62	1.77	12.1	3.58	23.6	40.7	75.9	190	441	1060
	Min	4.97	3.51	19.0	18.1	131	59.4	426	549	814	1540
	Median	8.23	3.96	28.2	18.3	151	124	470	841	1580	3160
	Max	11.5	6.78	42.9	24.4	178	135	574	906	1580	3540
	CV%	56.1	37.4	40.2	17.7	15.4	38.4	15.5	24.9	33.3	38.8
	Geometric Mean	7.55	4.55	28.4	20.1	152	99.7	486	748	1270	2580
	95% CI (Lower Mean)	-33.2	0.341	0.0430	11.4	94.7	4.85	302	293	228	102
	95% CI (Upper Mean)	49.7	9.16	60.0	29.2	212	207	679	1240	2420	5390
	N	2	3	3	3	3	3	3	3	3	3

Source: Table 17 of Study CL001_168 PK report
*Formulation A: PEG- (b) (4) liquid; Formulation B: PEG- (b) (4) liquid
Abbreviations: λ_z, elimination rate constant; $AUC_{0\text{-}inf}$, area under the curve from zero to infinity $AUC_{0\text{-}T}$, area under the curve to the last quantifiable time point; CI, confidence interval; CL/F, apparent systemic clearance; C_{max}, maximum concentration; CV%, coefficient of variation; PK, pharmacokinetics; SD, standard deviation; ;$t_{1/2}$, half-life; T_{max}, time to maximum concentration; Vz/F, apparent central volume of distribution.

Table 63. Summary Statistics for Pharmacokinetic Estimates by Formulation After Multiple Oral Administrations of Avacopan (Study CL001_168)

PK Parameter		Target CCX168 Dose (mg)															
		Cremophor								PEG-Cremophor							
		Day 1				Day 7				Day 1				Day 7			
		30 (1)£	30 (2)£	50 (1)£	50 (2)£	30 (1)£	30 (2)£	50 (1)£	50 (2)£	30 (1)£	30 (2)£	50 (1)£	50 (2)£	30 (1)£	30 (2)£	50 (1)£	50 (2)£
C_{max} (ng/mL)	Mean	85.1	279	199	470	164	182	387	364	109	270	205	375	158	199	463	354
	SD	11.4	47.5	73.9	302	16.9	31.8	157	187	10.1	99.5	73.8	76.4	31.6	88.5	179	114
	Min	74.1	228	144	196	150	146	237	196	98.8	169	121	291	122	112	299	286
	Median	84.4	287	170	419	160	196	374	329	110	272	237	395	169	196	435	290
	Max	96.9	322	283	794	183	205	550	566	119	368	258	440	182	289	654	486
	CV%	13.4	17.0	37.1	64.3	10.3	17.4	40.5	51.5	9.26	36.9	35.9	20.4	20.0	44.5	38.7	32.3
	Geometric Mean	84.6	276	191	402	164	180	365	332	109	257	195	370	155	185	440	343
	95% CI (Lower	56.8	161	15.4	-281	122	103	-2.77	-102	84.1	22.4	22.0	185	79.3	-20.9	17.7	70.0
	95% CI (Upper	113	397	383	1220	206	261	777	829	134	517	389	565	236	419	908	638
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
T_{max} (hr)	Mean	2.0	2.0	2.0	2.3	2.3	1.7	2.3	3.3	1.7	2.0	2.0	2.3	2.3	2.7	2.3	2.3
	SD	0	0	0.0	0.58	0.58	0.58	0.58	1.2	0.58	0.0	0	0.58	0.58	1.2	0.58	0.58
	Min	2.0	2.0	2.0	2.0	2.0	1.0	2.0	2.0	1.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
	Median	2.0	2.0	2.0	2.0	2.0	2.0	2.0	4.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
	Max	2.0	2.0	2.0	3.0	3.0	2.0	3.0	4.0	2.0	2.0	2.0	3.0	3.0	4.0	3.0	3.0
	CV%	0	0	0	25	25	35	25	35	35	0.0	0.0	25	25	43	25	25
	Geometric Mean	2.0	2.0	2.0	2.3	2.3	1.6	2.3	3.2	1.6	2.0	2.0	2.3	2.3	2.5	2.3	2.3
	95% CI (Lower	2.0	2.0	2.0	0.90	0.90	0.23	0.90	0.47	0.23	2.0	2.0	0.90	0.90	-0.20	0.90	0.90
	95% CI (Upper	2.0	2.0	2.0	3.8	3.8	3.1	3.8	6.2	3.1	2.0	2.0	3.8	3.8	5.5	3.8	3.8
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
$t_{1/2}$ (hr)	Mean	NA	NA	NA	NA	NA	104	NA	111	NA	NA	NA	NA	NA	155	NA	129
	SD	NA	NA	NA	NA	NA	14.1	NA	12.0	NA	NA	NA	NA	NA	12.0	NA	23.5
	Min	NA	NA	NA	NA	NA	90.7	NA	102	NA	NA	NA	NA	NA	148	NA	109
	Median	NA	NA	NA	NA	NA	101	NA	106	NA	NA	NA	NA	NA	149	NA	124
	Max	NA	NA	NA	NA	NA	119	NA	124	NA	NA	NA	NA	NA	169	NA	155
	CV%	NA	NA	NA	NA	NA	13.6	NA	10.8	NA	NA	NA	NA	NA	7.74	NA	18.2
	Geometric Mean	NA	NA	NA	NA	NA	103	NA	110	NA	NA	NA	NA	NA	155	NA	128
	95% CI (Lower Mean)	NA	NA	NA	NA	NA	68.6	NA	80.8	NA	NA	NA	NA	NA	126	NA	70.6
	95% CI (Upper Mean)	NA	NA	NA	NA	NA	139	NA	140	NA	NA	NA	NA	NA	185	NA	188
	N	NA	NA	NA	NA	NA	3	NA	3	NA	NA	NA	NA	NA	3	NA	3
CL/F (L/hr)	Mean	NA	NA	NA	NA	NA	6.23	NA	4.33	NA	NA	NA	NA	NA	5.49	NA	3.77
	SD	NA	NA	NA	NA	NA	1.47	NA	1.53	NA	NA	NA	NA	NA	2.90	NA	0.235
	Min	NA	NA	NA	NA	NA	4.90	NA	2.78	NA	NA	NA	NA	NA	3.38	NA	3.55
	Median	NA	NA	NA	NA	NA	5.97	NA	4.39	NA	NA	NA	NA	NA	4.28	NA	3.75
	Max	NA	NA	NA	NA	NA	7.81	NA	5.83	NA	NA	NA	NA	NA	8.79	NA	4.02
	CV%	NA	NA	NA	NA	NA	23.6	NA	35.3	NA	NA	NA	NA	NA	52.8	NA	6.22
	Geometric Mean	NA	NA	NA	NA	NA	6.11	NA	4.14	NA	NA	NA	NA	NA	5.03	NA	3.77
	95% CI (Lower Mean)	NA	NA	NA	NA	NA	2.57	NA	0.538	NA	NA	NA	NA	NA	-1.71	NA	3.19
	95% CI (Upper Mean)	NA	NA	NA	NA	NA	9.88	NA	8.13	NA	NA	NA	NA	NA	12.7	NA	4.36
	N	NA	NA	NA	NA	NA	3	NA	3	NA	NA	NA	NA	NA	3	NA	3
Vz/F (L)	Mean	NA	NA	NA	NA	NA	935	NA	689	NA	NA	NA	NA	NA	1220	NA	701
	SD	NA	NA	NA	NA	NA	262	NA	232	NA	NA	NA	NA	NA	590	NA	119
	Min	NA	NA	NA	NA	NA	641	NA	424	NA	NA	NA	NA	NA	729	NA	631
	Median	NA	NA	NA	NA	NA	1020	NA	787	NA	NA	NA	NA	NA	1050	NA	634
	Max	NA	NA	NA	NA	NA	1140	NA	857	NA	NA	NA	NA	NA	1870	NA	838
	CV%	NA	NA	NA	NA	NA	28.0	NA	33.7	NA	NA	NA	NA	NA	48.5	NA	17.0
	Geometric Mean	NA	NA	NA	NA	NA	908	NA	659	NA	NA	NA	NA	NA	1130	NA	694
	95% CI (Lower Mean)	NA	NA	NA	NA	NA	286	NA	112	NA	NA	NA	NA	NA	-250	NA	406
	95% CI (Upper Mean)	NA	NA	NA	NA	NA	1580	NA	1270	NA	NA	NA	NA	NA	2680	NA	996
	N	NA	NA	NA	NA	NA	3	NA	3	NA	NA	NA	NA	NA	3	NA	3

PK Parameter		Target CCX168 Dose (mg)															
		Cremophor								PEG-Cremophor							
		Day 1				Day 7				Day 1				Day 7			
		30 (1)£	30 (2)£	50 (1)£	50 (2)£	30 (1)£	30 (2)£	50 (1)£	50 (2)£	30 (1)£	30 (2)£	50 (1)£	50 (2)£	30 (1)£	30 (2)£	50 (1)£	50 (2)£
$AUC_{0\text{-}tau}$ (ng*hr/mL)[1]	Mean	373	723	801	1580	877	938	2400	2390	388	667	838	1230	883	995	2270	1970
	SD	51.4	83.4	390	1100	88.0	54.5	1320	1150	131	252	184	170	352	378	448	433
	Min	315	652	524	767	780	876	1320	1380	241	400	628	1090	556	582	2010	1640
	Median	392	703	632	1140	900	963	2010	2150	428	700	920	1190	837	1080	2010	1800
	Max	412	815	1250	2830	952	976	3870	3640	494	902	966	1420	1260	1320	2790	2460
	CV%	13.8	11.5	48.7	69.7	10.0	5.81	55.1	48.0	33.8	37.8	21.9	13.8	39.9	38.0	19.7	22.0
	Geometric Mean	370	720	745	1350	874	937	2170	2210	371	632	823	1220	836	940	2250	1940
	95% CI (Lower Mean)	245	516	-169	-1150	659	803	-883	-462	62.6	40.4	382	809	8.50	56.7	1160	893
	95% CI (Upper Mean)	501	930	1770	4310	1100	1070	5680	5250	713	1290	1290	1660	1760	1930	3390	3040
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
$AUC_{0\text{-}t}$ (ng*hr/mL)	Mean	373	723	801	1580	877	3560	2400	9160	388	667	838	1230	883	3970	2270	8880
	SD	51.4	83.4	390	1100	88.0	609	1320	3950	131	252	184	170	352	1720	448	913
	Min	315	652	524	767	780	2960	1320	5990	241	400	628	1090	556	2180	2010	7920
	Median	392	703	632	1140	900	3550	2010	7890	428	700	920	1190	837	4120	2010	8980
	Max	412	815	1250	2830	952	4180	3870	13600	494	902	966	1420	1260	5610	2790	9740
	CV%	13.8	11.5	48.7	69.7	10.0	17.1	55.1	43.2	33.8	37.8	21.9	13.8	39.9	43.3	19.7	10.3
	Geometric Mean	370	720	745	1350	874	3530	2170	8630	371	632	823	1220	836	3690	2250	8850
	95% CI (Lower Mean)	245	516	-169	-1150	659	2050	-883	-664	62.6	40.4	382	809	8.50	-302	1160	6620
	95% CI (Upper Mean)	501	930	1770	4310	1100	5070	5680	19000	713	1290	1290	1660	1760	8250	3390	11100
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
$AUC_{0\text{-}inf}$ (ng*hr/mL)	Mean	NA	NA	NA	NA	NA	5000	NA	12700	NA	NA	NA	NA	NA	6430	NA	13300
	SD	NA	NA	NA	NA	NA	1140	NA	4840	NA	NA	NA	NA	NA	2770	NA	820
	Min	NA	NA	NA	NA	NA	3840	NA	8570	NA	NA	NA	NA	NA	3410	NA	12400
	Median	NA	NA	NA	NA	NA	5020	NA	11400	NA	NA	NA	NA	NA	7000	NA	13300
	Max	NA	NA	NA	NA	NA	6130	NA	18000	NA	NA	NA	NA	NA	8860	NA	14100
	CV%	NA	NA	NA	NA	NA	22.9	NA	38.2	NA	NA	NA	NA	NA	43.1	NA	6.18
	Geometric Mean	NA	NA	NA	NA	NA	4910	NA	12100	NA	NA	NA	NA	NA	5960	NA	13300
	95% CI (Lower Mean)	NA	NA	NA	NA	NA	2160	NA	637	NA	NA	NA	NA	NA	-457	NA	11200
	95% CI (Upper Mean)	NA	NA	NA	NA	NA	7830	NA	24700	NA	NA	NA	NA	NA	13300	NA	15300
	N	NA	NA	NA	NA	NA	3	NA	3	NA	NA	NA	NA	NA	3	NA	3

£ The values in parentheses (1) and (2) indicate the first (morning, 0-12 hr) dose and the second (evening, 12-24 hr) dose, respectively

Source: Table 19 of Study CL001_168 PK report

Abbreviations: $AUC_{0\text{-}inf}$, area under the curve from zero to infinity; AUC_{tau}, area under the curve during a dosing interval; $AUC_{0\text{-}t}$, area under the curve to the last quantifiable time point; CI, confidence interval; CL/F, apparent systemic clearance; C_{max}, maximum concentration; CV%, coefficient of variation; PK, pharmacokinetics; SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time to maximum concentration; Vz/F, apparent central volume of distr bution.

Reviewer's comment: *Different formulations, including the proposed to-be-marketed drug product ((b) (4) Cremophor RH40/PEG-4000 capsule, 10 mg), were used in this study. However, the PK information of the proposed to-be-marketed formulation is limited.*

17.3.1.2.2. Mass Balance Study

Trial # CL004_168

Title: 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

Study period: 20 October 2014-05 December 2014

Objective:

- To perform mass balance following an oral dose of CCX168 to healthy subjects

- To determine the metabolic fate of CCX168 and describe the blood and plasma PK profiles, as well as the urine and fecal excretion profiles of CCX168 and its most significant metabolites
- To monitor the safety and tolerability profiles

Study design: This was a single-center, open-label, absorption, metabolism, and excretion (AME) study of a single oral dose solution of approximately (b) (4) mg/(b) (4) µCi [^{14}C]CCX168 in 6 healthy male subjects.

Figure 21. Study Design (Study CL004_168)

Screening	Check-in	Dosing	PK/Radioactivity Sampling	Study Completion[a]	Telephone Follow-up[b]
Days -21 to -2	Day -1	Day 1	Day 1 to Study Completion	Day 10 to Day 15	Day 29
	← Confinement →				

[a] All subjects were to remain in the clinic for a minimum of 9 days after the dosing day (Day 10). After the minimum stay, subjects were to be discharged from the clinic when they met the radioactivity recovery criteria or completed Day 15.
[b] A telephone follow-up occurred on Day 29 (±3 days).
Source: Figure 9-1 of Study CL004_168 PK CSR
Abbreviations: PK, pharmacokinetics.

Test product: [^{14}C]CCX168 ((b) (4) mCi/mmol (b) (4) µCi/mg) (Lot#: 148-071-000)

Sampling Schedule:

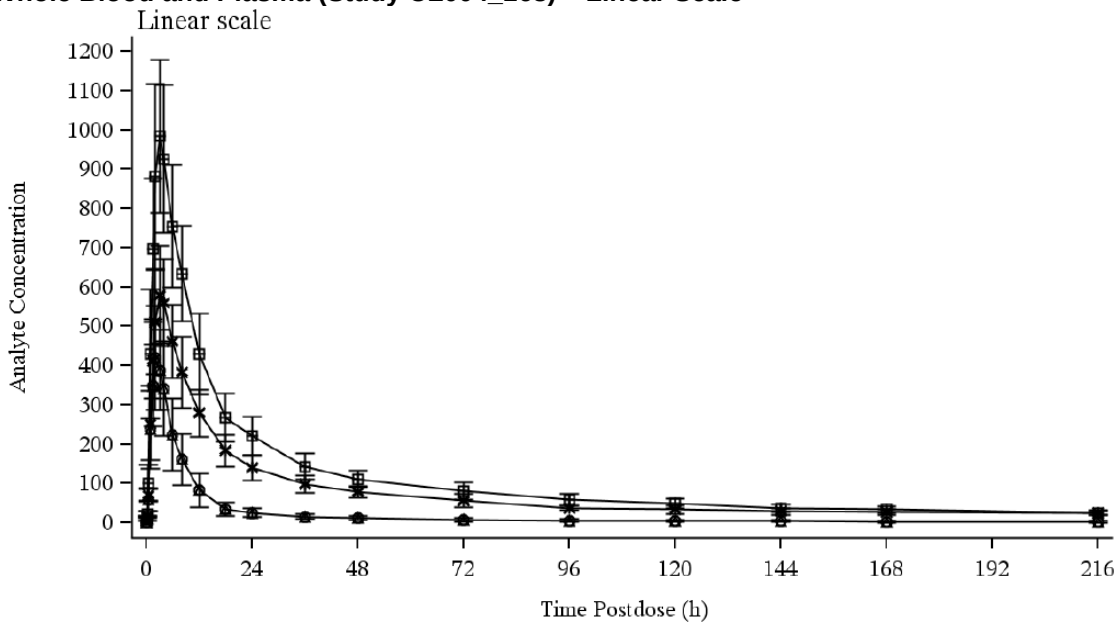
- Serial blood samples were collected predose (time 0) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, and 216 hours postdose.
- Serial urine samples were collected predose (-24 to 0 hours), at collection intervals of 0-8, 8-16, 16-24, 24-36, 36-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, and 192-216 hours, then for 24-hour intervals until the subject was discharged.
- Fecal samples were collected predose and for 24-hour intervals postdose until the subject was discharged.

Subjects were confined to the clinic for a minimum of 9 days, and until the total radioactivity from urine and feces combined, collected from 2 consecutive days, was less than 1% of the total dose of radioactivity administered for each of the 24-hour periods or at least 90% of the total radioactive CCX168 dose was excreted, up to a maximum of 14 days postdose (Day 15).

Results: The PK results were summarized as below.

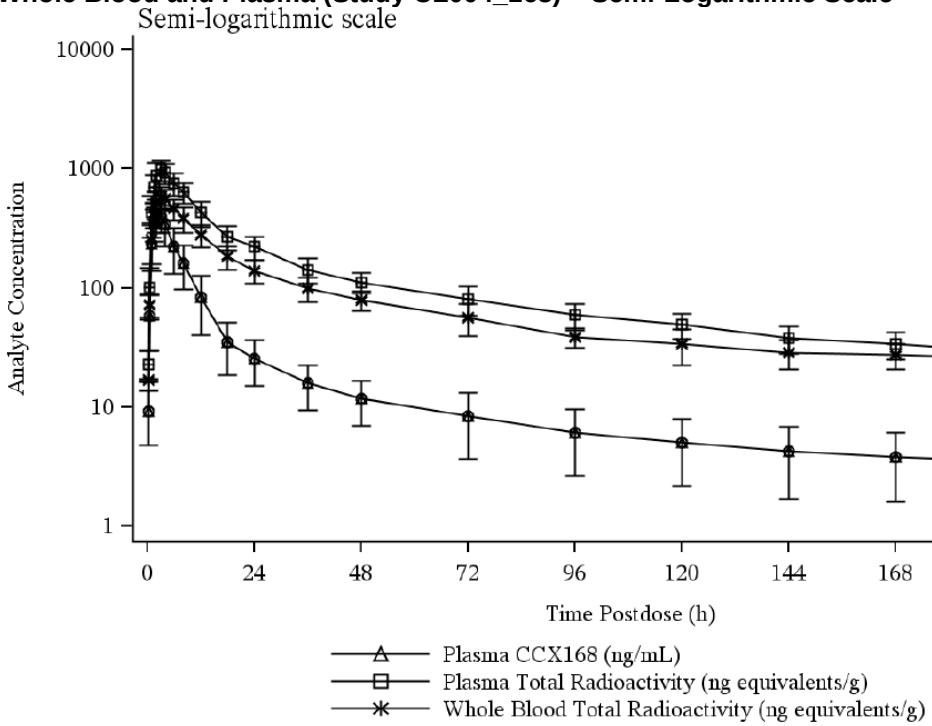
CCX168 Plasma PK and [^{14}C]CCX168 Total Radioactivity in Plasma

Figure 22. Arithmetic Mean Concentrations of Avacopan in Plasma and Total Radioactivity in Whole Blood and Plasma (Study CL004_168) – Linear Scale



Source: Figure 11-1 of Study CL004-168 CSR
Abbreviations: h, hour.

Figure 23. Arithmetic Mean Concentrations of Avacopan in Plasma and Total Radioactivity in Whole Blood and Plasma (Study CL004_168) – Semi-Logarithmic Scale



Source: Figure 11-1 of Study CL004-168 CSR
Abbreviations: h, hour.

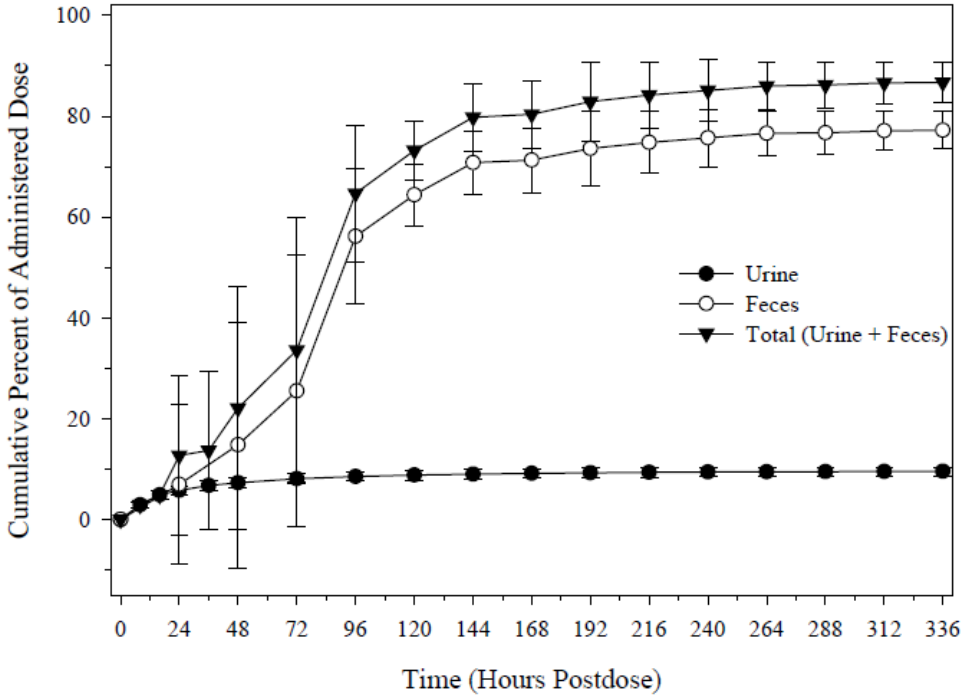
Table 64. Summary of Geometric Mean (CV%) PK Parameters for Avacopan in Plasma and Total Radioactivity in Plasma and Whole Blood (Study CL004_168)

Analyte (Matrix)	AUC_{0-t} (ng*h/mL)[b]	AUC_{0-inf} (ng*h/mL)[b]	AUC_{0-24} (ng*h/mL)[b]	C_{max} (ng/mL)[b]	t_{max}[a] (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)	λ_z (1/h)	AUC_{0-inf} Ratio	C_{max} Ratio
CCX168 (Plasma) (N=6)	4240 (44.4)	5170 (46.9)	2980 (43.0)	415 (32.1)	2.50 (2.00, 3.00)	207 (46.9)	19.4 (46.9)	5770 (59.3)	0.00336 (46.9)	0.18[c] (34.81)	0.42[c] (18.00)
Total Radioactivity (Plasma) (N=6)	23400 (21.3)	28000 (19.5)	11300 (21.0)	980 (20.6)	3.00 (2.00, 4.00)	124 (24.3)	3.57 (19.5)	636 (37.2)	0.00561 (24.3)	0.64[d] (13.87)	0.59[d] (3.17)
Total Radioactivity (Whole Blood) (N=6)	14500 (29.3)	18100 (32.8)	7020 (21.1)	577 (21.4)	3.00 (3.00, 4.00)	99.5 (54.5)	5.53 (32.8)	794 (30.4)	0.00697 (54.5)	NA	NA

Source: Table 14.2.1-1 through Table 14.2.1-5.
a Median (min, max) presented for t_{max}.
b Units for total radioactivity are in ng eq./g. Units for total radioactivity are ng equivalents*hr/g for AUC values.
c Ratio for Plasma CCX168 / Total Radioactivity in Plasma.
d Ratio for Total Radioactivity in Whole Blood / Total Radioactivity in Plasma.
Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from time 0 to Hour 24; AUC_{0-inf} = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to time t; CL/F = apparent total clearance; C_{max} = maximum observed concentration; NA = not applicable; $t_{1/2}$ = terminal half-life; t_{max} = time of occurrence of maximum observed concentration; V_z/F = apparent volume of distribution; λ_z = elimination rate constant.
Source: Table 11-1 of Study CL004-168 CSR

Excretion and Mass Balance

Figure 24. Mean (±SD) Cumulative Percentage of Dose Recovered (Study CL004_168)



Source: Figure 11-2 of Study CL004-168 CSR
Abbreviations: SD, standard deviation.

Table 65. Summary of Arithmetic Mean (SD) PK Parameters for Total Radioactivity in Urine and Feces (Study CL004_168)

Analyte (Matrix)	Total Ae (µg eq.)	Total % Fe (%)	CL_R (L/h)
Total Radioactivity (Urine) (n=6)	10,100 (952)	9.5 (0.88)	0.368 (0.0911)
Total Radioactivity (Feces) (n=6)	81,900 (3910)	77.2 (3.71)	NA
Total Radioactivity (Urine + Feces) (n=6)	92,000 (4320)	86.7 (4.04)	NA

Source: Radioactivity Report Table 6 and Table 8, Appendix 16.2.5.1 and Table 14.2.1-6.
Ae = Amount excreted in urine or feces.
Fe = Fraction excreted in urine or feces.
CL_R = renal clearance.
Abbreviations: NA = not applicable; n = number of subjects

Source: Table 11-2 of Study CL004-168 CSR
Abbreviations: PK, pharmacokinetics; SD, standard deviation.

Metabolite Profiling

Table 66. Summary of Avacopan Human Metabolites (Study CL004_168)

HPLC Peak No.	HPLC t_R (min)	% of Total Radioactivity in HPLC Profile (% of Radioactive Dose Shown in Parentheses)			Metabolite Identifier	LC-MS $[M+H]^+$ (m/z)	Plausible Description
		Plasma	Urine	Feces			
P1	4.5		16.9 (1.6)				
P2	5.75		25.9 (2.5)				
P3	7.75	3.3					
P4	9.75	1.6					
P5	13		15.9 (1.5)				
P6	14.75	1.6	4.5 (0.4)				
P7	18	2.7		1.7 (1.3)			
P8	20.5			2.4 (1.9)			
P9	21.75			1.7 (1.3)			
P10	23.75	1.1					
P11	24.25			2.1 (1.6)			
P12	25			2.9 (2.2)			
P13	26.25			2.5 (1.9)			
P14	28.25			4.2 (3.2)			
P15	29.25			1.9 (1.5)			
P16	31	1.5		3.2 (2.5)			
P17	32.75			3.6 (2.8)			
P18	35		1.9 (0.2)	3.7 (2.8)			
P19	35.5			2.2 (1.7)			
P20	36.75	3.1					
P21	38	2.1					
P22	39.75	2.0					
P23	40	2.5	4.0 (0.4)	3.9 (3.0)	M3	530	C ring methyl hydroxylation in M6
					M19*	544	$CH_3 \rightarrow COOH$ in M6
					M21*	628	Bis-oxidation and C ring $CH_3 \rightarrow COOH$
P24	40.25			2.6 (2.0)			
P25	42.25	9.0			M26	614	B ring mono-oxidation in M1
P26	43.5	2.0	2.1 (0.2)	7.7 (5.9)	M10/M11	614	B ring mono-oxidation in M1
P27	46.5			3.9 (3.0)	M16	614	A ring methyl hydroxylation in M1
P28	50			7.1 (5.5)	M22	531	$NH_2 \rightarrow OH$ and carbon mono-oxidation in M6
					M23	630	Tri-oxidation
	60.75**	<1.0			M6	514	De-alkylation of cyclopentane ring
P29	61.75	11.9	0.2 (0.02)	8.9 (6.9)	M1	598	C ring methyl hydroxylation

HPLC Peak No.	HPLC t_R (min)	% of Total Radioactivity in HPLC Profile (% of Radioactive Dose Shown in Parentheses)			Metabolite Identifier	LC-MS $[M+H]^+$ (m/z)	Plausible Description
		Plasma	Urine	Feces			
P30A	63.25	1.2			M8***	598	B ring mono-oxidation
P30B	63.75	1.2		1.0 (0.7)	M17***	598	B ring mono-oxidation
P30C	64.25	2.7			M18***	598	B ring mono-oxidation
P31	68			3.3 (2.5)	M9	598	A ring methyl mono-oxidation
P32	71.25	1.0					
P33	83.75	18	0.2 (0.02)	8.7 (6.7)	CCX168	582	CCX168
P34	111.5			2.3 (1.8)			
P35	112.75			2.4 (1.9)			
P36	115.25	1.7					
P37	116	2.2					

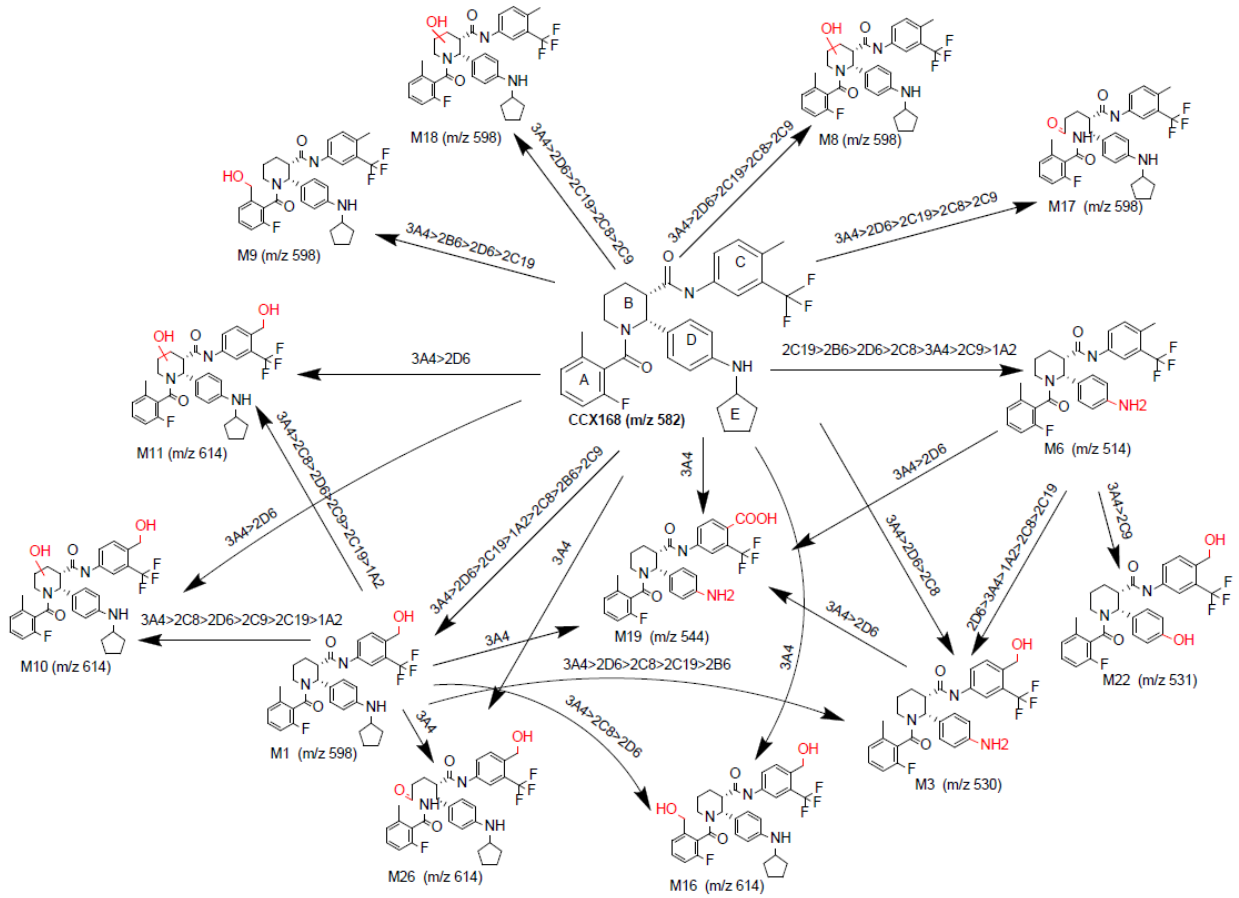
*M19 and M21 were only observed in the pooled fecal sample.

**M6 was detected in plasma through mass spectrometry at a minute level, but was below the level of detection in the radiometric HPLC trace. The abundance was estimated to be less than 1% of total radioactivity. The structure of M6 was confirmed by comparison with the authentic standard C0342414 (Figure 7).

***Partial peak overlapping was observed for M8, M17 and M18 in the HPLC trace; assignments of these metabolite identifiers may be interchangeable.

Source: Table 1 of Study CL004_168_MetID
Abbreviations: HPLC, high performance liquid chromatography; LC-MS, liquid chromatographic / mass spectrometric; t_R, adjusted retention time.

Figure 25. Proposed Metabolic Pathways for Avacopan (Study CL004_168)



Note: The rank order of the CYP450 isozymes in each pathway is based on the relative contribution of a given isozyme in the *in vitro* incubation to the formation of each metabolite from respective substrates including CCX168, M1, M3 and M6.

Source: Figure 11 of Summary of Clinical Pharmacology

Conclusions:

Following the single dose of oral solution of [^{14}C]CCX168, the mean apparent terminal elimination half-life was 207 hours for CCX168 in plasma and was 99.5 and 124 hours for total radioactivity in whole blood and plasma, respectively.

The total radioactivity recovery in the human mass balance study is 86.7%. Fecal elimination accounted for the majority (77.2%) of the administered dose, while renal elimination was a minor route (9.5%).

A metabolite profiling investigation of the mass balance samples found that most of the radioactivity in feces or urine was in the form of Phase I metabolites, suggesting that Phase I

metabolism, followed by biliary excretion of the metabolites, is the primary route of elimination for avacopan after absorption.

CCX168 was the most abundant drug-related component in human plasma, representing 18% of the plasma radioactivity. Two other notable components were oxidative metabolites CCX168-M1 (11.9%) and CCX168-M26 (9.0%).

17.3.1.2.3. Food Effect Study

Trial # CL007_168

Title: An Open-Label, Phase 1 Study in Healthy Volunteers to Evaluate the Pharmacokinetic Food Effect and Cardiac Safety of CCX168

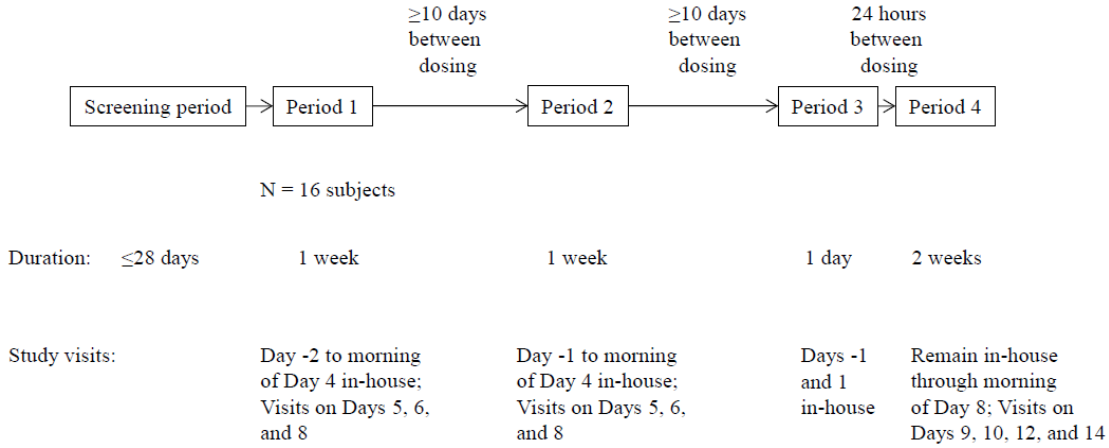
Study period: 03 December 2015- 09 February 2016

Objective:

- To evaluate the effect of a high-fat, high-calorie meal on the PK profile of CCX168 following oral administration of a single dose of 30 mg CCX168 to healthy volunteers
- Cardiac safety of CCX168 through intensive ECG measurements
- Safety and tolerability

Study design: This open-label phase 1 clinical trial enrolled a total of 16 healthy male or female subjects. Subjects were assigned (not randomized) to 2 sequences, ABCD and BACD, with 8 subjects in each sequence. Subjects participated in all 4 dosing periods. The meal was high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 900 to 1000 calories) and derived approximately 150, 250, and 500 - 600 calories from protein, carbohydrate, and fat, respectively. The effect of this high-fat, high-calorie meal on the PK profile of CCX168 was assessed in Periods 1 and 2.

Figure 26. Study Design (Study CL007_168)



Source: Figure 7-1 of Study CL007_168 CSR

Period 1: In a single-dose, 2-treatment (fed vs. fasted), 2-period, 2-sequence crossover design, the first group of 8 subjects received a single dose of 30 mg CCX168 in the fasted state (Treatment B) and the second group of 8 subjects received a single dose of 30 mg CCX168 after a high-fat, high-calorie meal (Treatment A).

Period 2: After a washout period of ≥10 days, the first group of 8 subjects received a single dose of 30 mg CCX168 after a high-fat, high-calorie meal (Treatment A) and the second group of 8 subjects received a single dose of 30 mg CCX168 in the fasted state (Treatment B).

Period 3: After a washout period of ≥10 days, all 16 subjects received 1 dose of 3 mg CCX168 in the fasted state (Treatment C).

Period 4: Subjects remained in the Phase 1 unit between Periods 3 and 4. The next day (24 hours after the 3 mg CCX168 dose), all 16 subjects took a single dose of 100 mg CCX168 on Day 1, and then 100 mg CCX168 twice daily from Day 2 through Day 6. On Day 7, only a morning dose of 100 mg CCX168 was taken and not an evening dose (Treatment D). If PK results from Periods 1 and 2 showed a significant positive effect of food on CCX168 plasma exposure, dosing in Period 4 may have occurred in the fed state.

Test product: CCX168 was orally administered. The 3 mg CCX168 dose was given as a dosing solution. The 30 mg and 100 mg doses were given as 10 mg hard gelatin capsules.

- Treatment A: 30 mg CCX168 (3 x 10 mg capsules) - fed
- Treatment B: 30 mg CCX168 (3 x 10 mg capsules) - fasted
- Treatment C: 3 mg CCX168 solution - fasted
- Treatment D: 100 mg CCX168 (10 x 10 mg capsules) as a single dose on the morning of Day 1, B.I.D. on Days 2 – 6, and a single dose on the morning of Day 7 – fasted

Sampling Schedule

Periods 1 and 2: pre-dose and at Hours 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 after administration of 30 mg CCX168; plasma samples were also collected at Hours 18, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 168 (Day 8).

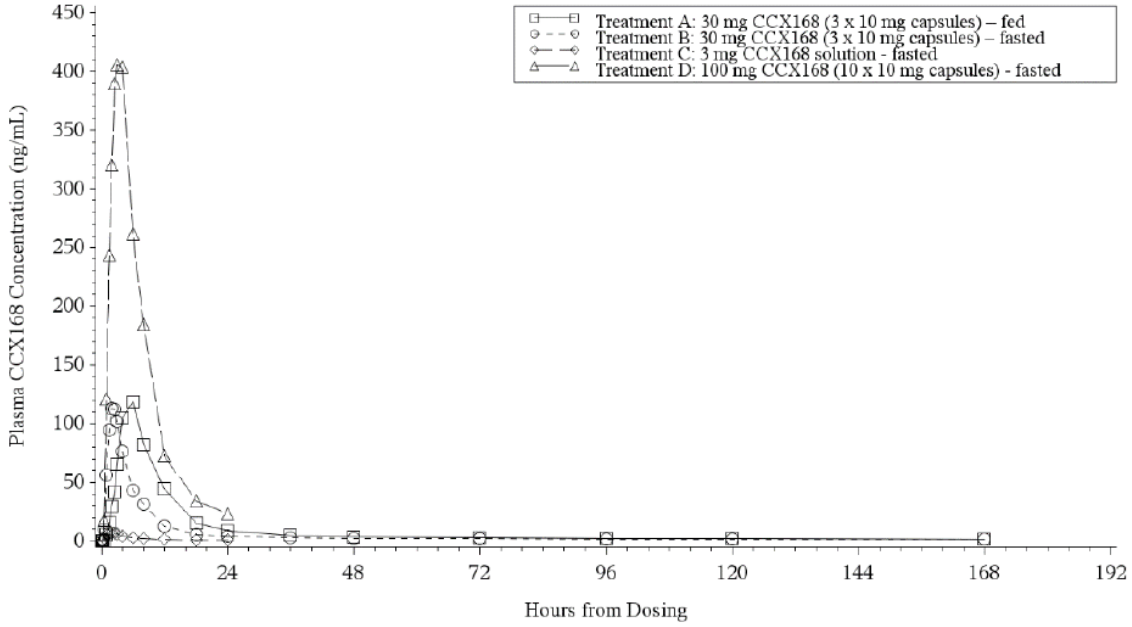
Period 3: pre-dose and at Hours 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 after administration of 30 mg CCX168; plasma samples were also collected at Hours 18 and 24 (Day 2).

Period 4: Serial blood samples were collected at pre-dose and at Hours 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 after administration of 100 mg CCX168 in the morning; plasma samples were also collected at Hours 18 and 24 (just prior to dosing) on Day 2, Hour 48 (prior to dosing) on Day 3, Hour 72 (prior to dosing on Day 4), Hour 96 (prior to dosing on Day 5), Hour 120 (prior to dosing on Day 6), Hours 144 (prior to dosing), 144.25, 144.5, 145, 145.5, 146, 146.5, 147, 148, 150, 152, and 156 on Day 7, Hours 162 and 168 on Day 8, Hour 192 on Day 9, Hour 216 on Day 10, Hour 264 on Day 12, and Hour 312 on Day 14.

Results: The PK profile and PK analysis of CCX168 and M1 following single or multiple doses of CCX168 were shown in the following figures and tables.

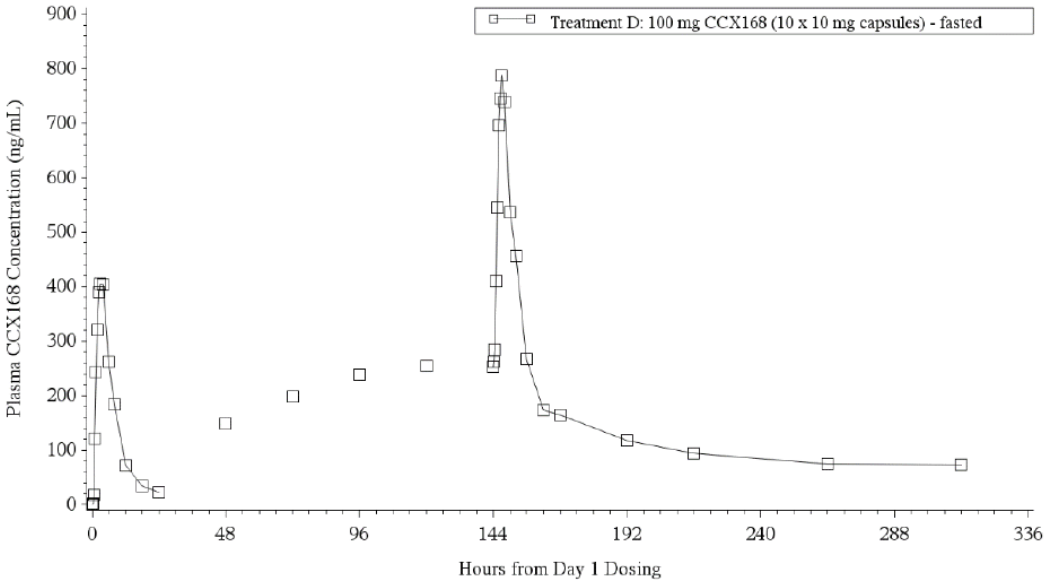
CCX168 PK

Figure 27. Arithmetic Mean Concentration-Time Profiles of Plasma Avacopan Following Administration of 3 mg, 30 mg, and 100 mg Avacopan - Day 1 (Study CL007_168)



Source: Figure 11-1 of Study CL007_168 CSR

Figure 28. Arithmetic Mean Concentration-Time Profiles of Plasma Avacopan Following Administration of 100 mg Avacopan Under Fasted Condition - Days 1-7 (Study CL007_168)



Source: Figure 11-2 of Study CL007_168 CSR

Table 67. Summary of the PK Parameters of Plasma Avacopan - Day 1 (Treatments A, B, and C, Study CL007_168)

	Treatment A		Treatment B		Treatment C	
Pharmacokinetic Parameters	**GM (GCV%)**	**n**	**GM (GCV%)**	**n**	**GM (GCV%)**	**n**
AUC_{0-t} (ng*hr/mL)	1410 (28.4)	16	826 (43.6)	16	40.4 (56.3)	8
AUC_{0-inf} (ng*hr/mL)	1650 (29.1)	16	934 (48.4)	14	53.2 (56.3)	8
AUC_{0-12} (ng*hr/mL)	799 (27.2)	16	560 (33.9)	16	37.2 (38.3)	8
$AUC_{\%extrap}$	14.1 ± 6.33	16	13.4 ± 4.92	14	23.9 ± 6.51	8
C_{max} (ng/mL)	128 (26.0)	16	119 (29.2)	16	7.84 (34.3)	8
T_{max} (hr)	6.00 (2.00, 8.01)	16	2.01 (1.50, 4.00)	16	2.00 (1.00, 4.00)	8
λ_z (1/hr)	0.00845 ± 0.00388	16	0.0118 ± 0.00566	14	0.130 ± 0.132	8
$t_{1/2}$ (hr)	97.6 ± 40.1	16	73.5 ± 35.5	14	8.25 ± 3.96*	8
CL/F (L/hr)	18.9 ± 5.23	16	35.0 ± 14.1	14	65.4 ± 47.5	8
V_z/F (L)	2580 ± 1100	16	3170 ± 961	14	588 ± 158	8

Treatment A = 30 mg CCX168 (3 x 10 mg capsules) – fed.
Treatment B = 30 mg CCX168 (3 x 10 mg capsules) – fasted.
Treatment C = 3 mg CCX168 solution – fasted.
Subjects 1, 2, 3, 7, 8, 12, and 15 were removed from the descriptive statistics for Treatment C since their predose concentrations were greater than 5% of their corresponding C_{max} value.
T_{max} is presented as Median (Minimum, Maximum).
$AUC_{\%extrap}$, λ_z, $t_{1/2}$, CL/F, and V_z/F are presented as Mean ± SD.
* = Shorter apparent terminal $t_{1/2}$ is not a reflection of the actual terminal phase, but rather the first, more rapid post-C_{max} decline in concentrations for this clearly biphasic elimination drug candidate.
Source: Tables 14.2.1.1.5 through 14.2.1.1.7
Program: /CA18247/sas_prg/pksas/adam_intext_pkparam.sas 24FEB2017 4:36

Source: Table 11-2 of Study CL007_168 CSR
Abbreviations: λ_z, elimination rate constant; AUC_{0-t}, area under the curve to the last quantifiable time point; AUC_{0-inf}, area under the curve from zero to infinity; AUC_{0-12h}, area under the curve from 0 to 12 hours; area under the curve; $AUC_{\%extrap}$, % extrapolated area under the cure; CL/F, apparent systemic clearance; C_{max}, maximum concentration; GCV%, geometric coefficient of variation; PK, pharmacokinetics; $t_{1/2}$, half-life; SD, standard deviation; T_{max}, time to maximum concentration; Vz/F, apparent central volume of distribution.

Table 68. Summary of the PK Parameters of Plasma Avacopan - Days 1 and 7 (Treatment D, Study CL007_168)

	Day 1		Day 7	
Pharmacokinetic Parameters	**GM (GCV%)**	**n**	**GM (GCV%)**	**n**
AUC_{0-t} (ng*hr/mL)	3030 (32.2)	15	NA	NA
AUC_{0-inf} (ng*hr/mL)	3250 (32.4)	15	NA	NA
AUC_{0-12} (ng*hr/mL)	2570 (30.3)	15	NA	NA
$AUC_{\%extrap}$	6.76 ± 2.06	15	NA	NA
C_{max} (ng/mL)	442 (28.1)	15	NA	NA
T_{max} (hr)	3.00 (1.50, 4.05)	15	NA	NA
λ_z (1/hr)	0.105 ± 0.0220	15	NA	NA
$t_{1/2}$ (hr)	6.91 ± 1.62	15	NA	NA
CL/F, Day 1 (L/hr)	32.3 ± 10.2	15	NA	NA
V_z/F (L)	327 ± 172	15	NA	NA
$C_{trough, Day 3}$ (ng/mL)	140 (35.2)	15	NA	NA
$C_{trough, Day 4}$ (ng/mL)	189 (33.2)	15	NA	NA
$C_{trough, Day 5}$ (ng/mL)	226 (33.4)	15	NA	NA
$C_{trough, Day 6}$ (ng/mL)	246 (27.5)	15	NA	NA
AUC_{0-tau} (ng*hr/mL)	NA	NA	5930 (22.8)	15
$C_{max,ss}$ (ng/mL)	NA	NA	825 (19.5)	15
$C_{min,ss}$ (ng/mL)	NA	NA	236 (33.1)	15
$C_{avg,ss}$ (ng/mL)	NA	NA	495 (22.8)	15
$T_{max,ss}$ (hr)	NA	NA	3.0 (2.0, 4.0)	15
$T_{min,ss}$ (hr)	NA	NA	12 (0.25, 12)	15
$\lambda_{z,ss}$ (1/hr)	NA	NA	0.00504 ± 0.00197	10
$t_{1/2,ss}$ (hr)	NA	NA	150 ± 38.2	10
CL/F, Day 7 (L/hr)	NA	NA	17.2 ± 3.71	15
Swing	NA	NA	2.63 ± 1.04	15
Fluctuation (%)	NA	NA	121 ± 31.4	15
R_{AUC}	NA	NA	2.36 ± 0.554	15
R_{Cmax}	NA	NA	1.90 ± 0.364	15

Treatment D = 100 mg CCX168 (10 x 10 mg capsules) as a single dose on the morning on Day 1, B.I.D on Days 2-6 and a single dose on the morning of Day 7 – fasted.
T_{max}, $T_{max,ss}$ and $T_{min,ss}$ are presented as Median (Minimum, Maximum).
$AUC_{\%extrap}$, λ_z, $\lambda_{z,ss}$, $t_{1/2}$, $t_{1/2,ss}$, CL/F, V_z/F, Swing, Fluctuation, R_{AUC}, and R_{Cmax} are presented as Mean ± SD.
NA = Not applicable.
Source: Tables 14.2.1.1.8 and 14.2.1.1.9
Program: /CA18247/sas_prg/pksas/adam_intext_pkparam2.sas 24FEB2017 4:31

Source: Table 11-3 of Study CL007_168 CSR
Abbreviations: λ_z, elimination rate constant; AUC_{0-t}, area under the curve to the last quantifiable time point; AUC_{0-inf}, area under the curve from zero to infinity; AUC_{0-12h}, area under the curve from 0 to 12 hours; area under the curve; $AUC_{\%extrap}$, % extrapolated area under the curve; BID, twice daily; CL/F, apparent systemic clearance; C_{max}, maximum concentration; C_{min}, minimum concentration; C_{trough}, trough concentration; GCV%, geometric coefficient of variation; PK, pharmacokinetics; $R_{AUC,}$, accumulation ratio of AUC; R_{cmax}, maximum observed concentration ratio; SD, standard deviation; SS, steady state; $t_{1/2,}$ half-life; T_{max}, time to maximum concentration; T_{min}, time to minimum concentration; Vz/F, apparent central volume of distribution.

Table 69. Summary of Statistical Comparisons of Plasma Avacopan PK Parameters: Treatment A (Fed) Versus Treatment B (Fasted) (Study CL007_168)

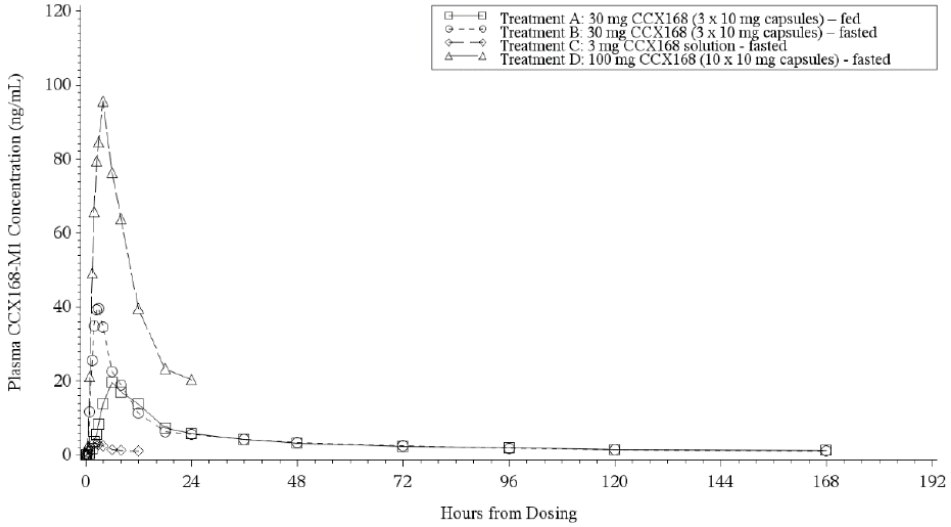
	Treatment A (Test)		Treatment B (Reference)			Confidence Intervals	
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	90% Confidence	Intra-subject CV%
AUC_{0-t} (ng*hr/mL)	1410.4	16	826.33	16	170.68	151.09 - 192.81	19.77
AUC_{0-inf} (ng*hr/mL)	1646.0	16	959.23	14	171.60	147.12 - 200.15	23.23
C_{max} (ng/mL)	128.1	16	118.6	16	107.98	92.05 - 126.67	26.06
T_{max} (hr)	5.379	16	2.286	16	235.29	208.37 - 262.21	25.79

Treatment A = 30 mg CCX168 (3 x 10 mg capsules) – fed (test).
Treatment B = 30 mg CCX168 (3 x 10 mg capsules) – fasted (reference).
AUC_{0-t}, AUC_{0-inf} and C_{max} parameters were ln-transformed prior to analysis. T_{max} was untransformed.
For ln-transformed PK parameters, geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from ANOVA. For the untransformed parameter T_{max}, the LSMs are straight from the ANOVA.
T_{max} is presented as the untransformed LSM.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio = 100*(test/reference).
For ln-transformed PK parameters, intra-subject CV (%CV) = 100*(square root (exp[MSE]-1)).
For the untransformed parameter T_{max}, intra-subject CV (%CV) = 100*(square root [MSE])/(Average of the LSM).
MSE = Residual variance from ANOVA.

Source: Table 11-4 of Study CL007_168 CSR
Abbreviations: AUC_{0-t}, area under the curve to the last quantifiable time point; AUC_{0-inf}, area under the curve from zero to infinity; C_{max}, maximum concentration; CV%, coefficient of variation; GMR, geometric mean ratio; MSE, mean square error.

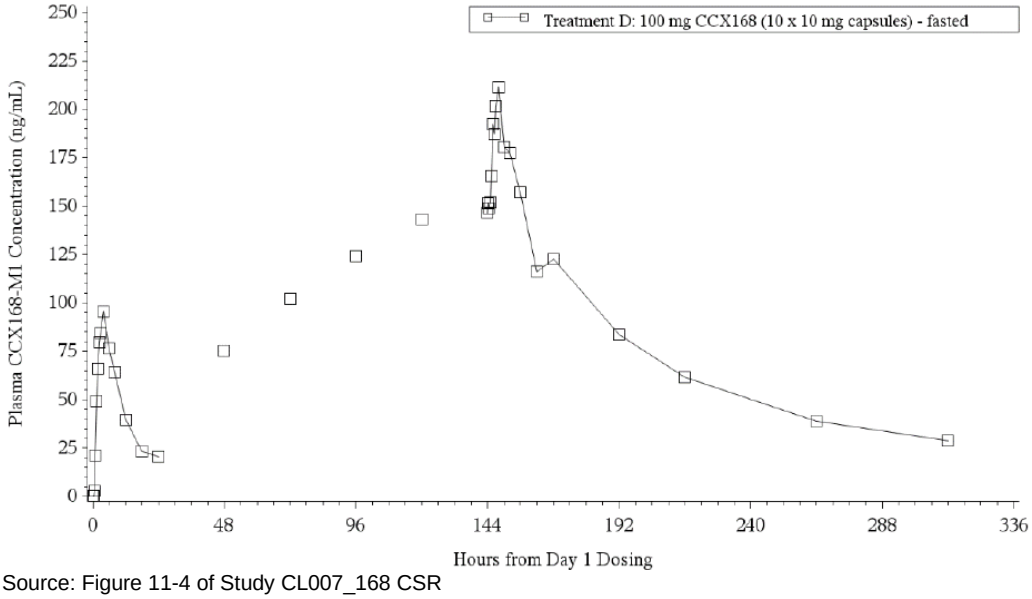
M1 PK

Figure 29. Arithmetic Mean Concentration-Time Profiles of Plasma M1 Following Administration of 3 mg, 30 mg, and 100 mg Avacopan - Day 1 (Study CL007_168)



Source: Figure 11-3 of Study CL007_168 CSR

Figure 30. Arithmetic Mean Concentration-Time Profiles of Plasma M1 Following Administration of 100 mg Avacopan Under Fasted Condition - Days 1-7 (Study CL007_168)



Source: Figure 11-4 of Study CL007_168 CSR

Table 70. Summary of the PK Parameters of Plasma M1 - Day 1 (Treatments A, B, and C, Study CL007_168)

	Treatment A		Treatment B		Treatment C	
Pharmacokinetic Parameters	**GM (GCV%)**	**n**	**GM (GCV%)**	**n**	**GM (GCV%)**	**n**
AUC_{0-t} (ng*hr/mL)	513 (27.6)	16	589 (29.4)	16	16.5 (19.8)	8
AUC_{0-inf} (ng*hr/mL)	610 (28.1)	16	683 (27.7)	16	26.6 (21.2)	7
AUC_{0-12} (ng*hr/mL)	148 (21.3)	16	259 (17.3)	16	19.9 (10.9)	7
$AUC_{\%extrap}$	15.8 ± 3.14	16	13.7 ± 4.44	16	34.0 ± 9.76	7
C_{max} (ng/mL)	20.3 (22.9)	16	41.4 (20.8)	16	3.41 (21.1)	8
T_{max} (hr)	6.00 (2.51, 12.0)	16	3.00 (2.00, 4.01)	16	2.00 (1.50, 4.00)	8
λ_z (1/hr)	0.0147 ± 0.00890	16	0.0156 ± 0.00653	16	0.152 ± 0.0649	7
$t_{1/2}$ (hr)	55.6 ± 17.3	16	51.3 ± 22.1	16	5.76 ± 3.52*	7

Treatment A = 30 mg CCX168 (3 x 10 mg capsules) – fed.
Treatment B = 30 mg CCX168 (3 x 10 mg capsules) – fasted.
Treatment C = 3 mg CCX168 solution – fasted.
Subjects 1, 2, 3, 7, 8, 12, and 15 were removed from the descriptive statistics for Treatment C since their predose concentrations were greater than 5% of their corresponding C_{max} value.
T_{max} is presented as Median (Minimum, Maximum).
$AUC_{\%extrap}$, λ_z, and $t_{1/2}$ are presented as Mean ± SD.
* = Shorter apparent terminal $t_{1/2}$ is not a reflection of the actual terminal phase, but rather the first, more rapid post-C_{max} decline in concentrations for this clearly biphasic elimination drug candidate.
Source: Tables 14.2.1.2.5 through 14.2.1.2.7
Program: /CA18247/sas_prg/pksas/adam_intext_pkparam.sas 24FEB2017 4:36

Source: Table 11-5 of Study CL007_168 CSR
Abbreviations: λ_z, elimination rate constant; AUC_{0-t}, area under the curve to the last quantifiable time point; AUC_{0-inf}, area under the curve from zero to infinity; AUC_{0-12h}, area under the curve from 0 to 12 hours; area under the curve; $AUC_{\%extrap}$, % extrapolated area under the curve; C_{max}, maximum concentration; GCV%, geometric coefficient of variation; GM, geometric mean; PK, pharmacokinetics; $t_{1/2}$, half-life; T_{max}, time to maximum concentration.

Table 71. Summary of the PK Parameters of Plasma M1 - Days 1 and 7 (Treatment D, Study CL007_168)

	Day 1		Day 7	
Pharmacokinetic Parameters	**GM (GCV%)**	**n**	**GM (GCV%)**	**n**
AUC_{0-t} (ng*hr/mL)	1040 (21.2)	15	NA	NA
AUC_{0-inf} (ng*hr/mL)	1320 (24.3)	15	NA	NA
AUC_{0-12} (ng*hr/mL)	726 (20.2)	15	NA	NA
$AUC_{\%extrap}$	21.5 ± 4.54	15	NA	NA
C_{max} (ng/mL)	98.5 (23.7)	15	NA	NA
T_{max} (hr)	4.00 (2.00, 6.00)	15	NA	NA
λ_z (1/hr)	0.0718 ± 0.0119	15	NA	NA
$t_{1/2}$ (hr)	9.94 ± 1.89	15	NA	NA
$C_{trough, Day 3}$ (ng/mL)	73.0 (25.5)	15	NA	NA
$C_{trough, Day 4}$ (ng/mL)	98.8 (26.2)	15	NA	NA
$C_{trough, Day 5}$ (ng/mL)	120 (27.0)	15	NA	NA
$C_{trough, Day 6}$ (ng/mL)	140 (23.5)	15	NA	NA
AUC_{0-tau} (ng*hr/mL)	NA	NA	2100 (20.5)	15
$C_{max,ss}$ (ng/mL)	NA	NA	214 (20.9)	15
$C_{min,ss}$ (ng/mL)	NA	NA	138 (25.1)	15
$C_{avg,ss}$ (ng/mL)	NA	NA	175 (20.5)	15
$T_{max,ss}$ (hr)	NA	NA	4.0 (2.1, 8.0)	15
$T_{min,ss}$ (hr)	NA	NA	1.0 (0.25, 12)	15
$\lambda_{z,ss}$ (1/hr)	NA	NA	0.00839 ± 0.00172	15
$t_{1/2,ss}$ (hr)	NA	NA	85.5 ± 15.2	15
Swing	NA	NA	0.571 ± 0.279	15
Fluctuation (%)	NA	NA	43.9 ± 17.0	15
R_{AUC}	NA	NA	2.90 ± 0.282	15
R_{Cmax}	NA	NA	2.20 ± 0.360	15

Treatment D = 100 mg CCX168 (10 x 10 mg capsules) as a single dose on the morning on Day 1, B.I.D on Days 2-6 and a single dose on the morning of Day 7 – fasted.
T_{max}, $T_{max,ss}$ and $T_{min,ss}$ are presented as Median (Minimum, Maximum).
$AUC_{\%extrap}$, λ_z, $\lambda_{z,ss}$, $t_{1/2}$, $t_{1/2,ss}$, Swing, Fluctuation, R_{AUC}, and R_{Cmax} are presented as Mean ± SD.
NA = Not applicable.
Source: Tables 14.2.1.2.8 and 14.2.1.2.9

Source: Table 11-6 of Study CL007_168 CSR
Abbreviations: λ_z, elimination rate constant; AUC_{0-t}, area under the curve to the last quantifiable time point; AUC_{0-inf}, area under the curve from zero to infinity; AUC_{0-12h}, area under the curve from 0 to 12 hours; area under the curve; $AUC_{\%extrap}$, % extrapolated area under the curve; BID, twice daily; CL/F, apparent systemic clearance; C_{max}, maximum concentration; C_{min}, minimum concentration; C_{trough}, trough concentration; GCV%, geometric coefficient of variation; PK, pharmacokinetics; R_{AUC}, accumulation ratio of AUC; R_{cmax}, maximum observed concentration ratio; SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time to maximum concentration; T_{min}, time to minimum concentration; Vz/F, apparent central volume of distribution.

Table 72. Summary of Statistical Comparisons of Plasma M1 PK Parameters: Treatment A (Fed) Versus Treatment B (Fasted) (Study CL007_168)

	Treatment A (Test)		Treatment B (Reference)			Confidence Intervals	
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	90% Confidence	Intra-subject CV%
AUC_{0-t} (ng*hr/mL)	513.29	16	588.95	16	87.15	83.10 - 91.40	7.65
AUC_{0-inf} (ng*hr/mL)	609.74	16	683.11	16	89.26	85.66 - 93.00	6.61
C_{max} (ng/mL)	20.33	16	41.37	16	49.15	44.81 - 53.91	14.94
T_{max} (hr)	6.410	16	2.880	16	222.54	191.70 - 253.37	30.70

Treatment A = 30 mg CCX168 (3 x 10 mg capsules) – fed (test).
Treatment B = 30 mg CCX168 (3 x 10 mg capsules) – fasted (reference).
AUC_{0-t}, AUC_{0-inf} and C_{max} parameters were ln-transformed prior to analysis. T_{max} was untransformed.
For ln-transformed PK parameters, geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from ANOVA. For the untransformed parameter T_{max}, the LSMs are straight from the ANOVA. T_{max} is presented as the untransformed LSM.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio = 100*(test/reference).
For ln-transformed PK parameters, intra-subject CV (%CV) = 100*(square root (exp[MSE]-1)).
For the untransformed parameter T_{max}, intra-subject CV (%CV) = 100*(square root [MSE])/(Average of the LSM).
MSE = Residual variance from ANOVA.

Source: Table 11-7 of Study CL007_168 CSR
Abbreviations: ANOVA, analysis of variance; AUC_{0-t}, area under the curve to the last quantifiable time point; AUC_{0-inf}, area under the curve from zero to infinity; C_{max}, maximum concentration; CV%, coefficient of variation; GMR, geometric mean ratio; MSE, mean square of error; T_{max}, time to maximum concentration.

Conclusions:

For CCX168: administration of a high-fat, high-calorie meal with 30 mg CCX168 increased AUC by approximately 72% but did not affect the C_{max} as compared to fasted condition. The median of T_{max} was delayed by approximately 4 hours under fed condition.

For metabolite M1: a high-fat, high-calorie meal did not affect the AUC, but reduced C_{max} by 51% as compared to fasted condition.

17.3.1.2.4. DDI Study

Trial # CL008_168

Title: An Open-Label, Phase 1 Study in Healthy Volunteers to Evaluate the Drug-Drug Interaction Potential of CCX168 with Concomitant Medications

Study period: 14 January 2016-15 March 2016

Objective: To evaluate the drug-drug interaction (DDI) potential for CCX168 and its metabolite CCX168-M1 to inhibit CYP3A4 and CYP2C9, and the effect of CYP3A4 inhibition and induction on CCX168 and CCX168-M1

Study design: This open-label, phase 1 clinical trial enrolled a total of 32 healthy male or female subjects. Subjects were enrolled in 2 cohorts, which were conducted in parallel. Cohort A enrolled 16 subjects and tested the effect of CCX168 as a perpetrator on the PK of a CYP3A4 substrate and a CYP2C9 substrate as well as the effect of a CYP3A4 inhibitor on the PK of CCX168. Cohort B enrolled 16 subjects and tested the effect of a CYP3A4 inducer on the PK of CCX168.

The doses and regimens for cohorts were as follows. CCX168 doses were taken in the fasted state with not more than 100 mL of water. No food was allowed for at least 2 hours postdose for the morning doses.

- Cohort A: 2 mg midazolam (a CYP3A4 probe drug) +200 mg celecoxib (a CYP2C9 probe drug) single dose on Days 1 and 13; 30 mg CCX168 BID on Days 3 to 18 and a single dose on the morning of Day 19; 200 mg itraconazole (a CYP3A4 inhibitor) QD on Days 16 to 19
- Cohort B: 30 mg CCX168 single dose on Days 1 and 14; 600 mg rifampin (a CYP3A4 inducer) QD on Days 4 to 17

Test product: The 30 mg CCX168 doses were given orally as 10 mg hard gelatin capsules (Batch No.: B150039).

Sampling Schedule:

Cohort A:

For midazolam and celecoxib PK:

- Day 1: predose, and at Hours 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 (Day 2), 24 (Day 2), and 48 (Day 3) after dosing on Day 1
- Day 13: predose and at Hours 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 (Day 14), 24 (Day 14), 48 (Day 15), and 72 (Day 16) after Day 13 dosing

For CCX168 and CCX168-M1 PK:

- Days 15 and 19: predose, and at Hours 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 following the morning dose on Days 15 and 19

Cohort B:

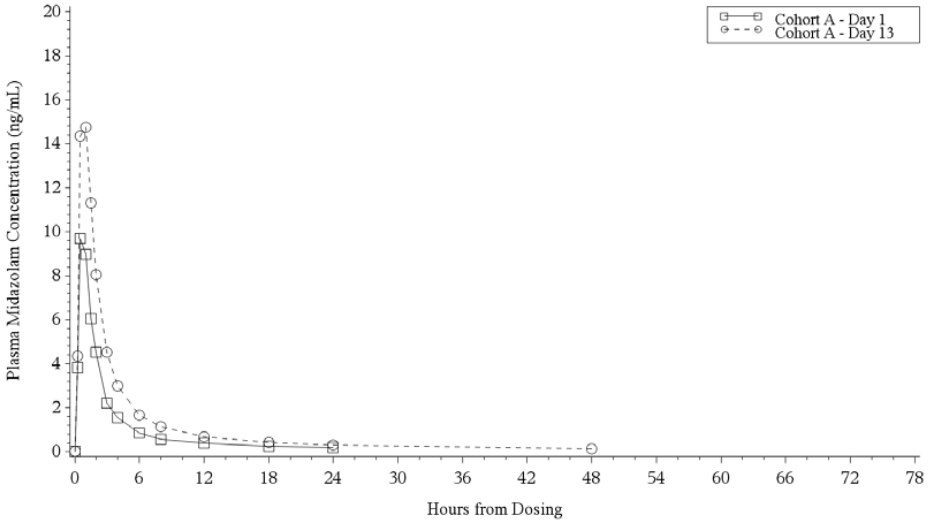
For CCX168 and CCX168-M1 PK:

- Day 1: predose, and at Hours 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 (Day 2), 24 (Day 2), 48 (Day 3), and 72 (Day 3) after Day 1 dosing
- Day 14: predose, and at Hours 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 (Day 2), 24 (Day 2), 48 (Day 3), and 72 (Day 3) after Day 14 dosing

Results: The PK results were summarized as below.

Midazolam PK Results (Cohort A)

Figure 31. Arithmetic Mean Plasma Concentration-Time Profiles of Plasma Midazolam on Days 1 and 13 (Cohort A, Study CL008_168)



Source: Figure 11-1 of Study CL008-168 CSR
Cohort A: 2 mg midazolam (a CYP3A4 probe drug) +200 mg celecox b (a CYP2C9 probe drug) single dose on Days 1 and 13; 30 mg CCX168 BID on Days 3 - 18 and a single dose on the morning of Day 19; 200 mg itraconazole (a CYP3A4 inhibitor) QD on Days 16 to 19

Table 73. Summary of the PK Parameters of Plasma Midazolam -Days 1 and 13 (Cohort A, Study CL008_168)

	Day 1		Day 13	
Pharmacokinetic Parameters	Geometric Mean (CV%)	n	Geometric Mean (CV%)	n
AUC_{0-t} (ng*hr/mL)	25.3 (28.1)	16	46.3 (31.5)	16
AUC_{inf} (ng*hr/mL)	26.7 (28.4)	16	48.3 (31.1)	16
$AUC_{\%extrap}$ (%)	5.14 ± 2.25	16	4.23 ± 2.08	16
C_{max} (ng/mL)	10.2 (30.4)	16	15.7 (26.6)	16
t_{max} (hr)	0.527 (0.499, 1.00)	16	0.748 (0.495, 1.50)	16
Lambda z (1/hr)	0.150 ± 0.0901	16	0.119 ± 0.0441	16
$t_{1/2}$ (hr)	5.60 ± 1.91	16	6.62 ± 2.43	16
CL/F (L/hr)	77.6 ± 21.2	16	43.2 ± 12.4	16
V_z/F (L)	592 ± 205	16	384 ± 95.6	16
Cohort A: 2 mg midazolam + 200 mg celecoxib single dose on Days 1 and 13; 30 mg CCX168 b.i.d. on Days 3 - 18 and a single dose on the morning of Day 19; 200 mg itraconazole q.d. on Days 16 - 19 t_{max} is presented as Median (Minimum, Maximum) $AUC_{\%extrap}$, Lambda z, $t_{1/2}$, CL/F, and V_z/F are presented as Mean ± SD				

Source: Table 11-2 of Study CL008-168 CSR
Abbreviations: $AUC_{0-\tau}$, area under the curve to the last quantifiable time point; AUC_{0-inf}, area under the curve from zero to infinity; $AUC_{\%extrap}$, % extrapolated area under the curve; BID, twice daily; CL/F, apparent systemic clearance; C_{max}, maximum concentration; CV%, coefficient of variation; Lambda z, elimination rate constant; PK, pharmacokinetics; q.d., once daily; $t_{1/2,}$ half-life; T_{max}, time to maximum concentration; Vz/F, apparent central volume of distribution.

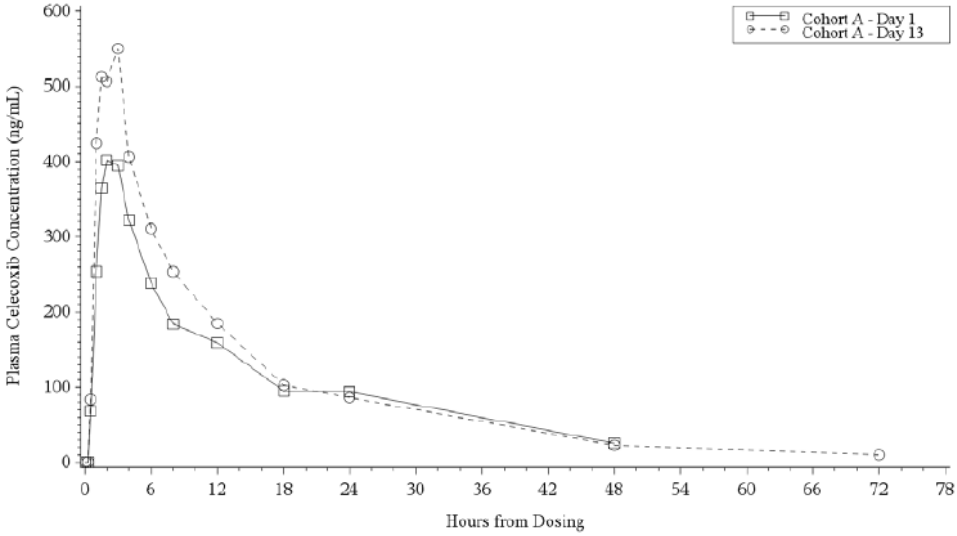
Table 74. Summary of Statistical PK Comparisons of Midazolam (Study CL008_168)

	Day 13 (Test)		Day 1 (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	Confidence Intervals 90% Confidence	Intra-subject CV%
AUC_{inf} (ng*hr/mL)	48.3	16	26.7	16	180.89	165.03 - 198.28	14.89
C_{max} (ng/mL)	15.7	16	10.2	16	154.56	141.10 - 169.31	14.78
t_{max} (hr)	0.810	16	0.722	16	112.20	86.81 - 137.59	38.61
$t_{1/2}$ (hr)	6.62	16	5.60	16	118.13	104.90 - 131.37	19.57
Cohort A: 2 mg midazolam + 200 mg celecoxib single dose on Days 1 and 13; 30 mg CCX168 b.i.d. on Days 3 - 18 and a single dose on the morning of Day 19; 200 mg itraconazole q.d. on Days 16 - 19 For ln-transformed PK parameters, geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA. For the untransformed PK parameters, the LSMs are straight from the ANOVA. Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA. Geometric Mean Ratio (GMR) = 100*(test/reference) For ln-transformed PK parameters, intra-subject CV (%CV) = 100*(square root (exp[MSE]-1)) For the untransformed parameters t_{max} and $t_{1/2}$, intra-subject CV (%CV) = 100*(square root [MSE])/(Average of the LSM)							

Source: Table 11-3 of Study CL008-168 CSR
Abbreviations: ANOVA, analysis of variance; AUC_{0-inf}, area under the curve from zero to infinity; b.i.d., twice daily; C_{max}, maximum concentration; CV%, coefficient of variation; GMR, geometric mean ratio; PK, pharmacokinetics; q.d., once daily; $t_{1/2,}$ half-life; T_{max}, time to maximum concentration.

Celecoxib PK results (Cohort A)

Figure 32. Arithmetic Mean Plasma Concentration-Time Profiles of Plasma Celecoxib on Days 1 and 13 (Cohort A, Study CL008_168)



Source: Figure 11-2 of Study CL008-168 CSR
Cohort A: 2 mg midazolam (a CYP3A4 probe drug) +200 mg celecox b (a CYP2C9 probe drug) single dose on Days 1 and 13; 30 mg CCX168 BID on Days 3 - 18 and a single dose on the morning of Day 19; 200 mg itraconazole (a CYP3A4 inhibitor) q.d. on Days 16 - 19

Table 75. Summary of the Pharmacokinetic Parameters of Plasma Celecoxib – Days 1 and 13 (Cohort A, Study CL008_168)

	Day 1		Day 13	
Pharmacokinetic Parameters	**Geometric Mean (CV%)**	**n**	**Geometric Mean (CV%)**	**n**
AUC_{0-t} (ng*hr/mL)	5180 (35.5)	16	6240 (31.5)	16
AUC_{inf} (ng*hr/mL)	5730 (37.3)	15	6610 (29.0)	16
$AUC_{\%extrap}$ (%)	8.23 ± 6.55	15	5.47 ± 5.28	16
C_{max} (ng/mL)	443 (46.0)	16	727 (17.4)	16
t_{max} (hr)	2.00 (0.996, 4.00)	16	2.25 (0.999, 6.00)	16
Lambda z (1/hr)	0.0615 ± 0.0214	15	0.0631 ± 0.0235	16
$t_{1/2}$ (hr)	12.7 ± 4.48	15	12.3 ± 4.21	16
CL/F (L/hr)	37.0 ± 13.0	15	31.3 ± 7.33	16
V_z/F (L)	643 ± 217	15	551 ± 215	16
Cohort A: 2 mg midazolam + 200 mg celecoxib single dose on Days 1 and 13; 30 mg CCX168 b.i.d. on Days 3 - 18 and a single dose on the morning of Day 19; 200 mg itraconazole q.d. on Days 16 - 19 t_{max} is presented as Median (Minimum, Maximum) $AUC_{\%extrap}$, Lambda z, $t_{1/2}$, CL/F, and V_z/F are presented as Mean ± SD				

Source: Table 11-4 of Study CL008-168 CSR
Abbreviations: AUC_{0-T}, area under the curve to the last quantifiable time point; AUC_{0-inf}, area under the curve from zero to infinity; $AUC_{\%extrap}$, % extrapolated area under the curve; BID, twice daily; CL/F, apparent systemic clearance; C_{max}, maximum concentration; CV%, coefficient of variation; PK, pharmacokinetics; q.d., once daily; $t_{1/2}$, half-life; T_{max}, time to maximum concentration; Vz/F, apparent central volume of distribution.

Table 76. Summary of Statistical PK Comparisons of Celecoxib (Study CL008_168)

	Day 13 (Test)		Day 1 (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	Confidence Intervals 90% Confidence	Intra-subject CV%
AUC_{inf} (ng*hr/mL)	6610	16	5750	15	114.96	103.46 - 127.74	16.57
C_{max} (ng/mL)	727	16	443	16	164.10	134.41 - 200.34	33.05
t_{max} (hr)	2.34	16	2.15	16	108.80	82.84 - 134.75	40.11
$t_{1/2}$ (hr)	12.3	16	12.8	15	96.28	75.78 - 116.78	32.95

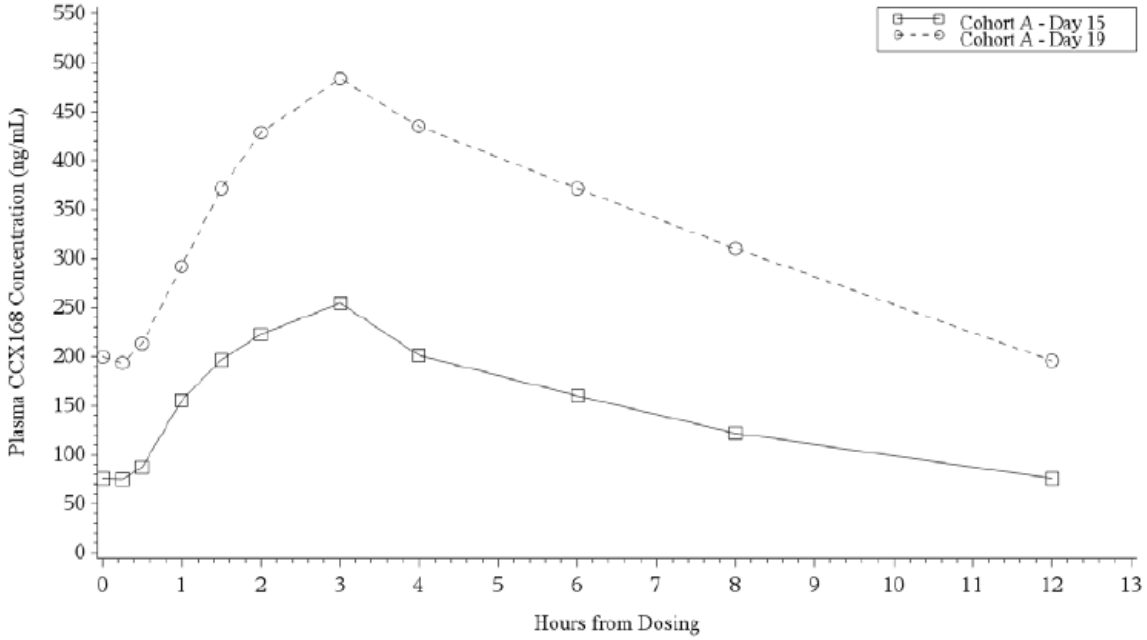
Cohort A: 2 mg midazolam + 200 mg celecoxib single dose on Days 1 and 13; 30 mg CCX168 b.i.d. on Days 3 - 18 and a single dose on the morning of Day 19; 200 mg itraconazole q.d. on Days 16 - 19

For ln-transformed PK parameters, geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA. For the untransformed PK parameters, the LSMs are straight from the ANOVA.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
For ln-transformed PK parameters, intra-subject CV (%CV) = 100*(square root (exp[MSE]-1))
For the untransformed parameters t_{max} and $t_{1/2}$, intra-subject CV (%CV) = 100*(square root [MSE])/(Average of the LSM)

Source: Table 11-5 of Study CL008-168 CSR
Abbreviations: ANOVA, analysis of variance; AUC_{0-inf}, area under the curve from zero to infinity; BID, twice daily; C_{max}, maximum concentration; CV%, coefficient of variation; MSE, mean square of error; PK, pharmacokinetics; q.d., once daily; $t_{1/2,}$ half-life; t_{max}, time to maximum concentration.

CCX168 PK Results (Cohort A)

Figure 33. Arithmetic Mean Plasma Concentration-Time Profiles of Plasma Avacopan on Days 15 and 19 (Cohort A, Study CL008_168)



Source: Figure 11-3 of Study CL008-168 CSR
Cohort A: 2 mg midazolam (a CYP3A4 probe drug) +200 mg celecox b (a CYP2C9 probe drug) single dose on Days 1 and 13; 30 mg CCX168 b.i.d. on Days 3 to 18 and a single dose on the morning of Day 19; 200 mg itraconazole (a CYP3A4 inhibitor) q.d. on Days 16 to 19
Abbreviations: b.i.d., twice daily; CYP, cytochrome P450 enzyme; q.d., once daily.

Table 77. Summary of the Pharmacokinetic Parameters of Plasma Avacopan – Days 15 and 19 (Cohort A, Study CL008_168)

	Day 15		Day 19	
Pharmacokinetic Parameters	Geometric Mean (CV%)	n	Geometric Mean (CV%)	n
$AUC_{0\text{-}tau}$ (ng*hr/mL)	1770 (17.6)	16	3880 (26.7)	16
$C_{max,ss}$ (ng/mL)	257 (20.6)	16	480 (20.3)	16
$C_{min,ss}$ (ng/mL)	69.8 (18.5)	16	174 (32.1)	16
$C_{avg,ss}$ (ng/mL)	147 (17.6)	16	323 (26.7)	16
$t_{max,ss}$ (hr)	3.00 (1.50, 3.05)	16	3.00 (2.00, 4.01)	16
$t_{min,ss}$ (hr)	6.2 (0.25, 12)	16	12 (0.25, 12)	16
CL/F (L/hr)	17.2 ± 2.92	16	7.98 ± 2.01	16
Swing	2.74 ± 0.737	16	1.81 ± 0.620	16
%Fluc (%)	127 ± 22.7	16	95.2 ± 21.8	16
Cohort A: 2 mg midazolam + 200 mg celecoxib single dose on Days 1 and 13; 30 mg CCX168 b.i.d. on Days 3 - 18 and a single dose on the morning of Day 19; 200 mg itraconazole q.d. on Days 16 - 19 $t_{max,ss}$ and $t_{min,ss}$ are presented as Median (Minimum, Maximum) CL/F, Swing, and %Fluc are presented as Mean ± SD				

Source: Table 11-6 of Study CL008-168 CSR
Abbreviations: %Fluc; fluctuation index; $AUC_{tau,}$ area under the curve during a dosing interval; BID, twice daily; CL/F, apparent systemic clearance; C_{max}, maximum concentration; CV%, coefficient of variation; PK, pharmacokinetics; q.d., once daily; $t_{1/2,}$ half-life; t_{max}, time to maximum concentration; t_{min}, time to minimum concentration.

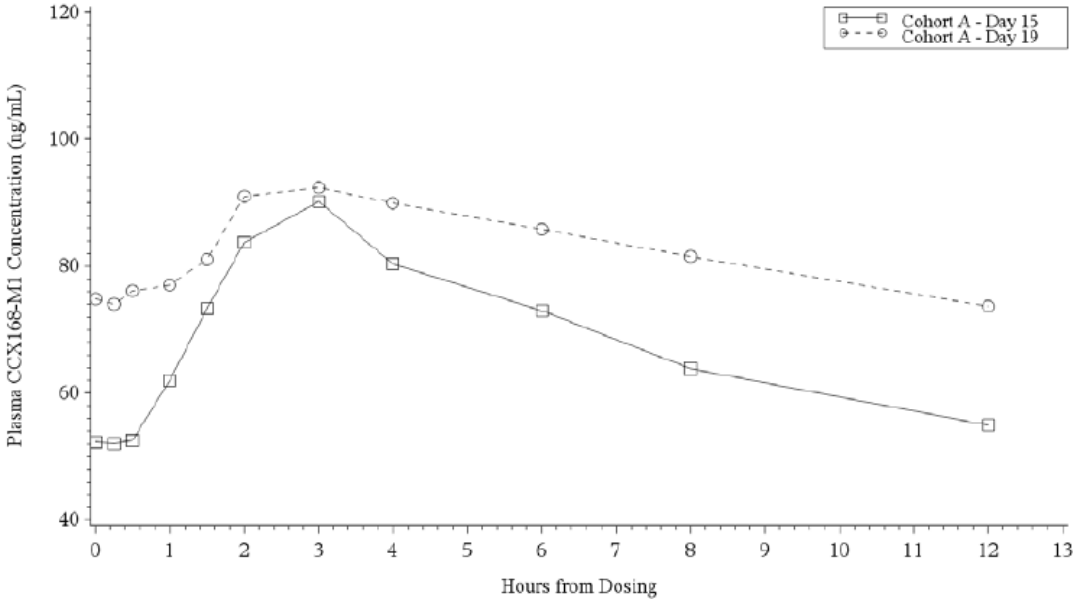
Table 78. Summary of Statistical PK Comparisons of Avacopan (Study CL008_168)

	Day 19 (Test)		Day 15 (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	Confidence Intervals 90% Confidence	Intra-subject CV%
$AUC_{0\text{-}tau}$ (ng*hr/mL)	3880	16	1770	16	219.20	199.66 - 240.64	15.15
$C_{max,ss}$ (ng/mL)	480	16	257	16	187.08	170.22 - 205.60	15.32
t_{max} (hr)	2.88	16	2.67	16	107.82	99.81 - 115.83	12.44
Cohort A: 2 mg midazolam + 200 mg celecoxib single dose on Days 1 and 13; 30 mg CCX168 b.i.d. on Days 3 - 18 and a single dose on the morning of Day 19; 200 mg itraconazole q.d. on Days 16 - 19 For ln-transformed PK parameters, geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA. For the untransformed PK parameters, the LSMs are straight from the ANOVA. Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA. Geometric Mean Ratio (GMR) = 100*(test/reference) For ln-transformed PK parameters, intra-subject CV (%CV) = 100*(square root (exp[MSE]-1)) For the untransformed parameters t_{max} and $t_{1/2}$, intra-subject CV (%CV) = 100*(square root [MSE])/(Average of the LSM)							

Source: Table 11-7 of Study CL008-168 CSR
Abbreviations: ANOVA, analysis of variance; $AUC_{tau,}$ area under the curve during a dosing interval; BID, twice daily; C_{max}, maximum concentration; CV%, coefficient of variation; GMR, geometric mean ratio; MSE, mean square of error; PK, pharmacokinetics; q.d., once daily; t_{max}, time to maximum concentration.

CCX168-M1 PK Results (Cohort A)

Figure 34. Arithmetic Mean Plasma Concentration-Time Profiles of Plasma M1 on Days 15 and 19 (Cohort A, Study CL008_168)



Source: Figure 11-4 of Study CL008-168 CSR
Cohort A: 2 mg midazolam (a CYP3A4 probe drug) +200 mg celecox b (a CYP2C9 probe drug) single dose on Days 1 and 13; 30 mg CCX168 b.i.d. on Days 3 to 18 and a single dose on the morning of Day 19; 200 mg itraconazole (a CYP3A4 inhibitor) q.d. on Days 16 to 19
Abbreviations: b.i.d., twice daily; q.d., once daily.

Table 79. Summary of the Pharmacokinetic Parameters of Plasma M1 -Days 15 and 19 (Cohort A, Study CL008_168)

	Day 15		Day 19	
Pharmacokinetic Parameters	Geometric Mean (CV%)	n	Geometric Mean (CV%)	n
$AUC_{0\text{-}tau}$ (ng*hr/mL)	819 (14.3)	16	976 (20.9)	16
$C_{max,ss}$ (ng/mL)	90.1 (15.4)	16	92.6 (19.8)	16
$C_{min,ss}$ (ng/mL)	50.3 (17.0)	16	67.8 (22.9)	16
$C_{avg,ss}$ (ng/mL)	68.3 (14.4)	16	81.3 (20.9)	16
$t_{max,ss}$ (hr)	3.00 (2.00, 3.05)	16	3.00 (0.526, 4.00)	16
$t_{min,ss}$ (hr)	0.50 (0.25, 12)	16	4.5 (0.25, 12)	16
Swing	0.799 ± 0.157	16	0.370 ± 0.104	16
%Fluc (%)	58.4 ± 9.00	16	30.5 ± 7.29	16
Cohort A: 2 mg midazolam + 200 mg celecoxib single dose on Days 1 and 13; 30 mg CCX168 b.i.d. on Days 3 - 18 and a single dose on the morning of Day 19; 200 mg itraconazole q.d. on Days 16 - 19 $t_{max,ss}$ and $t_{min,ss}$ are presented as Median (Minimum, Maximum) Swing and %Fluc are presented as Mean ± SD				

Source: Table 11-8 of Study CL008-168 CSR
Abbreviations: %Fluc; fluctuation index; $AUC_{tau,}$ area under the curve during a dosing interval; b.i.d., twice daily; C_{avg}, average concentration; C_{max}, maximum concentration; C_{min}, minimum concentration; CV%, coefficient of variation; PK, pharmacokinetics; q.d., once daily t_{max}, time to maximum concentration; t_{min}, time to minimum concentration.

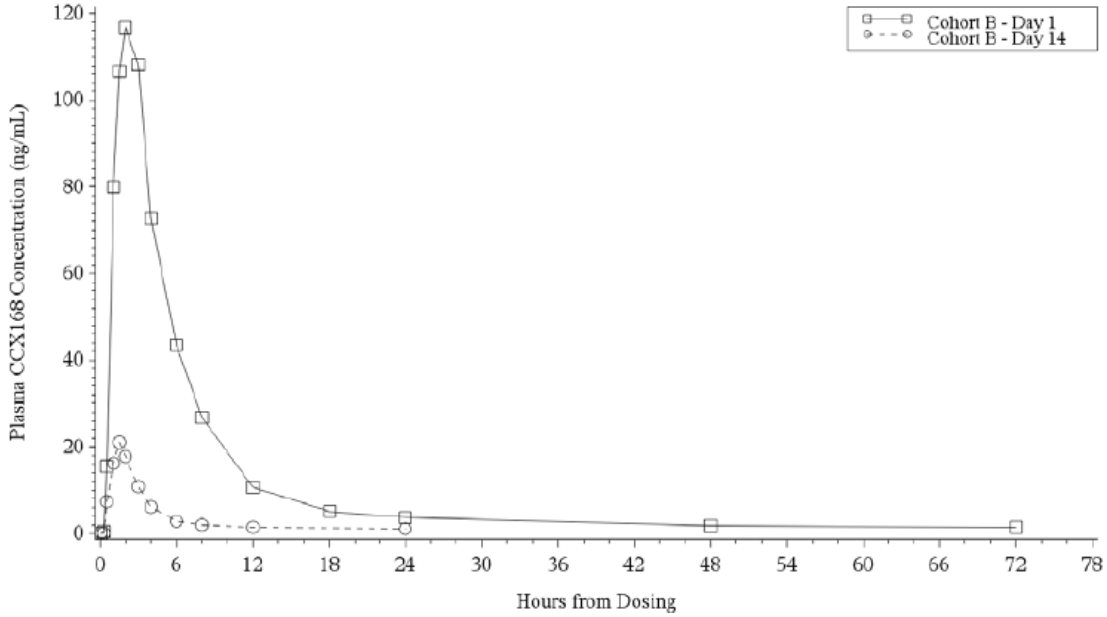
Table 80. Summary of Statistical PK Comparisons of M1 (Study CL008_168)

	Day 19 (Test)		Day 15 (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	Confidence Intervals 90% Confidence	Intra-subject CV%
$AUC_{0\text{-}tau}$ (ng*hr/mL)	976	16	819	16	119.09	110.98 - 127.79	11.41
$C_{max,ss}$ (ng/mL)	92.6	16	90.1	16	102.74	95.07 - 111.03	12.57
t_{max} (hr)	2.72	16	2.89	16	94.29	81.92 - 106.65	20.53
Cohort A: 2 mg midazolam + 200 mg celecoxib single dose on Days 1 and 13; 30 mg CCX168 b.i.d. on Days 3 - 18 and a single dose on the morning of Day 19; 200 mg itraconazole q.d. on Days 16 - 19 For ln-transformed PK parameters, geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA. For the untransformed PK parameters, the LSMs are straight from the ANOVA. Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA. Geometric Mean Ratio (GMR) = 100*(test/reference) For ln-transformed PK parameters, intra-subject CV (%CV) = 100*(square root (exp[MSE]-1)) For the untransformed parameters t_{max} and $t_{1/2}$, intra-subject CV (%CV) = 100*(square root [MSE])/(Average of the LSM)							

Source: Table 11-9 of Study CL008-168 CSR
Abbreviations: ANOVA, analysis of variance; $AUC_{tau,}$ area under the curve during a dosing interval; b.i.d., twice daily; C_{avg}, average concentration; C_{max}, maximum concentration; CV%, coefficient of variation; GMR, geometric mean ratio; MSE, mean square of error; PK, pharmacokinetics; q.d., once daily; $t_{1/2}$, half-life; t_{max}, time to maximum concentration.

CCX168 PK results (Cohort B)

Figure 35. Arithmetic Mean Plasma Concentration-Time Profiles of Plasma Avacopan on Days 1 and 14 (Cohort B, Study CL008_168)



Source: Figure 11-5 of Study CL008-168 CSR
Cohort B: 30 mg CCX168 single dose on Days 1 and 14; 600 mg rifampin (a CYP3A4 inducer) QD on Days 4 to 17
Abbreviations: CYP, cytochrome P450 enzyme; QD, once daily.

Table 81. Summary of the Pharmacokinetic Parameters of Plasma Avacopan – Days 1 and 14 (Cohort B, Study CL008_168)

	Day 1		Day 14	
Pharmacokinetic Parameters	Geometric Mean (CV%)	n	Geometric Mean (CV%)	n
AUC_{0-t} (ng*hr/mL)	709 (40.6)	16	54.6 (66.3)	13
AUC_{inf} (ng*hr/mL)	769 (39.2)	16	54.5 (55.7)	12
$AUC_{\%extrap}$ (%)	7.76 ± 2.35	16	8.06 ± 2.57	12
C_{max} (ng/mL)	122 (35.3)	16	24.1 (40.9)	13
t_{max} (hr)	2.00 (1.50, 3.01)	16	1.50 (0.916, 3.00)	13
Lambda z (1/hr)	0.0269 ± 0.0126	16	0.379 ± 0.0644	12
$t_{1/2}$ (hr)	28.7 ± 7.51	16	1.87 ± 0.289	12
CL/F (L/hr)	41.7 ± 16.0	16	633 ± 403	12
V_z/F (L)	1660 ± 607	16	1610 ± 736	12
Cohort B: 30 mg CCX168 single dose on Days 1 and 14; 600 mg rifampicin q.d. on Days 4 - 17 t_{max} is presented as Median (Minimum, Maximum) $AUC_{\%extrap}$, Lambda z, $t_{1/2}$, CL/F, and V_z/F are presented as Mean ± SD				

Source: Table 11-10 of Study CL008-168 CSR
Abbreviations: AUC_{0-t}, area under the curve to the last quantifiable time point; AUC_{0-inf}, area under the curve from zero to infinity; $AUC_{\%extrap}$, % extrapolated area under the curve; CL/F, apparent systemic clearance; C_{max}, maximum concentration; CV%, coefficient of variation; Lambda z, elimination rate constant; q.d., once daily; SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time to maximum concentration; Vz/F, apparent central volume of distribution.

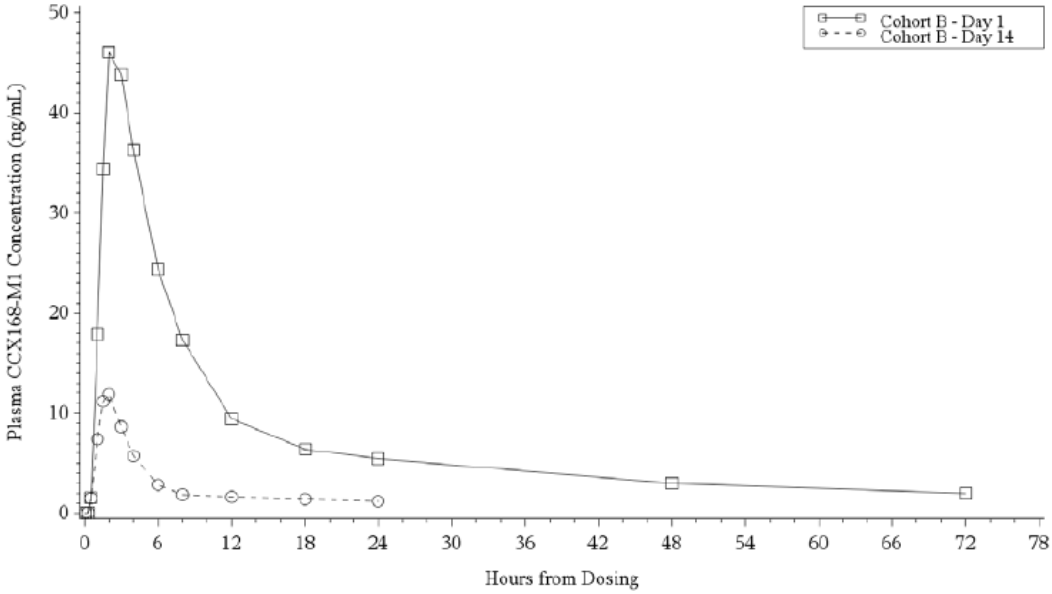
Table 82. Summary of Statistical PK Comparisons of Plasma Avacopan (Cohort B, Study CL008_168)

	Day 14 (Test)		Day 1 (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	Confidence Intervals 90% Confidence	Intra-subject CV%
AUC_{inf} (ng*hr/mL)	57.0	12	769	16	7.42	5.77 - 9.54	36.99
C_{max} (ng/mL)	25.4	13	122	16	20.89	17.77 - 24.57	23.99
t_{max} (hr)	1.41	13	2.16	16	65.21	50.41 - 80.01	26.43
$t_{1/2}$ (hr)	1.88	12	28.7	16	6.55	-6.83 - 19.93	36.51
Cohort B: 30 mg CCX168 single dose on Days 1 and 14; 600 mg rifampicin q.d. on Days 4 - 17 For ln-transformed PK parameters, geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA. For the untransformed PK parameters, the LSMs are straight from the ANOVA. Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA. Geometric Mean Ratio (GMR) = 100*(test/reference) For ln-transformed PK parameters, intra-subject CV (%CV) = 100*(square root (exp[MSE]-1)) For the untransformed parameters t_{max} and $t_{1/2}$, intra-subject CV (%CV) = 100*(square root [MSE])/(Average of the LSM)							

Source: Table 11-11 of Study CL008-168 CSR
Abbreviations: ANOVA, analysis of variance; AUC_{inf}, area under the curve to infinity; C_{max}, maximum concentration; CV%, coefficient of variation; GMR; geometric mean ratio; MSE, mean square of error; PK, pharmacokinetics; q.d., once daily; $t_{1/2}$, half-life; t_{max}, time to maximum concentration.

CCX168-M1 PK results (Cohort B)

Figure 36. Arithmetic Mean Plasma Concentration-Time Profiles of Plasma M1 on Days 1 and 14 (Cohort B, Study CL008_168)



Source: Figure 11-6 of Study CL008-168 CSR
Cohort B: 30 mg CCX168 single dose on Days 1 and 14; 600 mg rifampin (a CYP3A4 inducer) QD on Days 4 to 17
Abbreviations: QD, once daily.

Table 83. Summary of the PK Parameters of Plasma M1 -Days 1 and 14 (Cohort B, Study CL008_168)

	Day 1		Day 14	
Pharmacokinetic Parameters	Geometric Mean (CV%)	n	Geometric Mean (CV%)	n
AUC_{0-t} (ng*hr/mL)	517 (17.8)	16	41.6 (58.5)	13
AUC_{inf} (ng*hr/mL)	613 (18.0)	16	44.9 (49.5)	12
$AUC_{\%extrap}$ (%)	15.6 ± 5.07	16	13.9 ± 6.53	12
C_{max} (ng/mL)	47.5 (20.6)	16	12.5 (41.9)	13
t_{max} (hr)	2.02 (2.00, 3.05)	16	1.50 (0.916, 3.00)	13
Lambda z (1/hr)	0.0215 ± 0.00417	16	0.291 ± 0.100	12
$t_{1/2}$ (hr)	33.7 ± 8.08	16	3.74 ± 5.01	12
Cohort B: 30 mg CCX168 single dose on Days 1 and 14; 600 mg rifampicin q.d. on Days 4 - 17 t_{max} is presented as Median (Minimum, Maximum) $AUC_{\%extrap}$, Lambda z, and $t_{1/2}$ are presented as Mean ± SD				

Source: Table 11-12 of Study CL008-168 CSR
Abbreviations: AUC_{0-t}, area under the curve to the last quantifiable time point; AUC_{inf}, area under the curve to infinity; $AUC_{\%extrap}$, % extrapolated area under the curve; C_{max}, maximum concentration; CV%, coefficient of variation; Lambda z, elimination rate constant; q.d., once daily; SD, standard deviation; $t_{1/2}$, half-life; t_{max}, time to maximum concentration.

Table 84. Summary of Statistical PK Comparisons of Plasma M1 (Cohort B, Study CL008_168)

	Day 14 (Test)		Day 1 (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	Confidence Intervals 90% Confidence	Intra-subject CV%
AUC_{inf} (ng*hr/mL)	45.6	12	613	16	7.44	6.20 - 8.93	26.42
C_{max} (ng/mL)	12.7	13	47.5	16	26.70	23.16 - 30.78	21.02
t_{max} (hr)	1.67	13	2.39	16	70.01	57.02 - 83.01	22.65
$t_{1/2}$ (hr)	3.74	12	33.7	16	11.11	-3.04 - 25.27	37.16

Cohort B: 30 mg CCX168 single dose on Days 1 and 14; 600 mg rifampicin q.d. on Days 4 - 17

For ln-transformed PK parameters, geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA. For the untransformed PK parameters, the LSMs are straight from the ANOVA.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
For ln-transformed PK parameters, intra-subject CV (%CV) = 100*(square root (exp[MSE]-1))
For the untransformed parameters t_{max} and $t_{1/2}$, intra-subject CV (%CV) = 100*(square root [MSE])/(Average of the LSM)

Source: Table 11-13 of Study CL008-168 CSR
Abbreviations: AUC_{inf}, area under the curve to infinity; C_{max}, maximum concentration; CV%, coefficient of variation; MSE, mean square of error; PK, pharmacokinetics; q.d., once daily; SD, standard deviation; $t_{1/2}$, half-life; t_{max}, time to maximum concentration.

Conclusions:

Cohort A

- When coadministered with CCX168, midazolam (a CYP3A4 probe drug) AUC and Cmax increased by 81% and 55%, respectively.
- When coadministered with CCX168, celecoxib (a CYP2C9 probe drug) AUC and Cmax increased by 15% and 64%, respectively.
- When coadministered with itraconazole (a strong CYP3A4 inhibitor), CCX168 AUC and C_{max} increased by 119% and 87%, respectively, and CCX168-M1 AUC and C_{max} increased by 19% and 3%, respectively.

Cohort B

- When coadministered with rifampin (a strong CYP3A4 inducer), CCX168 AUC and C_{max} decreased by 93% and 79%, respectively, and similar exposure decrease were observed for CCX168-M1.

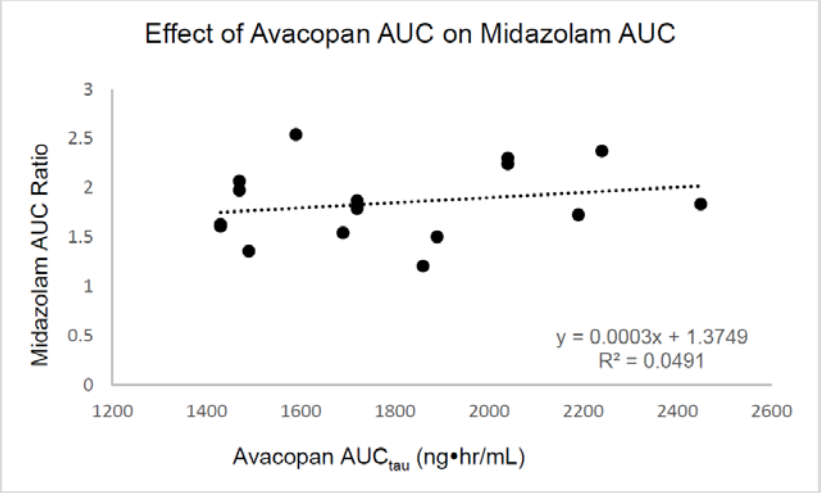
Reviewer's comments: *Avacopan (CCX168) is proposed to be administered with food. While in this DDI study, avacopan doses were administered under fasted condition. Study results showed that a high-fat, high-calorie meal increased CCX168 AUC by ~72% but did not affect the C_{max} as compared to fasted condition. For metabolite M1, a high-fat, high-calorie meal did not affect the AUC, but reduced C_{max} by 51%. When CYP3A4 substrates such as*

midazolam is co-administered with avacopan under fed condition, the effect of avacopan on systemic exposure of CYP3A4 substrates could be higher but has not been studied.

The clinical pharmacology review team requested the Applicant to justify the effect of avacopan on CYP3A4 substrates under fed condition (IRs dated November 24, 2020, and January 26, 2021). The Applicant provided IR responses on December 07, 2020 and February 05, 2021. The Applicant believed that in the FDA Guidance on drug interaction studies, C_{max} was generally used in the "basic models" and "static mechanistic models" to assess the potential of an investigational drug being a modulator of metabolizing enzymes, while a high-fat, high-calorie meal did not affect avacopan C_{max} and reduced M1 C_{max} by 51%. The Applicant further examined the relationship between avacopan exposure and midazolam exposure in individual subjects in this DDI study (Figure 37, Figure 38, Table 85) and concluded that the 1.72-fold change in the avacopan exposure due to the food effect is not expected to significantly amplify the DDI effect on CYP3A4 substrates such as midazolam.

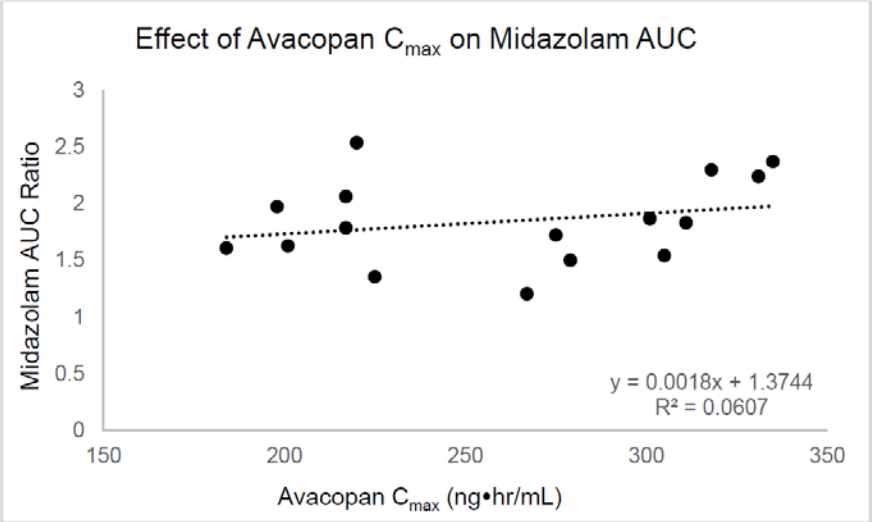
The review team remained concerned regarding the impact of avacopan under fed condition on CYP3A4 substrates. Caution should be exercised when CYP3A4 substrates with narrow therapeutic window are co-administered with avacopan.

Figure 37. Effect of Avacopan AUC on Midazolam AUC



Source: Figure 1 of IR response dated February 05, 2021
Abbreviations: AUC_{tau}, area under the curve during a dosing interval.

Figure 38. Effect of Avacopan C_{max} on Midazolam AUC



Source: Figure 2 of IR response dated February 05, 2021
Abbreviations: AUC, area under the curve; C_{max}, maximum concentration.

Table 85. Effect of Avacopan AUC on CYP3A4 DDI

Avacopan	**Value**
Maximum AUC (Subject 108)	2,450 ng•hr/mL
Minimum AUC (Subject 113)	1,430 ng•hr/mL
Max/Min AUC Ratio	1.71
Midazolam	**Value**
AUC Ratio in Subject 108 (After vs. Before Administration of Avacopan 30 mg BID)	1.83
AUC Ratio in Subject 113 (After vs. Before Administration of Avacopan 30 mg BID)	1.63
Ratio of Avacopan DDI Effect on Midazolam Exposure (Subject 108 vs. Subject 113)	1.12

Source: Table 1 of IR response dated February 05, 2021
Abbreviations: AUC, area under the curve; BID, twice daily; DDI, drug-drug interactions.

In Cohort A, a single oral dose of 2 mg midazolam and a single oral dose of 200 mg celecoxib were given concurrently on Day 1 and Day 13. The clinical pharmacology review team requested the Applicant to provide justification regarding the drug interaction potential between midazolam and celecoxib (IR dated November 24, 2020). The Applicant provided IR responses on December 07, 2020. In the University of Washington drug interaction database published in October 2020, celecoxib is not listed as an inhibitor of CYP3A4 and midazolam is not listed as an inhibitor of CYP2C9. In addition, the prescribing information of celecoxib indicates that it is not an inhibitor of CYP3A4, while the prescribing information of midazolam does not indicate its effect on CYP2C9. Therefore, celecoxib and midazolam were

not expected to interact with each other when administered concurrently. The Applicant's justification is reasonable.

Per the FDA guidance for industry entitled "Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (January, 2020)", if a DDI study with strong index inhibitors or inducers indicates that there is a clinically significant interaction, evaluating the impact of other moderate inhibitors or inducers is recommended to gain a full understanding of the investigational drug's DDI potential in a clinical interaction study or through modeling and simulation approaches, such as PBPK modeling. Especially, the DDI study results indicated rifampin (a strong CYP3A4 inducer) decreased CCX168 AUC and C_{max} by 93% and 79%, respectively, and decreases similar exposure for M1. The clinical pharmacology review team has encouraged the Applicant to perform PBPK modeling to justify the effect of moderate and weak CYP 3A4 inhibitors and inducers (IR dated November 24, 2020). The Applicant believed that current information is sufficient and PBPK modeling would not be much more predictive (IR responses dated December 07, 2020). The review team remained concerned, especially regarding the impact of moderate CYP3A4 inducers on avacopan.

17.3.1.2.5. PK Study in Subjects With Hepatic Impairment

Trial # CL013_168

Title: 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

Study period: 17 April 2018-03 July 2018

Objective:

- To evaluate the PK and CCX168 and CCX168-M1 in subjects with mild or moderate hepatic impairment
- To evaluate the safety and tolerability

Study design: This was a phase 1, open label, single dose study to evaluate the effect of mild or moderate hepatic impairment (as defined using Child-Pugh Classification of the Severity of Liver Disease criteria) on the PK, safety, and tolerability of a single oral dose of 30 mg avacopan compared to demographically-matched healthy subjects with normal hepatic function. A single dose of avacopan 30 mg was administered as three 10 mg hard gelatin capsules given in a fasted state (4 hours prior to food) with approximately 100 mL water.

Group 1 Mild: approximately 8 subjects with mild hepatic impairment (C-P Class A, score of 5 to 6 points)

Group 2 Moderate: approximately 8 subjects with moderate hepatic impairment (C-P Class B, score of 7 to 9 points)

Group 3 Healthy: approximately 8 – 10 healthy control subjects with normal hepatic function demographically matched to patients in Group 1 and 2. Matching was done on sex, age (±10 years), BMI (±20%) for each matched pair of subjects. If the match rate in the mild impairment group was <50%, additional healthy subjects were recruited; it was expected that not more than 2 additional subjects would be needed.

Test product: Avacopan hard gelatin capsules (10 mg) (Lot No. S16009)

Sampling schedule:

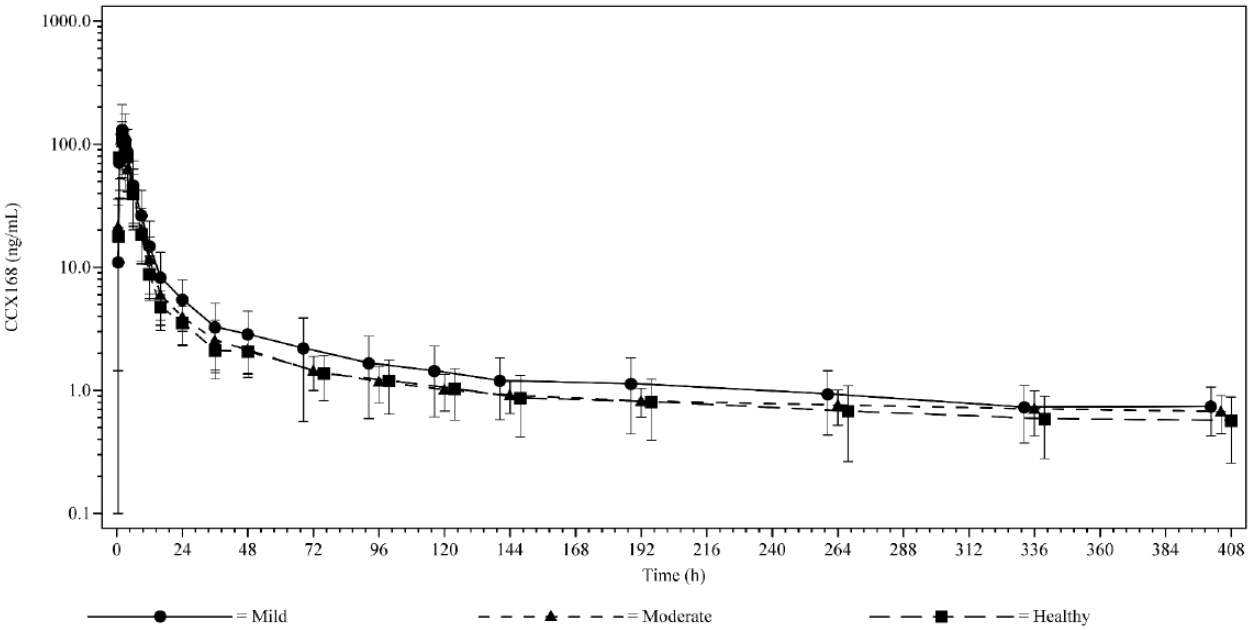
Blood samples were collected at pre-dose and 0.5, 1, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48, 72, 96, 120, 144, 192, 264, and 336 hours post-dose and at the final follow-up visit at approximately Day 18 or 408 hours.

Results: The PK results were summarized as below.

CCX168 PK Results

One subjects (subject (b) (6)) with mild hepatic impairment has plasma concentrations of avacopan that were approximately 2-fold higher than the subject with the next highest plasma exposure levels. Review of the subject's medical history (type 2 diabetes mellitus) and medications (metformin) are unlikely to explain the outlier. The body weight (84.8 kg), sex (male), age (61 years) and ethnicity (Hispanic) also did not differ in this subject. The PK analysis the statistics were computed both with and without Subject (b) (6)

Figure 39. Semi-Log Mean (±SD) Plasma Avacopan Concentration (ng/mL) vs. Time Point by Hepatic Impairment Group (Study CL013_168)



Source: Figure 2 of Study CL013-168 CSR
Abbreviations: SD, standard deviation.

Table 86. Summary of Plasma Avacopan Pharmacokinetic Parameters (Study CL013_168)

Parameter	Mild (N=8)	Mild (Excluding Subject (b) (6)) (N=7)	Moderate (N=8)	Healthy (N=8)
$AUC_{0\text{-}12h}$ (h*ng/mL)				
n	8	7	8	8
Mean (SD)	649 (320)	546 (139)	535 (180)	564 (143)
CV (%)	49.2	25.5	33.7	25.3
Geometric Mean (CV %)	598 (42.7)	531 (25.7)	507 (36.5)	548 (26.8)
90% CI for Geometric Mean	454, 787	441, 640	400, 643	459, 654
Median	550	501	551	569
Min, Max	372, 1370	372, 778	307, 797	371, 746
$AUC_{0\text{-}6h}$ (h*ng/mL)				
n	8	7	8	8
Mean (SD)	477 (240)	399 (95.7)	394 (118)	435 (110)
CV (%)	50.2	24.0	30.0	25.3
Geometric Mean (CV %)	439 (42.4)	389 (23.9)	377 (32.4)	422 (27.5)
90% CI for Geometric Mean	335, 577	327, 463	305, 466	352, 506
Median	413	398	415	446
Min, Max	272, 1030	272, 573	243, 554	272, 558
$AUC_{0\text{-}inf}$ (h*ng/mL)				
n*	5	4	2	6
Mean (SD)	1770 (884)	1410 (414)	1360 (4.99)	1290 (446)
CV (%)	49.8	29.3	0.4	34.7
Geometric Mean (CV %)	1620 (48.7)	1370 (30.4)	1360 (0.4)	1220 (37.0)
90% CI for Geometric Mean	1040, 2520	963, 1940	1340, 1380	909, 1640
Median	1440	1380	1360	1310
Min, Max	945, 3220	945, 1950	1360, 1360	802, 1970
AUC_{last} (h*ng/mL)				
n	8	7	8	8
Mean (SD)	1260 (637)	1050 (239)	1000 (317)	988 (317)
CV (%)	50.5	22.7	31.6	32.1
Geometric Mean (CV %)	1160 (42.1)	1030 (22.7)	955 (35.0)	940 (35.5)
90% CI for Geometric Mean	887, 1520	873, 1210	761, 1200	747, 1180
Median	1070	1010	1090	1070
Min, Max	789, 2740	789, 1440	573, 1470	556, 1450
CL/F (L/h)				
n*	5	4	2	6
Mean (SD)	20.0 (8.39)	22.7 (6.80)	22.0 (0.0808)	25.9 (9.33)
CV (%)	41.9	30.0	0.4	36.0
Geometric Mean (CV %)	18.5 (48.7)	21.9 (30.4)	22.0 (0.4)	24.6 (37.0)
90% CI for Geometric Mean	11.9, 28.7	15.5, 31.1	21.7, 22.4	18.3, 33.0
Median	20.8	21.8	22.0	22.8
Min, Max	9.32, 31.7	15.4, 31.7	22.0, 22.1	15.2, 37.4

Parameter	Mild (N=8)	Mild (Excluding Subject (b) (6)) (N=7)	Moderate (N=8)	Healthy (N=8)
C_{max} (ng/mL)				
n	8	7	8	8
Mean (SD)	135.2750 (75.97629)	109.6000 (24.12212)	106.2875 (31.70698)	125.2750 (24.76586)
CV (%)	56.2	22.0	29.8	19.8
Geometric Mean (CV %)	122.9137 (44.8)	107.4517 (21.5)	101.8130 (33.0)	122.9071 (21.8)
90% CI for Geometric Mean	92.27190, 163.73112	91.93374, 125.58895	82.07662, 126.29512	106.40521, 141.96825
Median	106.6500	99.3000	108.5000	134.0000
Min, Max	83.700, 315.000	83.700, 147.000	62.700, 146.000	80.200, 161.000
λ_Z (/h)				
n*	5	4	2	6
Mean (SD)	0.0026 (0.0005)	0.0025 (0.0005)	0.0031 (0.0010)	0.0024 (0.0005)
CV (%)	18.1	19.4	31.3	23.0
Geometric Mean (CV %)	0.0026 (20.2)	0.0025 (21.3)	0.0030 (32.6)	0.0023 (22.5)
90% CI for Geometric Mean	0.0021, 0.0031	0.0020, 0.0032	0.0007, 0.0126	0.0019, 0.0028
Median	0.0029	0.0027	0.0031	0.0022
Min, Max	0.0019, 0.0030	0.0019, 0.0029	0.0024, 0.0038	0.0018, 0.0031
$t_{1/2z}$ (h)				
n*	5	4	2	6
Mean (SD)	271 (59.5)	282 (63.3)	234 (73.1)	304 (64.2)
CV (%)	21.9	22.5	31.3	21.1
Geometric Mean (CV %)	267 (20.2)	277 (21.3)	228 (32.6)	298 (22.6)
90% CI for Geometric Mean	220, 323	216, 354	55.1, 943	248, 358
Median	239	258	234	317
Min, Max	230, 372	237, 372	182, 285	225, 375
t_{max} (h)				
n	8	7	8	8
Mean (SD)	2.13 (0.64)	2.14 (0.69)	2.25 (0.71)	2.13 (0.83)
CV (%)	30.2	32.2	31.4	39.3
Geometric Mean (CV %)	2.03 (35.0)	2.03 (37.9)	2.18 (24.9)	2.00 (38.4)
90% CI for Geometric Mean	1.62, 2.55	1.55, 2.66	1.85, 2.57	1.56, 2.56
Median	2.00	2.00	2.00	2.00
Min, Max	1.00, 3.00	1.00, 3.00	2.00, 4.00	1.00, 4.00
V_z/F (L)				
n*	5	4	2	6
Mean (SD)	7710 (2940)	8870 (1620)	7430 (2350)	11300 (4670)
CV (%)	38.1	18.3	31.6	41.4
Geometric Mean (CV %)	7110 (52.3)	8760 (18.3)	7250 (33.0)	10600 (40.4)
90% CI for Geometric Mean	4450, 11400	7070, 10800	1720, 30500	7670, 14500
Median	8280	8710	7430	10600
Min, Max	3090, 11000	7110, 11000	5770, 9100	7090, 19400

Source: Section 14, Table 14.2.3.1.1 and Table 14.2.3.1.2.
*Note: for the parameters AUC_{0-inf}, CL/F, V_z/F and $t_{1/2z}$ the number of subjects was decreased because $t_{1/2z}$ could not be reliably determined in some subjects

Source: Table 6 of Study CL013-168 CSR
Abbreviations: λ_Z, elimination rate constant; AUC_{0-6h}, area under the curve from 0 to 6 hours; AUC_{0-12h}, area under the curve from 0 to 12 hours; AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; BID, twice daily; CI, confidence interval; CL/F, apparent systemic clearance; C_{max}, maximum concentration; CV%, coefficient of variation; SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time to maximum concentration; T_{min}, time to minimum concentration; Vz/F, apparent central volume of distribution.

Table 87. Summary of Geometric Mean Ratios of Plasma Avacopan Pharmacokinetic Parameters (Study CL013_168)

Parameter	n	Mean (SE)	Geometric LS Mean (SE)[a]	% Ratio: 100*Hepatic Impairment/Healthy		CV (%)[a]
				Geometric LS Mean Ratio (SE)[a]	90% CI[a]	
$AUC_{0\text{-}inf}$ (h*ng/mL)						
Mild	5	1770 (395)	1620 (280)	1.3290 (0.3110)	0.8696, 2.0312	40.1
Moderate	2	1360 (3.53)	1360 (372)	1.1152 (0.3519)	0.6294, 1.9759	
Healthy	6	1290 (182)	1220 (193)			
AUC_{last} (h*ng/mL)						
Mild	8	1260 (225)	1160 (150)	1.2367 (0.2249)	0.9044, 1.6911	37.6
Moderate	8	1000 (112)	955 (123)	1.0161 (0.1848)	0.7431, 1.3895	
Healthy	8	988 (112)	940 (121)			
C_{max} (ng/mL)						
Mild	8	135.2750 (26.86167)	122.9137 (14.47979)	1.0001 (0.1666)	0.7508, 1.3321	34.3
Moderate	8	106.2875 (11.21011)	101.8130 (11.99402)	0.8284 (0.1380)	0.6219, 1.1034	
Healthy	8	125.2750 (8.75605)	122.9071 (14.47901)			

a: From an ANOVA model on the log-transformed results with effect hepatic impairment group.
Source: Section 14, Table 14.2.3.2.1.

Source: Table 7 of Study CL013-168 CSR
Abbreviations: ANOVA, analysis of variance; AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; CI, confidence interval; C_{max}, maximum concentration; CV%, coefficient of variation; SE, standard error.

Table 88. Summary of Geometric Mean Ratios of Plasma Avacopan Pharmacokinetic Parameters (Excluding Subject (b) (6)) (Study CL013_168)

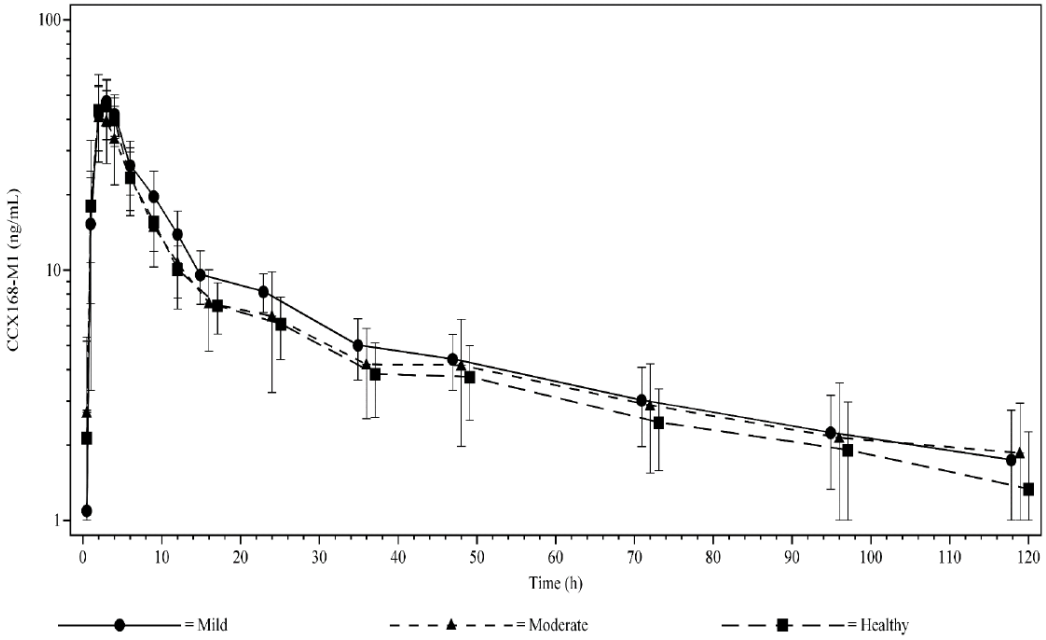
Parameter	n	Mean (SE)	Geometric LS Mean (SE)[a]	% Ratio: 100*Hepatic Impairment/Healthy		CV (%)[a]
				Geometric LS Mean Ratio (SE)[a]	90% CI[a]	
$AUC_{0\text{-}inf}$ (h*ng/mL)						
Mild	4	1410 (207)	1370 (217)	1.1198 (0.2295)	0.7691, 1.6303	32.6
Moderate	2	1360 (3.53)	1360 (306)	1.1152 (0.2891)	0.6934, 1.7935	
Healthy	6	1290 (182)	1220 (158)			
AUC_{last} (h*ng/mL)						
Mild	7	1050 (90.3)	1030 (121)	1.0941 (0.1762)	0.8287, 1.4445	31.9
Moderate	8	1000 (112)	955 (105)	1.0161 (0.1581)	0.7769, 1.3290	
Healthy	8	988 (112)	940 (103)			
C_{max} (ng/mL)						
Mild	7	109.6000 (9.11730)	107.4517 (10.43094)	0.8743 (0.1162)	0.6951, 1.0995	26.1
Moderate	8	106.2875 (11.21011)	101.8130 (9.24522)	0.8284 (0.1064)	0.6638, 1.0338	
Healthy	8	125.2750 (8.75605)	122.9071 (11.16070)			

a: From an ANOVA model on the log-transformed results with effect hepatic impairment group.
Source: Section 14, Table 14.2.3.2.2.

Source: Table 8 of Study CL013-168 CSR
Abbreviations: ANOVA, analysis of variance; AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; CI, confidence interval; C_{max}, maximum concentration; CV%, coefficient of variation; SE, standard error.

CCX168-M1 PK Results

Figure 40. Semi-Log Mean (±SD) Plasma M1 Concentration (ng/mL) vs. Time Point by Hepatic Impairment Group (Study CL013_168)



Source: Figure 4 of Study CL013-168 CSR
Abbreviations: SD, standard deviation.

Table 89. Summary of Plasma M1 Pharmacokinetic Parameters (Study CL013_168)

Parameter	Mild (N=8)	Mild (Excluding Subject (b) (6)) (N=7)	Moderate (N=8)	Healthy (N=8)
$AUC_{0\text{-}12h}$ (h*ng/mL)				
n	8	7	8	8
Mean (SD)	311 (50.9)	301 (46.7)	265 (73.1)	284 (48.8)
CV (%)	16.4	15.5	27.6	17.2
Geometric Mean (CV %)	307 (17.2)	298 (16.2)	256 (28.6)	281 (17.8)
90% CI for Geometric Mean	274, 344	265, 335	212, 309	249, 316
Median	313	291	260	295
Min, Max	225, 377	225, 359	171, 389	217, 350
$AUC_{0\text{-}6h}$ (h*ng/mL)				
n	8	7	8	8
Mean (SD)	191 (35.4)	188 (37.1)	169 (49.9)	187 (42.9)
CV (%)	18.5	19.7	29.5	22.9
Geometric Mean (CV %)	188 (20.6)	185 (21.6)	162 (30.8)	182 (26.5)
90% CI for Geometric Mean	164, 215	158, 216	133, 199	153, 217
Median	206	199	159	202
Min, Max	126, 223	126, 223	101, 245	107, 242
$AUC_{0\text{-}inf}$ (h*ng/mL)				
n	8	7	8	8
Mean (SD)	972 (285)	911 (245)	995 (346)	841 (283)
CV (%)	29.3	26.9	34.8	33.6
Geometric Mean (CV %)	936 (29.7)	885 (26.6)	943 (36.5)	799 (36.0)
90% CI for Geometric Mean	771, 1140	730, 1070	744, 1200	632, 1010
Median	875	829	897	843
Min, Max	621, 1400	621, 1320	508, 1580	446, 1330
AUC_{last} (h*ng/mL)				
n	8	7	8	8
Mean (SD)	843 (250)	788 (211)	818 (306)	694 (210)
CV (%)	29.7	26.8	37.4	30.3
Geometric Mean (CV %)	813 (29.1)	766 (25.4)	776 (34.7)	665 (32.7)
90% CI for Geometric Mean	672, 984	638, 921	619, 973	538, 824
Median	734	732	728	721
Min, Max	560, 1230	560, 1190	468, 1480	408, 968

Parameter	Mild (N=8)	Mild (Excluding Subject (b) (6)) (N=7)	Moderate (N=8)	Healthy (N=8)
C_{max} (ng/mL)				
n	8	7	8	8
Mean (SD)	48.550 (10.9245)	47.171 (11.0227)	42.038 (12.4133)	49.600 (12.1273)
CV (%)	22.5	23.4	29.5	24.5
Geometric Mean (CV %)	47.358 (25.0)	45.984 (25.4)	40.379 (31.5)	48.172 (27.1)
90% CI for Geometric Mean	40.1660, 55.8389	38.2728, 55.2491	32.8536, 49.6279	40.2919, 57.5925
Median	50.500	48.100	40.400	49.900
Min, Max	29.50, 62.90	29.50, 62.90	24.60, 57.60	28.90, 66.70
λ_Z (/h)				
n	8	7	8	8
Mean (SD)	0.0122 (0.0054)	0.0125 (0.0058)	0.0107 (0.0105)	0.0128 (0.0092)
CV (%)	44.1	46.2	98.1	72.4
Geometric Mean (CV %)	0.0112 (48.5)	0.0113 (52.7)	0.0079 (93.4)	0.0108 (63.5)
90% CI for Geometric Mean	0.0082, 0.0152	0.0079, 0.0163	0.0046, 0.0134	0.0073, 0.0159
Median	0.0115	0.0127	0.0070	0.0106
Min, Max	0.0062, 0.0207	0.0062, 0.0207	0.0026, 0.0353	0.0050, 0.0342
$t_{1/2z}$ (h)				
n	8	7	8	8
Mean (SD)	67.9 (30.4)	68.0 (32.8)	111 (76.1)	73.1 (36.5)
CV (%)	44.8	48.3	68.5	50.0
Geometric Mean (CV %)	62.0 (48.5)	61.3 (52.7)	87.8 (93.4)	64.3 (63.5)
90% CI for Geometric Mean	45.6, 84.4	42.6, 88.2	51.7, 149	43.5, 94.9
Median	60.7	54.4	104	65.7
Min, Max	33.5, 112	33.5, 112	19.6, 265	20.2, 140
t_{max} (h)				
n	8	7	8	8
Mean (SD)	3.13 (0.64)	3.14 (0.69)	2.50 (0.76)	2.88 (0.83)
CV (%)	20.5	22.0	30.2	29.0
Geometric Mean (CV %)	3.06 (21.8)	3.07 (23.6)	2.41 (27.9)	2.77 (30.1)
90% CI for Geometric Mean	2.65, 3.54	2.59, 3.65	2.01, 2.90	2.27, 3.37
Median	3.00	3.00	2.00	3.00
Min, Max	2.00, 4.00	2.00, 4.00	2.00, 4.00	2.00, 4.00
Source: Section 14, Table 14.2.4.1.1 and Table 14.2.4.1.2				

Source: Table 9 of Study CL013-168 CSR
Abbreviations: λ_Z, elimination rate constant; $AUC_{0\text{-}6h}$, area under the curve from 0 to 6 hours; $AUC_{0\text{-}12h}$, area under the curve from 0 to 12 hours; AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; BID, twice daily; CI, confidence interval; C_{max}, maximum concentration; CV%, coefficient of variation; SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time to maximum concentration.

Table 90. Summary of Geometric Mean Ratios of Plasma M1 Pharmacokinetic Parameters (Study CL013_168)

Parameter	n	Mean (SE)	Geometric LS Mean (SE)[a]	% Ratio: 100*Hepatic Impairment/Healthy		CV (%)[a]
				Geometric LS Mean Ratio (SE)[a]	90% CI[a]	
$AUC_{0\text{-}inf}$ (h*ng/mL)						
Mild	8	972 (101)	936 (110)	1.1722 (0.1949)	0.8806, 1.5605	34.2
Moderate	8	995 (122)	943 (111)	1.1806 (0.1963)	0.8868, 1.5716	
Healthy	8	841 (100)	799 (93.9)			
AUC_{last} (h*ng/mL)						
Mild	8	843 (88.5)	813 (90.4)	1.2218 (0.1920)	0.9323, 1.6013	32.2
Moderate	8	818 (108)	776 (86.3)	1.1664 (0.1833)	0.8900, 1.5286	
Healthy	8	694 (74.3)	665 (74.0)			
C_{max} (ng/mL)						
Mild	8	48.550 (3.8624)	47.358 (4.5996)	0.9831 (0.1350)	0.7762, 1.2452	28.0
Moderate	8	42.038 (4.3888)	40.379 (3.9217)	0.8382 (0.1151)	0.6618, 1.0617	
Healthy	8	49.600 (4.2876)	48.172 (4.6786)			

a: From an ANOVA model on the log-transformed results with effect hepatic impairment group.
Source: Section 14, Table 14.2.4.2.1.

Source: Table 10 of Study CL013-168 CSR
Abbreviations: ANOVA, analysis of variance; AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; CI, confidence interval; C_{max}, maximum concentration; CV%, coefficient of variation; LS, least square; SE, standard error.

Table 91. Summary of Geometric Mean Ratios of Plasma M1 Pharmacokinetic Parameters (Excluding Subject (b) (6)) (Study CL013_168)

Parameter	n	Mean (SE)	Geometric LS Mean (SE)[a]	% Ratio: 100*Hepatic Impairment/Healthy		CV (%)[a]
				Geometric LS Mean Ratio (SE)[a]	90% CI[a]	
$AUC_{0\text{-}inf}$ (h*ng/mL)						
Mild	7	911 (92.7)	885 (109)	1.1072 (0.1874)	0.8269, 1.4826	33.6
Moderate	8	995 (122)	943 (109)	1.1806 (0.1931)	0.8904, 1.5653	
Healthy	8	841 (100)	799 (92.4)			
AUC_{last} (h*ng/mL)						
Mild	7	788 (79.9)	766 (88.8)	1.1518 (0.1828)	0.8760, 1.5144	31.4
Moderate	8	818 (108)	776 (84.1)	1.1664 (0.1788)	0.8954, 1.5193	
Healthy	8	694 (74.3)	665 (72.1)			
C_{max} (ng/mL)						
Mild	7	47.171 (4.1662)	45.984 (4.8169)	0.9546 (0.1369)	0.7454, 1.2225	28.3
Moderate	8	42.038 (4.3888)	40.379 (3.9565)	0.8382 (0.1162)	0.6600, 1.0645	
Healthy	8	49.600 (4.2876)	48.172 (4.7201)			

a: From an ANOVA model on the log-transformed results with effect hepatic impairment group.
Source: Section 14, Table 14.2.4.2.2.

Source: Table 11 of Study CL013-168 CSR
Abbreviations: ANOVA, analysis of variance; AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; CI, confidence interval; C_{max}, maximum concentration; CV%, coefficient of variation; LS, least square; SE, standard error.

Conclusions:

Following a single oral 30 mg dose of avacopan, the C_{max} and AUC_{last} of avacopan in subjects with mild or moderate hepatic impairment are generally comparable to healthy subjects.

Following a single oral 30 mg dose of avacopan, the C_{max}, AUC_{last}, and AUC_{inf} of avacopan metabolite M1 in subjects with mild or moderate hepatic impairment are generally comparable to healthy subjects.

17.3.1.2.6. PK Study in Japanese and Caucasian Healthy Males

Trial # CCX1101

Title: A phase I clinical study of CCX168 in Japanese and Caucasian healthy adult males

Study period: 23 October 2017-26 January 2018

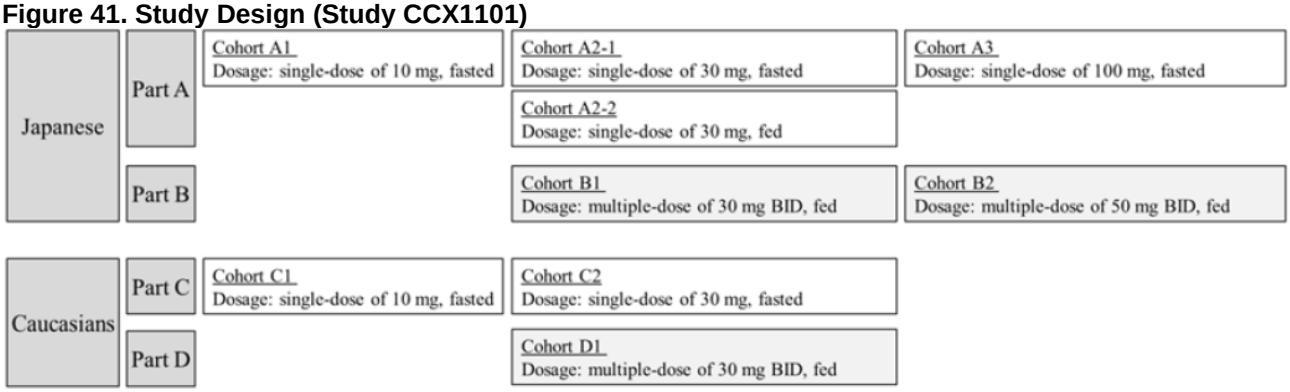
Objective:

- To investigate the safety and PK of a single dose and BID dose of CCX168 in Japanese healthy adult males
- To compare the PK of CCX168 in Japanese and Caucasian healthy adult males

Study design: This study consisted of 4 parts:

- Part A: A randomized, single-blind, placebo-controlled, single-dose study in 30 Japanese subjects. Study drug was orally administered to Cohort A2-2 with 200 mL of water 30 minutes after commencing breakfast. At least 14 days of washout period was placed between Cohorts A2-1 and A2-2.
- Part B: A randomized, single-blind, placebo-controlled, multiple-dose study in 20 Japanese subjects. The study drug was orally administered BID (12-hour interval) with 200 mL of water 30 minutes after commencing breakfast and dinner.
- Part C: A randomized, single-blind, placebo-controlled, single-dose study in 20 Caucasian subjects.
- Part D: A randomized, single-blind, placebo-controlled, multiple-dose study in 10 Caucasian subjects. The study drug was orally administered with 200 mL of water 30 minutes after commencing breakfast and dinner.

Figure 41. Study Design (Study CCX1101)



Source: Figure 9-1 of Study CCX1101 CSR

Test product: CCX168 capsule (10 mg): a hard gelatin capsule containing 10 mg of CCX168 (Lot Number: 3158127)

Sampling Schedule:

Parts A and C (single dose): Blood samples were collected predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72 hours and Day 8 (follow-up).

Parts B and D (multiple dose):

- Day 1: predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18 hours
- Days 2 to 6: predose and 12 hours
- Day 7: predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 35, 48, 72, 168 hours

Results: The PK results of CCX168 and M1 following single or multiple doses of CCX168 were shown as below.

CCX168

Table 92. Plasma PK Parameters of Avacopan After a Single Dose of 10 mg, 30 mg, and 100 mg Avacopan (Study CCX1101)

	10 mg (fasted)		30 mg (fasted)		30 mg (fed)	100 mg (fasted)
PK Parameter	Japanese (n=8)	Caucasians (n=8)	Japanese (n=8)	Caucasians (n=8)	Japanese (n=8)	Japanese (n=8)
C_{max} (ng/mL)	37.5 (27.1, 49.6)	39.5 (28.5, 55.9)	122.5 (65.5, 188.0)	113.3 (76.8, 209.0)	132.7 (63.3, 215.0)	515.4 (386.0, 623.0)
t_{max} (hr) [a]	1.50 (1.00, 3.00)	1.50 (1.00, 2.00)	1.50 (1.00, 2.00)	2.00 (1.50, 2.50)	2.50 (1.50, 3.00)	2.00 (1.50, 3.00)
$AUC_{0-\infty}$ (ng*hr/mL)	117.3 (78.0, 228.3)	130.2 (81.3, 240.3)	607.3 (296.2, 1046.4)	648.3 (329.4, 1068.3)	1279.6 (590.0, 1947.5)	4036.1 (2454.0, 5410.7)
$t_{1/2}$ (hr)	3.89 (2.17, 6.25)	4.47 (1.64, 6.36)	39.36 (11.72, 61.31)	41.58 (10.64, 83.26)	99.08 (39.84, 214.40)	80.52 (66.34, 100.52)
CL/F (L/hr)	85.3 (43.8, 128.2)	76.8 (41.6, 122.9)	49.4 (28.7, 101.3)	46.3 (28.1, 91.1)	23.5 (15.4, 50.9)	24.8 (18.5, 40.8)
V_z/F (L)	478.8 (318, 817)	495.2 (291, 697)	2805.2 (1712, 3890)	2776.3 (1398, 4060)	3351.3 (2417, 5367)	2878.2 (2264, 4353)

Source: Table 14.2-5 and Table 14.2-7
Data are expressed as geometric mean (min, max).
[a] t_{max} is presented as median (min, max).
Source: Table 11-2 of Study CCX1101 CSR
Abbreviations: $AUC_{0-\infty}$, area under the curve from zero to infinity; CL/F, apparent systemic clearance; C_{max}, maximum concentration; PK, pharmacokinetics; $t_{1/2}$, half-life; t_{max}, time to maximum concentration; Vz/F, apparent central volume of distr bution.

Table 93. PK Parameters of Avacopan After a Single Dose of Avacopan 30 mg Under Fed or Fasted Conditions (Study CCX1101)

		Two-Sided 90% Confidence Interval	
Parameter	Ratio [a]	Lower	Upper
C_{max} (ng/mL)	1.08	0.96	1.22
$AUC_{0-\infty}$ (ng*hr/mL)	2.11	1.92	2.32
AUC_{0-tz} (ng*hr/mL)	1.93	1.85	2.02

Source: Table 14.2-11
Data are adjusted geometric mean ratio (90% CI).
[a] Ratio (fed/fasted) of adjusted means of the parameters between fed and fasted conditions

Source: Table 11-8 of Study CCX1101 CSR
Abbreviations: $AUC_{0-\infty}$, area under the curve from zero to infinity; AUC_{0-z}, area under the curve from to the last quantifiable concentration; CI, confidence interval; C_{max}, maximum concentration; PK, pharmacokinetics.

Table 94. Plasma PK Parameters of Avacopan After Multiple Doses (Day 1) (Study CCX1101)

PK parameter	Japanese		Caucasians
	30 mg BID	50 mg BID	30 mg BID
	CCX168 (n=8)	CCX168 (n=8)	CCX168 (n=8)
C_{max} (ng/mL)	136.3 (109.0, 195.0)	200.6 (133.0, 263.0)	101.8 (65.0, 172.0)
t_{max} (hr) [a)]	2.50 (2.00, 4.00)	2.50 (2.00, 6.00)	2.50 (1.50, 4.00)
AUC_{τ} (ng*hr/mL)	624.4 (354.0, 858.2)	999.4 (835.6, 1066.1)	467.0 (326.9, 842.7)
$t_{1/2}$ (hr)	5.93 (4.19, 10.18)	7.30 (4.03, 11.89)	6.44 (4.28, 12.33)

Source: Table 14.2-6 and Table 14.2-8
Data are expressed as geometric mean (min, max).
[a)] t_{max} is presented as median (min, max).

Source: Table 11-3 of Study CCX1101 CSR
Abbreviations: $AUC_{0-\tau}$ = area under the curve to the last quantifiable time point; BID, twice daily; C_{max}, maximum concentration; PK, pharmacokinetics; $t_{1/2}$, half-life; t_{max}, time to maximum concentration.

Table 95. Plasma PK Parameters of Avacopan After Multiple Doses (Day 7) (Study CCX1101)

PK parameter	Japanese		Caucasians
	30 mg BID	50 mg BID	30 mg BID
	CCX168 (n=8)	CCX168 (n=8)	CCX168 (n=8)
C_{max} (ng/mL)	246.6 (169.0, 335.0)	464.3 (331.0, 623.0)	179.3 (144.0, 278.0)
t_{max} (hr) [a)]	2.75 (2.00, 4.00)	2.50 (2.00, 4.00)	2.50 (2.00, 3.00)
AUC_{tau} (ng*hr/mL)	1479.3 (711.5, 2335.2)	2717.5 (2032.9, 4423.9)	995.4 (803.2, 1604.7)
$t_{1/2}$ (hr)	146.89 (107.42, 194.59)	138.70 (95.51, 209.32)	149.14 (113.01, 225.80)
$R_{A,Cmax}$	1.81 (1.35, 2.56)	2.31 (1.28, 4.68)	1.76 (1.21, 2.35)
$R_{A,AUCtau}$	2.37 (1.90, 2.74)	2.72 (1.95, 4.37)	2.13 (1.82, 2.65)

Source: Table 14.2-6, Table 14.2-8, Table 14.2-9, and Table 14.2-10
Data are expressed as geometric mean (min, max).
[a)] t_{max} is presented as median (min, max).

Source: Table 11-4 of Study CCX1101 CSR
Abbreviations; AUC_{tau}, area under the curve during a dosing interval; BID, twice daily; C_{max}, maximum concentration; PK, pharmacokinetics; R_{AUC}, accumulation ratio of AUC; R_{cmax}, maximum observed concentration ratio; $t_{1/2}$, half-life; t_{max}, time to maximum concentration.

CCX168-M1

Table 96. Plasma PK Parameters of M1 After a Single Dose of Avacopan (Study CCX1101)

PK parameter	10 mg (fasted)		30 mg (fasted)		30 mg (fed)	100 mg (fasted)
	Japanese (n=8)	Caucasians (n=8)	Japanese (n=8)	Caucasians (n=8)	Japanese (n=8)	Japanese (n=8)
C_{max} (ng/mL)	17.6 (10.6, 21.9)	16.9 (13.3, 22.7)	54.6 (33.2, 69.6)	41.4 (30.7, 53.2)	32.8 (19.8,53.0)	169.0 (151.0, 193.0)
t_{max} (hr) [a]	1.75 (1.50, 3.00)	2.00 (1.50, 2.50)	2.25 (2.00, 2.50)	2.50 (2.00, 3.00)	3.00 (2.50,4.00)	2.50 (2.00, 4.00)
$AUC_{0-\infty}$ (ng*hr/mL)	146.1 (107.5, 275.4)	173.2 (136.4, 260.6)	594.8 (291.5, 923.3)	492.5 (331.8, 740.5)	665.3 (399.2,1041.7)	2568.5 (1729.1, 3258.6)
$t_{1/2}$ (hr)	15.40 (11.09, 24.94)	24.57 (16.71, 42.61)	30.07 (18.62, 46.12)	27.71 (13.97, 54.81)	43.08 (29.51,70.93)	40.08 (25.53, 55.46)
MR, C_{max}	0.47 (0.39, 0.59)	0.43 (0.36, 0.51)	0.45 (0.37, 0.51)	0.37 (0.19, 0.51)	0.25 (0.20, 0.31)	0.33 (0.26, 0.43)
MR, $AUC_{0-\infty}$	1.25 (0.96, 1.66)	1.33 (0.92, 2.04)	0.98 (0.86, 1.20)	0.76 (0.47, 1.01)	0.52 (0.39, 0.68)	0.64 (0.54, 0.70)

Source: Table 14.2-5 and Table 14.2-7
Data are expressed as geometric mean (min, max).
[a] t_{max} is presented as median (min, max).
Source: Table 11-5 of Study CCX1101 CSR
Abbreviations: $AUC_{0-\infty}$, area under the curve from zero to infinity; BID, twice daily; C_{max}, maximum concentration; MR, metabolic ratio; PK, pharmacokinetics; $t_{1/2}$, half-life; t_{max}, time to maximum concentration.

Table 97. PK Parameters of M1 After a Single Dose of Avacopan 30 mg Under Fed or Fasted Conditions (Study CCX1101)

Parameter	Ratio [a]	Two-Sided 90% Confidence Interval	
		Lower	Upper
C_{max} (ng/mL)	0.60	0.55	0.66
$AUC_{0-\infty}$ (ng*hr/mL)	1.12	1.03	1.21
AUC_{0-tz} (ng*hr/mL)	1.11	1.01	1.21

Source: Table 14.2-11
Data are adjusted geometric mean ratio (90% CI).
[a] Ratio (fed/fasted) of adjusted means of the parameters between fed and fasted conditions
Source: Table 11-9 of Study CCX1101 CSR
Abbreviations: $AUC_{0-\infty}$, area under the curve from zero to infinity; AUC_{0-z}, area under the curve from to the last quantifiable concentration; CI, confidence interval; C_{max}, maximum concentration; PK, pharmacokinetics.

Table 98. Plasma PK Parameters of M1 After Multiple Doses of Avacopan (Day 1) (Study CCX1101)

PK parameter	Japanese		Caucasians
	30 mg BID	50 mg BID	30 mg BID
	CCX168 (n=8)	CCX168 (n=8)	CCX168 (n=8)
C_{max} (ng/mL)	36.7 (31.2, 47.2)	55.1 (33.9, 61.9)	29.8 (25.2, 35.2)
t_{max} (hr) [a]	2.50 (2.00, 4.00)	3.50 (2.50, 6.00)	3.50 (2.00, 4.00)
AUC_{τ} (ng*hr/mL)	246.4 (186.0, 301.2)	388.3 (289.1, 476.4)	193.5 (159.3, 242.4)
$t_{1/2}$ (hr)	13.51 (8.69, 18.98)	15.41 (11.33, 24.72)	12.34 (8.55, 20.02)
MR, C_{max}	0.27 (0.21, 0.39)	0.28 (0.23, 0.37)	0.29 (0.20, 0.40)
MR, AUC_{τ}	0.40 (0.29, 0.54)	0.39 (0.29, 0.47)	0.41 (0.29, 0.59)

Source: Table 14.2-6 and Table 14.2-8
Data are expressed as geometric mean (min, max).
[a] t_{max} is presented as median (min, max).
Source: Table 11-6 of Study CCX1101 CSR
Abbreviations: $AUC_{0-\tau}$, area under the curve to the last quantifiable time point; BID, twice daily; C_{max}, maximum concentration; MR, metabolic ratio; PK, pharmacokinetics; $t_{1/2}$, half-life; t_{max}, time to maximum concentration.

Table 99. Plasma PK Parameters of M1 After Multiple Doses of Avacopan (Day 7) (Study CCX1101)

PK parameter	Japanese		Caucasians
	30 mg BID	50 mg BID	30 mg BID
	CCX168 (n=8)	CCX168 (n=8)	CCX168 (n=8)
C_{max} (ng/mL)	79.9 (61.1, 98.9)	130.8 (108.0, 155.0)	56.1 (44.3, 77.4)
t_{max} (hr) [a]	4.00 (2.50, 4.00)	4.00 (2.50, 6.00)	4.00 (3.00, 4.00)
AUC_{τ} (ng*hr/mL)	700.1 (448.9, 890.5)	1207.1 (956.7, 1550.4)	489.1 (381.3, 670.2)
$t_{1/2}$ (hr)	63.63 (57.54, 69.62)	64.99 (49.81, 93.67)	63.38 (54.11, 75.13)
$R_{A,Cmax}$	2.18 (1.79, 3.05)	2.37 (1.98, 3.78)	1.88 (1.61, 2.31)
$R_{A,AUC\tau}$	2.84 (2.41, 3.56)	3.11 (2.54, 4.54)	2.53 (2.19, 3.10)
MR, C_{max}	0.32 (0.27, 0.41)	0.28 (0.21, 0.38)	0.31 (0.28, 0.37)
MR, AUC_{τ}	0.47 (0.38, 0.63)	0.44 (0.30, 0.52)	0.49 (0.42, 0.57)

Source: Table 14.2-6, Table 14.2-8, Table 14.2-9, and Table 14.2-10
Data are expressed as geometric mean (min, max).
[a] t_{max} is presented as median (min, max).
Source: Table 11-7 of Study CCX1101 CSR
Abbreviations: $AUC_{0-\tau}$, area under the curve to the last quantifiable time point; BID, twice daily; C_{max}, maximum concentration; MR, metabolic ratio; PK, pharmacokinetics; $R_{AUC,}$, accumulation ratio of AUC; R_{cmax}, maximum observed concentration ratio; $t_{1/2}$, half-life; t_{max}, time to maximum concentration.

Conclusions:

- Following a single dose of 10 mg and 30 mg CCX168 under fasted condition, CCX168 and CCX168-M1 PK were generally comparable between Japanese and Caucasian subjects.
- After multiple doses of 30 mg CCX168, CCX168 and CCX168-M1 exposure appeared slightly higher in Japanese subjects than in Caucasian subjects
- Food intake increased CCX168 AUC by 111% but did not affect CCX168 C_{max}.
- Food intake did not affect CCX168-M1 AUC but reduced C_{max} by 40%.

17.3.1.2.7. Phase 2 Study

Trial # CL002_168

Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis on Background Cyclophosphamide or Rituximab Treatment

Study period: 27 September 2011- 18 January 2016

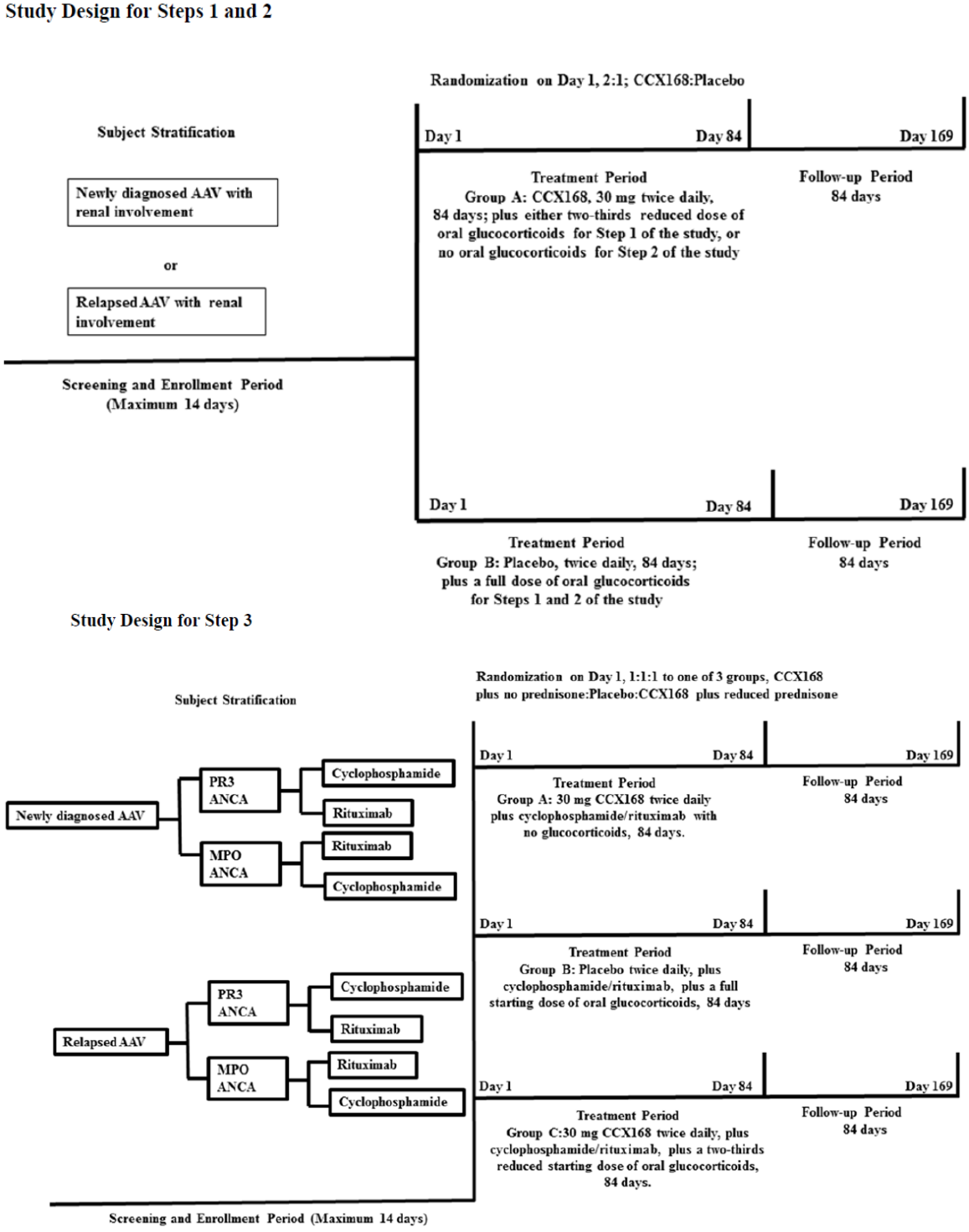
Objective: To evaluate the efficacy, safety, and tolerability of CCX168 in subjects with ANCA-associated vasculitis

Study design: This study was a randomized, double-blind, placebo-controlled, phase 2 clinical study to assess the safety, tolerability, and efficacy of CCX168 in subjects with ANCA-associated vasculitis (AAV) on background cyclophosphamide or rituximab treatment. To protect the blinding, a double-dummy design was utilized. The study included 3 steps as shown below. There were three groups in the study enrolling a total of 67 subjects, with a 12-week treatment period and a 12-week follow-up period:

- High dose prednisone standard of care group: These subjects received CCX168-matching placebo plus cyclophosphamide or rituximab plus a full starting dose of prednisone (60 mg per day for bodyweight ≥55 kg; 45 mg for bodyweight <55 kg)
- CCX168 plus low dose prednisone group: These subjects received CCX168 30 mg twice daily plus cyclophosphamide or rituximab plus a one-third starting dose of prednisone (20 mg per day for bodyweight ≥55 kg; 15 mg for bodyweight <55 kg)
- CCX168 plus no prednisone group: These subjects received CCX168 30 mg twice daily plus cyclophosphamide or rituximab plus prednisone-matching placebo

Up to 10 mg prednisone equivalent was allowed in all subjects when they entered the study and then this dose was to be tapered off over the following 6 weeks.

Figure 42. Study Design (Study CL002_168)



Source: Figures 1 and 2 of Study CL002_168 CSR
Abbreviations: AAV, ANCA-associated vasculitis; ANCA, anti-neutrophilic cytoplasmic antibody.

Test product: CCX168 capsule (10mg) (Lot# 101263249, B140015A, B140038, B150015, and 111308838)

Sampling Schedule:

Blood samples on Day 1 were collected just prior to the morning dose on that day, and at 0.5, 1, 2, 3, 4, and 6 hours following the morning dose. The date and time of the last dose prior to the sample collections on Days 8, 15, 22, 29, 43, 57, 71, and 85.

Results: The PK results were summarized as below.

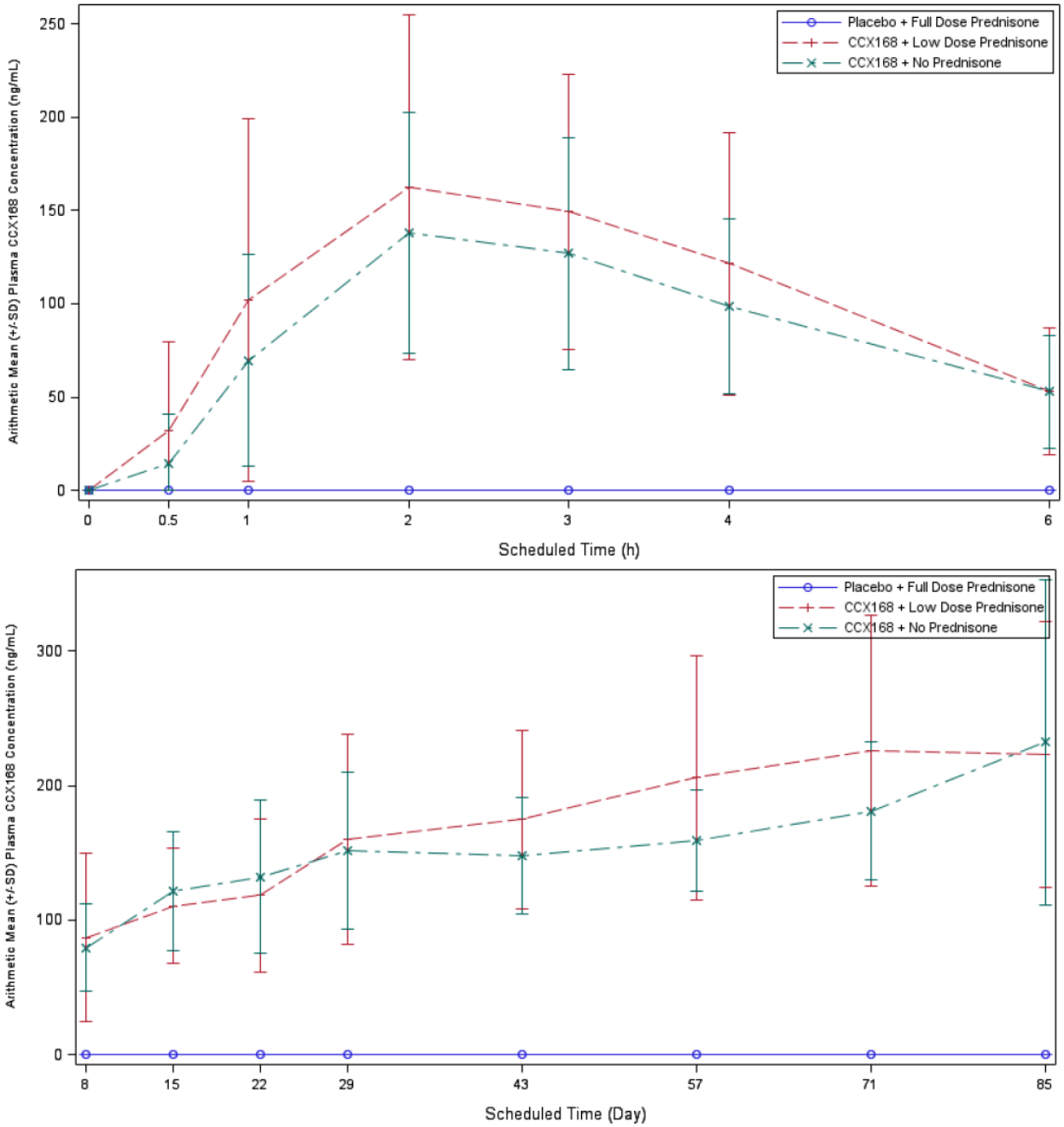
CCX168 PK

Table 100. Summarized Plasma Concentrations (ng/mL) and Derived PK Parameters for Avacopan (Study CL002_168)

	CCX168 + no dose of prednisone			CCX168 + low dose of prednisone			Placebo + full dose of prednisone		
Visit Description	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**
Day 1, pre-dose	0	0	22	0	0	21	0	0	23
Day 1, 0.5 hr post-dose	14.3	26.3	21	31.9	47.7	20	0	0	23
Day 1, 1 hr post-dose	69.7	56.9	21	102	97.1	20	0	0	22
Day 1, 2 hrs post-dose	138	64.5	21	163	92.3	20	0	0	21
Day 1, 3 hrs post-dose	127	62.4	21	149	73.5	20	0	0	9
Day 1, 4 hrs post-dose	98.4	46.8	21	121	70.6	19	0	0	9
Day 1, 6 hrs post-dose	52.8	30.5	21	52.9	33.9	19	0	0	10
Day 8	79.2	32.4	18	87.1	62.2	21	0	0	17
Day 15	122	44.3	18	110	42.7	19	0	0	20
Day 22	132	56.8	18	119	56.9	20	0	0	21
Day 29	152	58.2	17	160	78.1	21	0	0	19
Day 43	148	43.4	5	175	66.6	10	0	0	10
Day 57	159	38.0	6	206	90.5	10	0	0	8
Day 71	181	51.2	5	226	101	11	0	0	9
Day 85	232	121	16	223	98.7	17	0	0	17
PK Parameters									
Day 1 C_{max} (ng/mL)	166	55.2	21	214	76.2	18	0	0	9
Day 1 t_{max} (hr)	2.85	1.19	21	2.35	1.02	18	NA	NA	0
Day 1 AUC_{0-6} (ng•hr/mL)	526	174	21	643	253	18	0	0	9
Days 57 – 85 C_{min} (ng/mL)	177	44.8	5	219	96.8	9	0	0	7

Source: Table 10.2.1.1; Table 10.2.2; Table 10.2.3.1
Abbreviations: Day 1 AUC_{0-6} = area under the plasma concentration-time curve for the first 6 hours following the first dose on Day 1; Day 1 C_{max} = observed maximum (plasma) concentration on Day 1; Days 57 – 85 C_{min} = observed trough level plasma concentrations at post-Day 1 visits of Days 57 – 85; Day 1 t_{max} = time of observed maximum (plasma) concentration on Day 1; NA = not available; SD = standard deviation.
LLOQ of CCX168 = 1.00 ng/mL
Source: Table 3 of Study CL002_168 PK report
Abbreviations: C_{max}, maximum concentration C_{min}, minimum concentration; LLOQ, lower limit of quantification; PK, pharmacokinetics.

Figure 43. Mean Concentration – Time Profile of Avacopan Versus Nominal Elapsed Time on Day 1 (Top Panel) and Days 8 – 85 (Bottom Panel) (Study CL002_168)



Source: Figures 3 and 4 of Study CL002_168 PK report

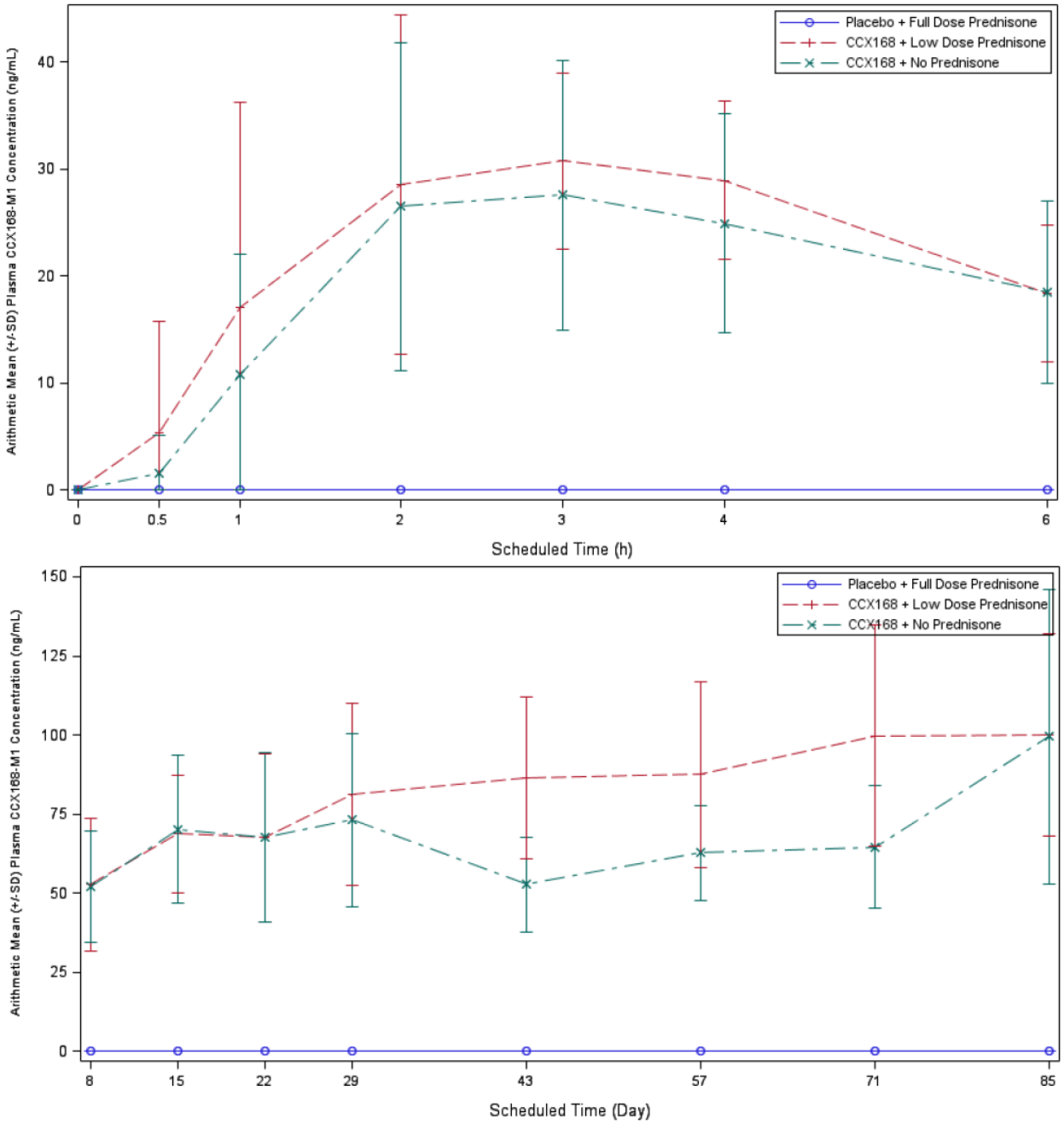
CCX168-M1 PK

Table 101. Summarized Plasma Concentrations (ng/mL) and Derived PK Parameters for M1 (Study CL002_168)

	CCX168 + no dose of prednisone			CCX168 + low dose of prednisone			Placebo + full dose of prednisone		
Visit Description	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**
Day 1, pre-dose	0	0	22	0	0	21	0	0	23
Day 1, 0.5 hr post-dose	1.53	3.58	21	5.33	10.4	20	0	0	23
Day 1, 1 hr post-dose	10.8	11.2	21	17.0	19.1	20	0	0	22
Day 1, 2 hrs post-dose	26.5	15.3	21	28.6	15.8	20	0	0	21
Day 1, 3 hrs post-dose	27.5	12.6	21	30.8	8.25	20	0	0	9
Day 1, 4 hrs post-dose	24.9	10.2	21	29.0	7.36	19	0	0	9
Day 1, 6 hrs post-dose	18.5	8.51	21	18.3	6.37	19	0	0	10
Day 8	51.9	17.5	18	52.6	21.0	21	0	0	17
Day 15	70.1	23.4	18	68.7	18.6	19	0	0	20
Day 22	67.7	26.8	18	67.5	26.5	20	0	0	21
Day 29	73.1	27.5	17	81.1	28.8	21	0	0	19
Day 43	52.8	15.0	5	86.6	25.6	10	0	0	10
Day 57	62.8	15.0	6	87.5	29.4	10	0	0	8
Day 71	64.5	19.3	5	99.7	35.0	11	0	0	9
Day 85	99.4	46.4	16	100	32.0	17	0	0	17
PK Parameters									
Day 1 C_{max} (ng/mL)	33.5	13.1	21	37.3	9.63	18	0	0	9
Day 1 t_{max} (hr)	3.04	1.22	21	2.75	0.990	18	NA	NA	0
Day 1 AUC_{0-6} (ng•hr/mL)	119	44.0	21	137	42.7	18	0	0	9
Days 57 – 85 C_{min} (ng/mL)	63.0	17.1	5	94.5	31.6	9	0	0	7

Source: Table 10.2.1.1; Table 10.2.2; Table 10.2.3.1
Abbreviations: Day 1 AUC_{0-6} = area under the plasma concentration-time curve for the first 6 hours following the first dose on Day 1; Day 1 C_{max} = observed maximum (plasma) concentration on Day 1; Days 57 – 85 C_{min} = observed trough level plasma concentrations at post-Day 1 visits of Days 57 – 85; Day 1 t_{max} = time of observed maximum (plasma) concentration on Day 1; NA = not available; SD = standard deviation.
LLOQ of CCX168-M1 = 1.00 ng/mL
Source: Table 6 of Study CL002_168 PK report
Abbreviations: C_{max}, maximum concentration; C_{min}, minimum concentration; LLOQ, lower limit of quantification; PK, pharmacokinetics.

Figure 44. Mean Concentration – Time Profile of M1 Versus Nominal Elapsed Time on Day 1 (Top Panel) and Days 8 – 85 (Bottom Panel) (Study CL002_168)



Source: Figures 5 and 6 of Study CL002_168 PK report

Exposure to Prednisone and Prednisolone in Plasma

Table 102. Summarized Plasma Concentrations (ng/mL) of Prednisone (Study CL002_168)

	CCX168 + no dose of prednisone			CCX168 + low dose of prednisone			Placebo + full dose of prednisone		
Visit Description	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**
Day 1, pre-dose	0.983	3.68	14	2.80	9.20	14	0.362	1.30	13
Day 1, 0.5 hr post-dose	3.48	8.73	13	3.83	9.23	13	1.69	4.20	13
Day 1, 1 hr post-dose	4.14	8.91	13	8.44	10.5	13	13.3	13.0	12
Day 1, 2 hrs post-dose	4.83	9.47	13	12.6	10.1	12	26.1	12.4	12
Day 1, 3 hrs post-dose	6.44	10.5	13	18.1	9.60	12	28.8	9.04	12
Day 1, 4 hrs post-dose	4.29	8.56	13	17.2	9.17	11	29.4	9.33	12
Day 1, 6 hrs post-dose	6.16	10.4	13	15.4	7.68	11	29.8	9.62	12
Day 8	0	0	14	1.12	4.19	14	4.47	6.33	12
Day 15	1.96	7.32	14	0.265	0.918	12	0.508	1.24	12
Day 22	2.02	7.56	14	0	0	14	0.852	1.28	12
Day 29	0	0	12	0.154	0.575	14	0.297	0.986	11
Day 43	0	0	7	0.371	1.28	12	0.960	1.56	10
Day 57	0	0	7	0	0	11	0.223	0.670	9
Day 71	0	0	7	1.33	4.97	14	2.25	7.10	10
Day 85	0	0	12	0	0	12	1.15	2.27	11

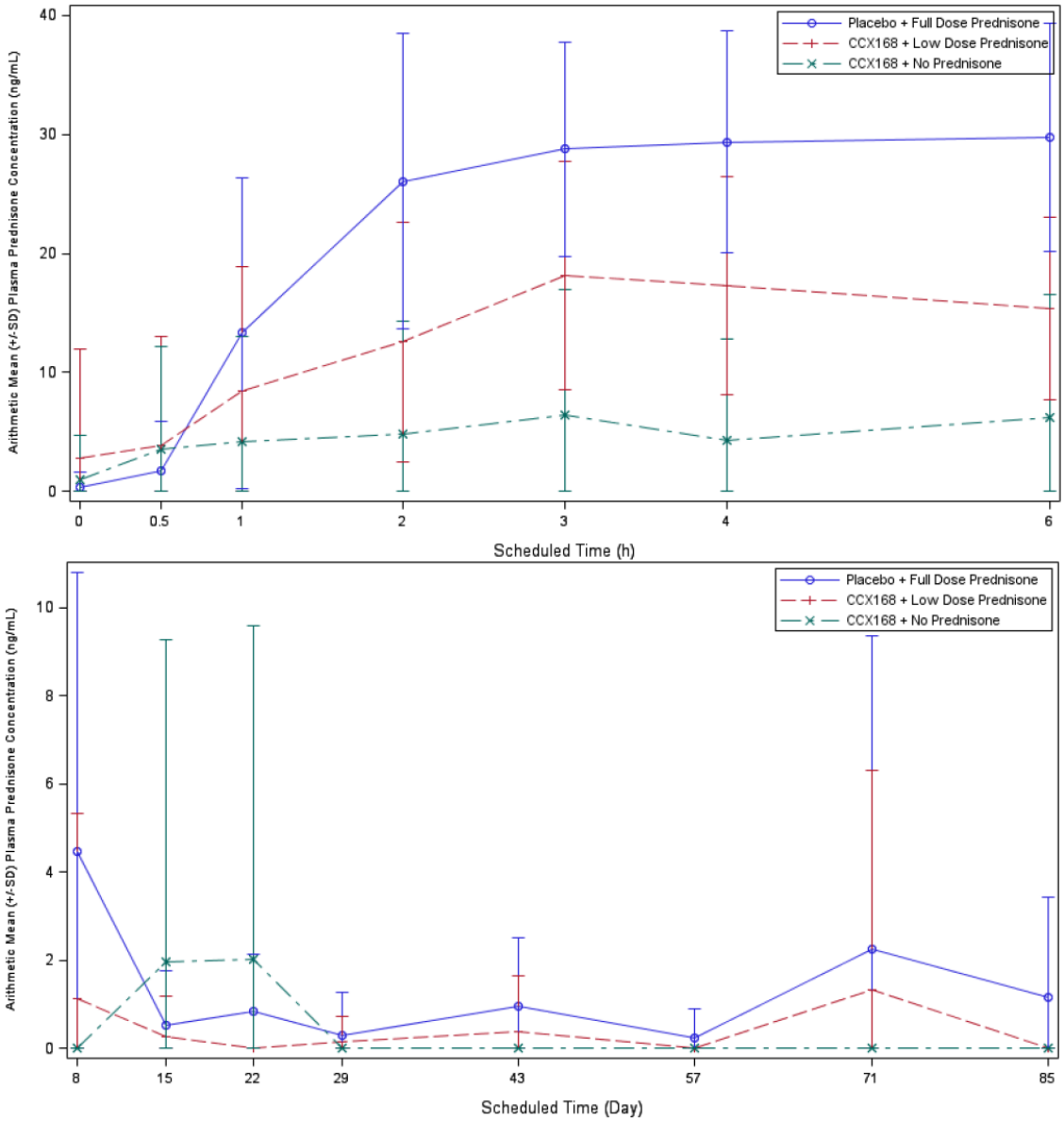
Source: Table 10.2.1.2; Table 10.2.3.2
Abbreviation: SD = standard deviation.
LLOQ of Prednisone = 2.00 ng/mL
Source: Table 11 of Study CL002_168 PK report
Abbreviations: LLOQ, lower limit of quantification.

Table 103. Summarized Plasma Concentrations (ng/mL) of Prednisolone (Study CL002_168)

	CCX168 + no dose of prednisone			CCX168 + low dose of prednisone			Placebo + full dose of prednisone		
Visit Description	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**
Day 1, pre-dose	43.2	155	14	64.1	221	14	3.59	13.0	13
Day 1, 0.5 hr post-dose	64.1	157	13	90.2	193	13	42.6	87.1	13
Day 1, 1 hr post-dose	74.2	154	13	180	197	13	278	200	12
Day 1, 2 hrs post-dose	90.8	194	13	290	210	12	575	243	12
Day 1, 3 hrs post-dose	136	255	13	332	123	12	575	155	12
Day 1, 4 hrs post-dose	64.5	137	13	299	119	11	545	140	12
Day 1, 6 hrs post-dose	95.4	183	13	212	85.1	11	445	84.6	12
Day 8	0.826	3.09	14	21.1	47.4	14	70.8	112	12
Day 15	40.0	147	14	7.67	10.3	12	15.2	13.2	12
Day 22	42.5	155	14	4.35	5.71	14	15.9	12.8	12
Day 29	0.493	1.71	12	2.66	5.17	14	13.6	10.9	11
Day 43	0	0	7	6.00	9.83	12	16.8	16.1	10
Day 57	0	0	7	1.66	3.76	11	8.31	9.96	9
Day 71	0	0	7	24.4	89.9	14	27.9	64.2	10
Day 85	0	0	12	0.444	1.54	12	10.4	15.4	11

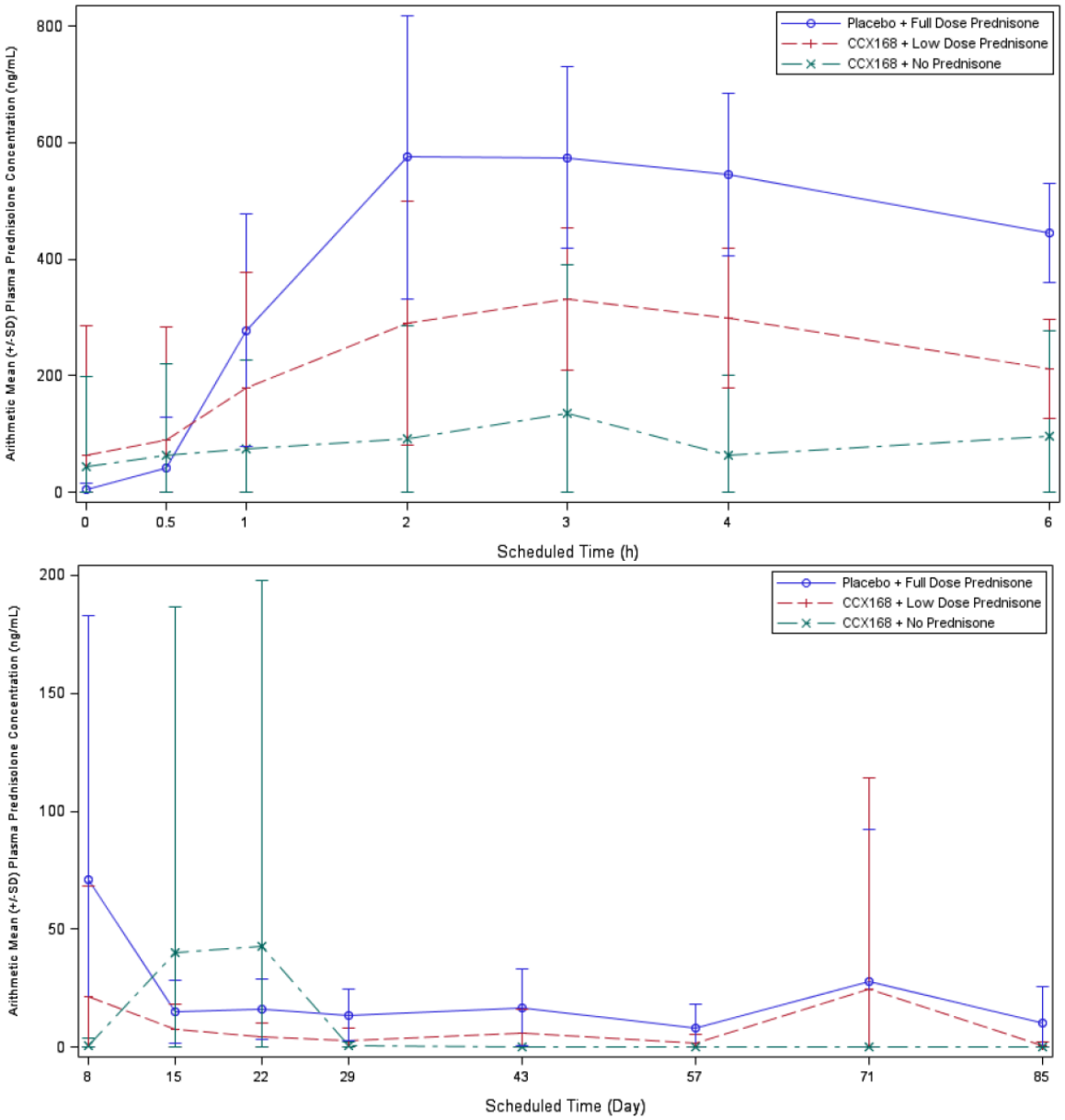
Source: Table 10.2.1.2; Table 10.2.3.2
Abbreviation: SD = standard deviation.
LLOQ of Prednisolone = 5.00 ng/mL
Source: Table 12 of Study CL002_168 PK report
Abbreviations: LLOQ, lower limit of quantification.

Figure 45. Mean ± SD Concentration – Time Profile of Prednisone Versus Time on Day 1 (Top Panel) and Days 8 – 85 (Bottom Panel) in Linear Scales (Study CL002_168)



Source: Figure 7 of Study CL002_168 PK report
Abbreviations: SD, standard deviation.

Figure 46. Mean ± SD Concentration – Time Profile of Prednisolone Versus Time on Day 1 (Top Panel) and Days 8 – 85 (Bottom Panel) in Linear Scales (Study CL002_168)



Source: Figure 8 of Study CL002_168 PK report
Abbreviations: SD, standard deviation.

Conclusions:

Following the administration of an oral dose of 30 mg of CCX168 BID in subjects with AAV without prednisone or with a low dose of prednisone on background cyclophosphamide or

rituximab treatment, the mean plasma trough concentrations of CCX168 and metabolite CCX168-M1 continuously increased.

Reviewer's comments

Prednisone is a CYP3A4 substrate, and a CYP3A4 inhibitor such as avacopan may increase the exposure of prednisone. In Study CL002_168, prednisone and prednisolone concentrations were measured using validated LC/MS assays. Since the CYP3A4 inhibitory effect of avacopan may not be reflected at early timepoint yet, PK comparison on Day 1 may not be informative. During Days 8-85, since prednisone and prednisolone concentrations in most of subjects could not be accurately quantified (below the lower limit of quantification (LLOQ)), prednisone and prednisolone exposure could not be adequately compared among treatment groups (Table 105 and Table 105).

Table 104. The Number of Subjects With Prednisone Concentration Below the LLOQ (2 ng/mL) During Days 8-85 in Study CL002_168

Treatment Arm	Day 8	Day 15	Day 22	Day 29	Day 43	Day 57	Day 71	Day 85
Avacopan 30mg BID + low dose pred.	13/14	11/12	14/14	13/14	11/12	11/11	13/14	12/12
Avacopan 30mg BID + no pred.	14/14	13/14	13/14	12/12	7/7	7/7	7/7	12/12
High dose pred.+ SOC	4/12	10/12	8/12	10/11	7/10	8/9	9/10	8/11

Source: Reviewer analysis
Abbreviations: BID, twice daily; LLOQ, lower limit of quantification; Pred, prednisone; SOC, standard of care.

Table 105. The Number of Subjects With Prednisolone Concentration Below the LLOQ (5 ng/mL) During Days 8-85 in Study CL002_168

Treatment arm	Day 8	Day 15	Day 22	Day 29	Day 43	Day 57	Day 71	Day 85
Avacopan 30mg BID + low dose pred.	3/14	5/12	7/14	10/14	7/12	9/11	12/14	11/12
Avacopan 30mg BID + no pred.	13/14	12/14	12/14	11/12	7/7	7/7	7/7	12/12
High dose pred. + SOC	0/12	2/12	0/12	1/11	0/10	4/9	2/10	6/11

Source: Reviewer analysis
Abbreviations: BID, twice daily; LLOQ, lower limit of quantification; Pred, prednisone; SOC, standard of care.

17.3.1.2.8. Phase 2 Dose-Ranging Study

Trial # CL003_168

Title: A Randomized, Double-Blind, Placebo-Controlled, Dose Assessment Phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects With Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis

Study period: 04 February 2015- 19 July 2016

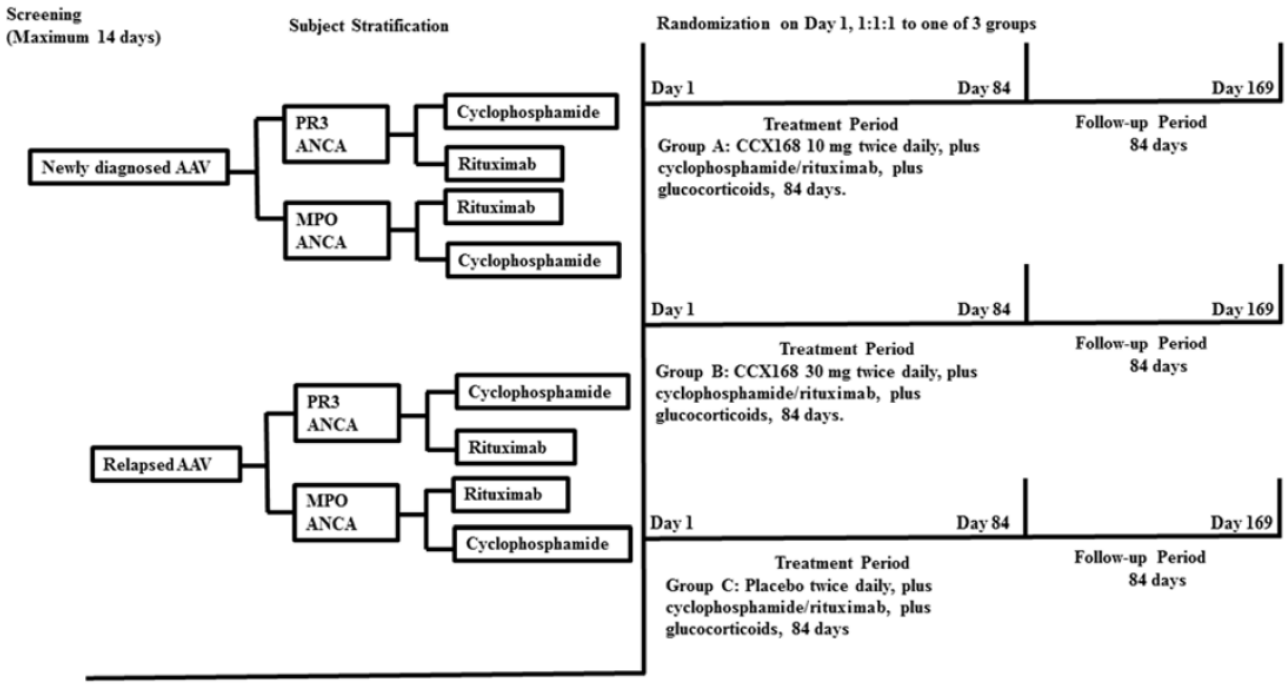
Objective: Efficacy, safety, PK

Study design: This study was a randomized, double-blind, placebo-controlled, phase 2 clinical study in subjects with new or relapsed AAV on background standard of care treatment. Up to ~45 subjects were randomized 1:1:1 to 1 of 3 groups:

- Group A: CCX168 10 mg twice daily plus cyclophosphamide/rituximab plus glucocorticoids,
- Group B: CCX168 30 mg twice daily plus cyclophosphamide/rituximab plus glucocorticoids, or
- Group C: Placebo twice daily plus cyclophosphamide/rituximab plus glucocorticoids.

If necessary, rescue glucocorticoids were to be given to subjects with worsening disease. All subjects were to receive prednisone 60 mg orally per day starting on Day 1 with a tapered dose, per protocol-specified schedule. Subjects in the cyclophosphamide stratum were to receive IV cyclophosphamide (15 mg/kg on Days 1, 15, 29, 57, and 85) as part of standard of care treatment and oral azathioprine (to a target dose of 2 mg/kg/day, starting on Day 99). Subjects in the rituximab stratum were to receive 375 mg/m2 rituximab IV once weekly for 4 weeks starting on Day 1. No oral azathioprine was to be given to subjects receiving rituximab.

Figure 47. Study Design (Study CL003_168)



Source: Figure 1 of Study CL003_168 CSR
Abbreviations: AAV, ANCA-associated vasculitis; ANCA, anti-neutrophilic cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase-3.

Test product: CCX168 capsules manufacturer's lot numbers: B140015A and B150015.

Sampling Schedule:

Plasma samples were collected on Days 1, 8, 15, 22, 29, 43, 57, 71, and 85. The blood samples on Day 1 were collected just prior to the morning dose on that day, and at 0.5, 1, 2, 3, 4, and 6 hours following the morning dose.

Plasma concentrations of CCX168 and potential metabolites, cyclophosphamide and its metabolites, rituximab, prednisone, and prednisolone were measured in these samples.

Results: The PK results were summarized as below.

CCX168 PK

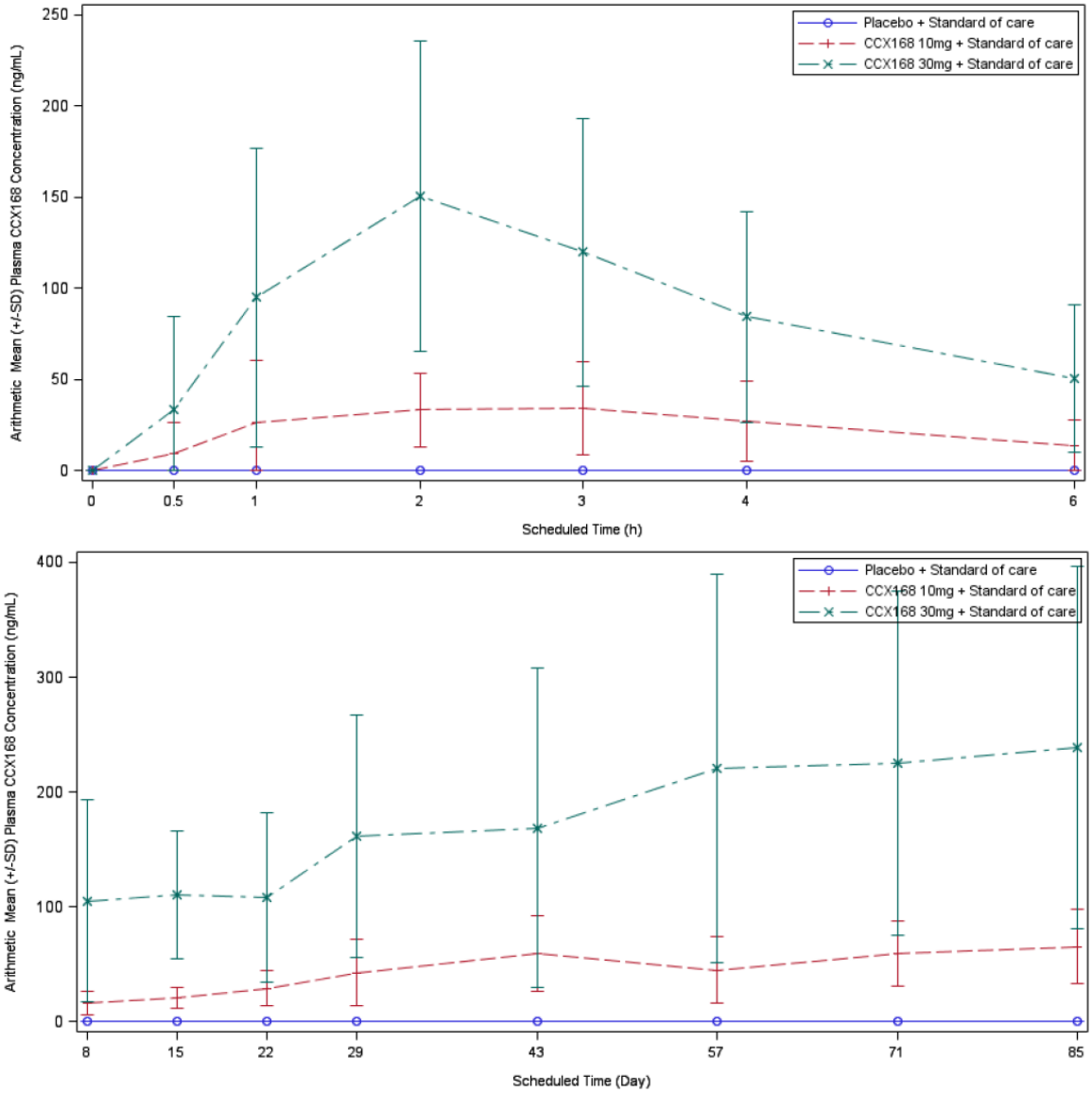
Table 106. Summarized Plasma Concentrations (ng/mL) and Derived PK Parameters for Avacopan (Study CL003_168)

	CCX168 10 mg BID			CCX168 30 mg BID			Placebo		
Visit Description	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**
Day 1, pre-dose	0	0	13	0	0	16	0	0	13
Day 1, 0.5 hr post-dose	9.59	16.7	13	33.2	51.0	15	0	0	13
Day 1, 1 hr post-dose	26.2	33.8	13	94.9	81.7	16	0	0	13
Day 1, 2 hr post-dose	33.1	20.1	13	151	85.4	16	0	0	12
Day 1, 3 hr post-dose	34.0	25.7	13	120	73.4	15	0	0	12
Day 1, 4 hr post-dose	27.0	21.8	13	84.5	57.9	15	0	0	11
Day 1, 6 hr post-dose	13.5	14.1	13	50.5	40.5	15	0	0	11
Day 8	15.9	10.1	11	105	87.7	15	0	0	12
Day 15	20.9	9.12	10	111	55.6	12	0	0	11
Day 22	28.7	15.2	12	108	74.0	13	0	0	12
Day 29	42.5	28.9	8	161	106	10	0	0	9
Day 43	59.4	32.9	6	169	139	10	0	0	10
Day 57	44.8	28.8	6	220	169	11	0	0	9
Day 71	59.3	28.0	10	225	150	10	0	0	9
Day 85	65.4	32.0	7	238	158	12	0	0	9
PK Parameters									
Day 1 C_{max} (ng/mL)	51.2	32.0	13	177	92.0	15	0	0	11
Day 1 t_{max} (hr)	2.31	0.855	13	1.81	0.687	15	NA	NA	0
Day 1 AUC_{0-6} (ng•hr/mL)	146	79.7	13	542	257	15	0	0	11
Days 57 – 85 C_{min} (ng/mL)	56.3	32.6	5	223	159	9	0	0	7

Source: Table 10.2.1.1; Table 10.2.2; Table 10.2.3.1
Abbreviations: BID = twice daily; Day 1 AUC_{0-6} = area under the plasma concentration-time curve for the first 6 hours following the first dose on Day 1; Day 1 C_{max} = observed maximum (plasma) concentration on Day 1; Days 57 – 85 C_{min} = observed trough level plasma concentrations at post-Day 1 visits of Days 57 – 85; Day 1 t_{max} = time of observed maximum (plasma) concentration on Day 1; NA = not available; SD = standard deviation.
LLOQ of CCX168 = 1.00 ng/mL

Source: Table 3 of Study CL003_168 PK report
Abbreviations: BID, twice daily; C_{max}, maximum concentration C_{min}, minimum concentration; LLOQ, lower limit of quantification; PK, pharmacokinetics; t_{max}, time to maximum concentration.

Figure 48. Mean ± SD Concentration – Time Profile of Avacopan Versus Time on Day 1 (Top Panel) and Days 8-85 (Bottom Panel) (Study CL003_168)



Source: Adapted from Figured 3 and 4 of Study CL003_168 PK report
Abbreviations: SD, standard deviation.

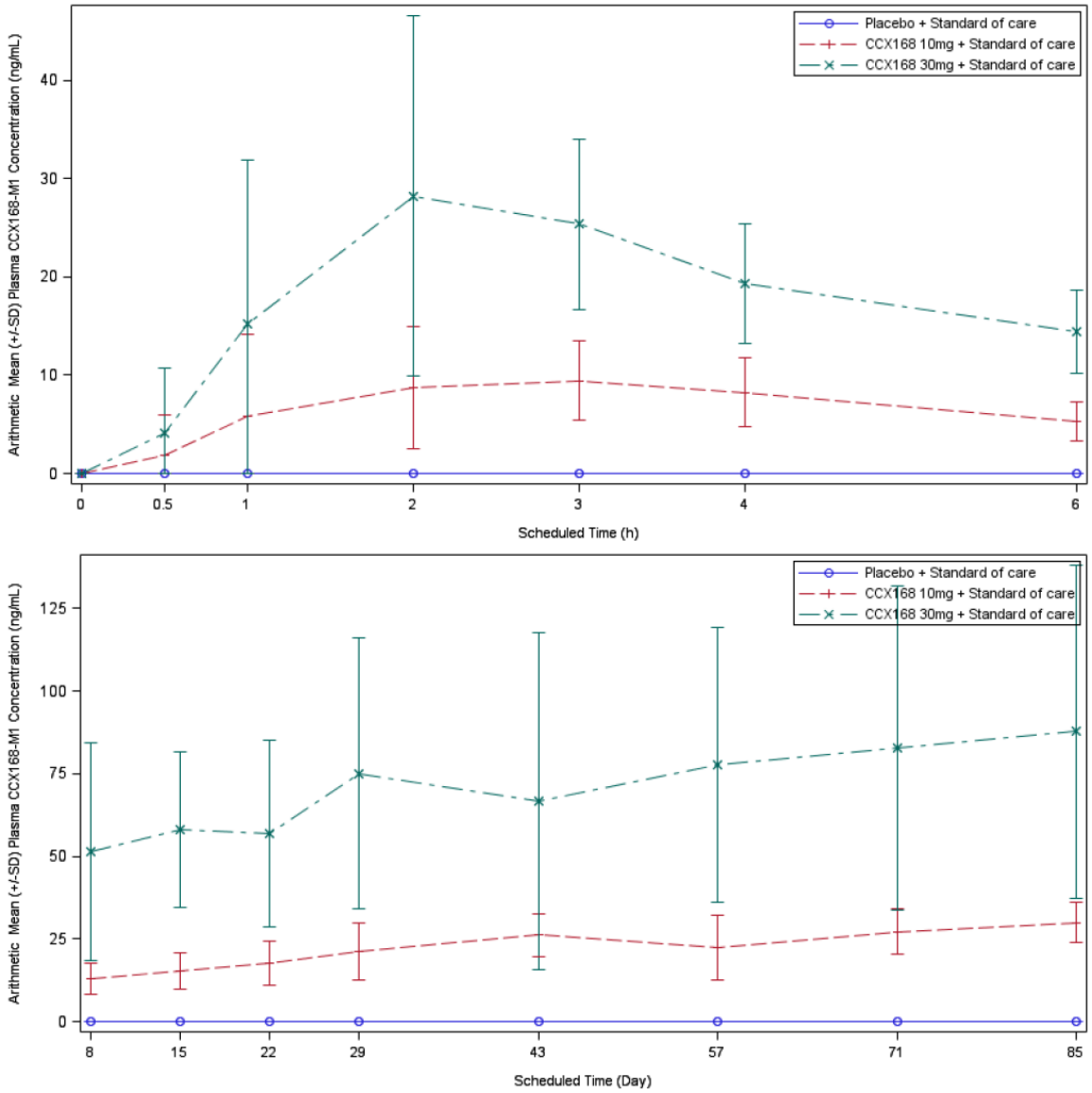
CCX168-M1 PK

Table 107. Summarized Plasma Concentrations (ng/mL) and Derived PK Parameters for M1 (Study CL003_168)

	CCX168 10 mg BID			CCX168 30 mg BID			Placebo		
Visit Description	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**
Day 1, pre-dose	0	0	13	0	0	16	0	0	13
Day 1, 0.5 hr post-dose	1.86	4.10	13	4.10	6.61	15	0	0	13
Day 1, 1 hr post-dose	5.86	8.29	13	15.3	16.6	16	0	0	13
Day 1, 2 hr post-dose	8.77	6.19	13	28.2	18.3	16	0	0	12
Day 1, 3 hr post-dose	9.46	4.00	13	25.3	8.62	15	0	0	12
Day 1, 4 hr post-dose	8.24	3.52	13	19.4	6.08	15	0	0	11
Day 1, 6 hr post-dose	5.26	1.99	13	14.4	4.23	15	0	0	11
Day 8	13.1	4.68	11	51.4	32.8	15	0	0	12
Day 15	15.5	5.56	10	58.1	23.4	12	0	0	11
Day 22	17.6	6.72	12	56.9	28.2	13	0	0	12
Day 29	21.2	8.59	8	75.1	40.8	10	0	0	9
Day 43	26.2	6.44	6	66.8	51.0	10	0	0	10
Day 57	22.5	9.88	6	77.6	41.5	11	0	0	9
Day 71	27.3	6.88	10	82.7	49.0	10	0	0	9
Day 85	30.0	6.21	7	87.8	50.3	12	0	0	9
PK Parameters									
Day 1 C_{max} (ng/mL)	12.1	6.12	13	31.6	17.7	15	0	0	11
Day 1 t_{max} (hr)	2.85	1.07	13	2.54	1.19	15	NA	NA	0
Day 1 AUC_{0-6} (ng•hr/mL)	41.2	18.9	13	112	46.1	15	0	0	11
Days 57 – 85 C_{min} (ng/mL)	27.4	8.42	5	76.1	45.5	9	0	0	7

Source: Table 10.2.1.1; Table 10.2.2; Table 10.2.3.1
Abbreviations: BID = twice daily; Day 1 AUC_{0-6} = area under the plasma concentration-time curve for the first 6 hours following the first dose on Day 1; Day 1 C_{max} = observed maximum (plasma) concentration on Day 1; Days 57 – 85 C_{min} = observed trough level plasma concentrations at post-Day 1 visits of Days 57 – 85; Day 1 t_{max} = time of observed maximum (plasma) concentration on Day 1; NA = not available; SD = standard deviation.
LLOQ of CCX168-M1 = 1.00 ng/mL
Source: Table 4 of Study CL003_168 PK report
Abbreviations: BID, twice daily; C_{max}, maximum concentration C_{min}, minimum concentration; LLOQ, lower limit of quantification; PK, pharmacokinetics; t_{max}, time to maximum concentration.

Figure 49. Mean ± SD Concentration – Time Profile of M1 Versus Time on Day 1 (Top Panel) and Days 8-85 (Bottom Panel) (Study CL003_168)



Source: Adapted from Figured 5 and 6 of Study CL003_168 PK report
Abbreviations: SD, standard deviation.

Exposure to Prednisone and Prednisolone in Plasma

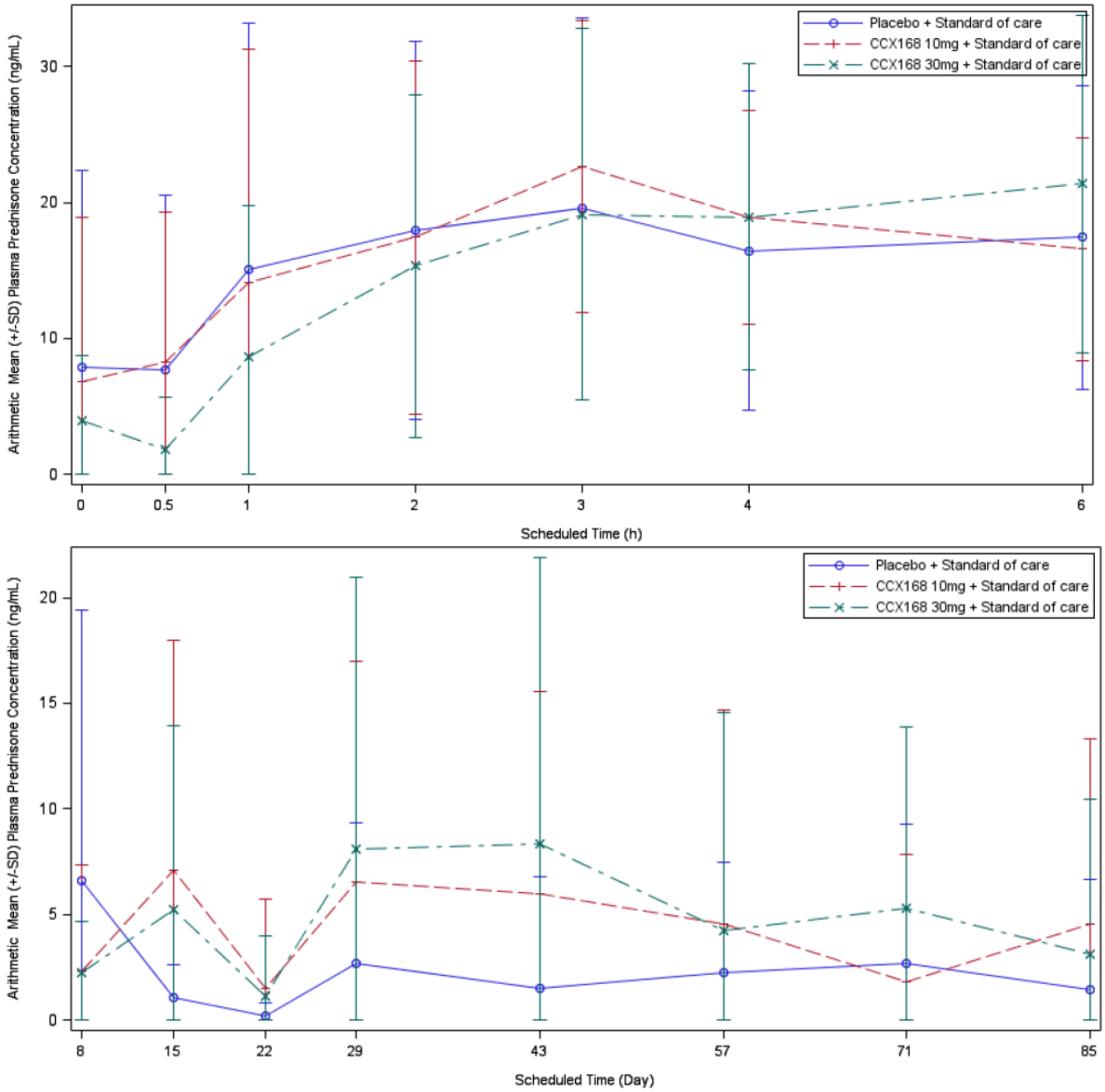
Table 108. Summarized Plasma Concentrations (ng/mL) of Prednisone (Study CL003_168)

	CCX168 10 mg BID			CCX168 30 mg BID			Placebo		
Visit Description	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**
Day 1, pre-dose	6.79	12.1	13	3.99	4.70	16	7.92	14.4	13
Day 1, 0.5 hr post-dose	8.24	11.0	13	1.81	3.84	15	7.64	12.9	13
Day 1, 1 hr post-dose	14.1	17.2	13	8.66	11.1	16	15.0	18.2	13
Day 1, 2 hr post-dose	17.5	13.0	13	15.3	12.6	16	18.0	13.9	12
Day 1, 3 hr post-dose	22.6	10.7	13	19.1	13.7	15	19.5	14.1	12
Day 1, 4 hr post-dose	18.9	7.88	13	18.9	11.3	15	16.4	11.7	11
Day 1, 6 hr post-dose	16.6	8.23	13	21.4	12.4	15	17.4	11.1	11
Day 8	2.34	5.03	12	2.25	2.39	16	6.57	12.8	13
Day 15	7.12	10.9	13	5.22	8.74	16	1.08	1.56	11
Day 22	1.51	4.24	13	1.12	2.84	16	0.180	0.624	12
Day 29	6.54	10.5	13	8.07	12.9	16	2.68	6.66	13
Day 43	6.00	9.58	13	8.32	13.6	14	1.48	5.32	13
Day 57	4.55	10.1	12	4.22	10.4	15	2.23	5.28	13
Day 71	1.82	6.05	11	5.28	8.60	14	2.69	6.58	13
Day 85	4.58	8.74	11	3.11	7.35	16	1.45	5.24	13

Source: Table 10.2.1.2; Table 10.2.3.2
Abbreviations: BID = twice daily; SD = standard deviation.
LLOQ of Prednisone = 2.00 ng/mL

Source: Table 5 of Study CL003_168 PK report
Abbreviations: LLOQ, lower limit of quantification.

Figure 50. Mean ± SD Concentration – Time Profile of Prednisone Versus Time on Day 1 (Top Panel) and Days 8 – 85 (Bottom Panel) in Linear Scales (Study CL003_168)



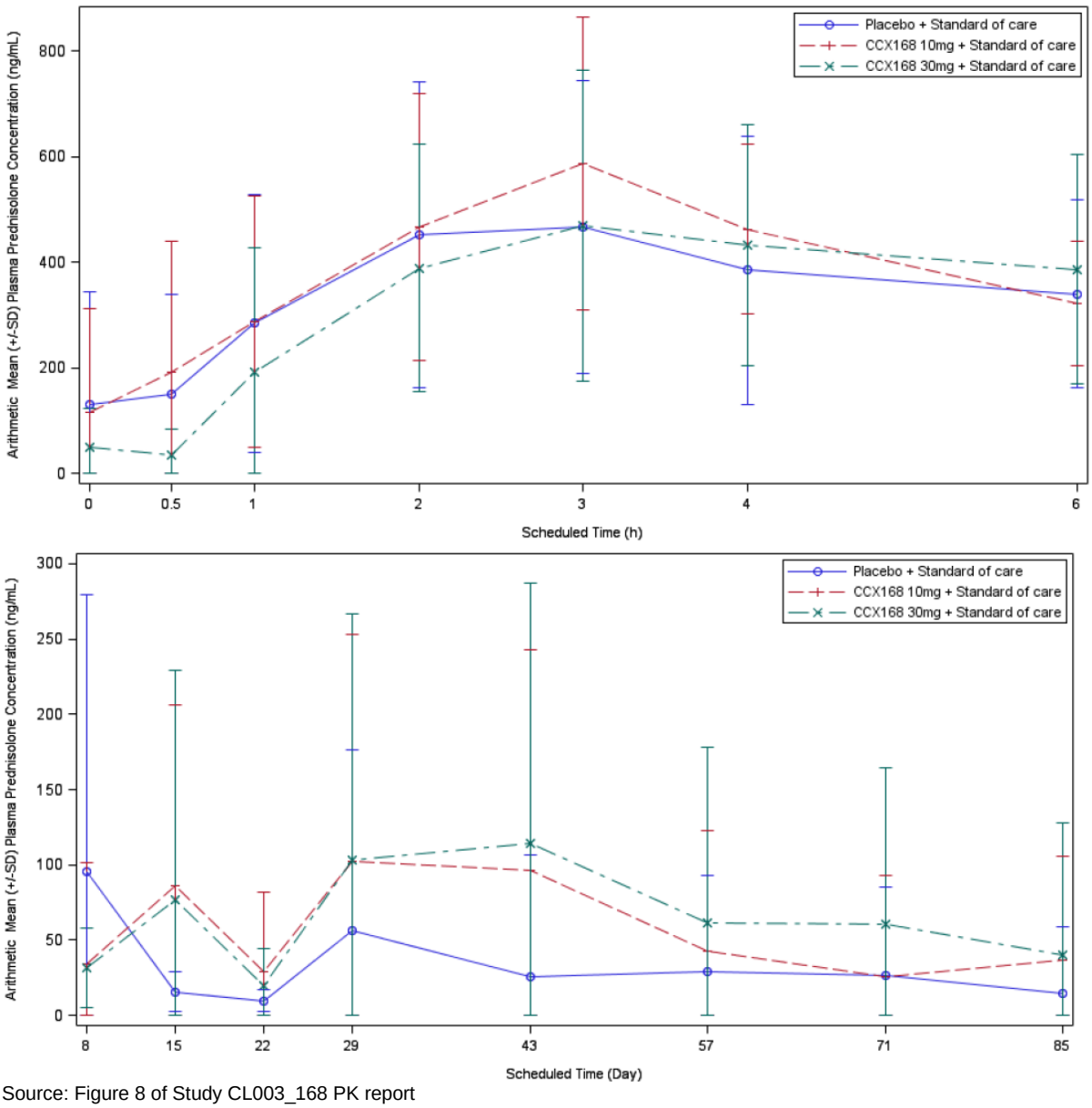
Source: Figure 7 of Study CL003_168 PK report
Abbreviations: SD, standard deviation.

Table 109. Summarized Plasma Concentrations (ng/mL) of Prednisolone (Study CL003_168)

	CCX168 10 mg BID			CCX168 30 mg BID			Placebo		
Visit Description	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**
Day 1, pre-dose	116	196	13	50.3	73.5	16	129	215	13
Day 1, 0.5 hr post-dose	193	247	13	33.9	50.1	15	150	189	13
Day 1, 1 hr post-dose	288	238	13	191	236	16	284	245	13
Day 1, 2 hr post-dose	466	253	13	389	233	16	452	290	12
Day 1, 3 hr post-dose	587	277	13	470	295	15	466	278	12
Day 1, 4 hr post-dose	462	160	13	433	228	15	385	254	11
Day 1, 6 hr post-dose	322	118	13	386	217	15	339	178	11
Day 8	34.0	67.2	12	31.9	26.3	16	95.9	184	13
Day 15	85.9	120	13	76.5	153	16	15.6	13.2	11
Day 22	29.1	52.4	13	20.1	24.3	16	9.73	7.15	12
Day 29	102	151	13	104	163	16	56.3	120	13
Day 43	96.4	147	13	114	173	14	25.3	81.0	13
Day 57	42.6	80.1	12	61.3	117	15	28.9	64.0	13
Day 71	25.4	67.3	11	60.5	104	14	26.6	58.3	13
Day 85	37.1	68.7	11	40.0	87.9	16	14.8	44.0	13

Source: Table 10.2.1.2; Table 10.2.3.2
Abbreviations: BID = twice daily; SD = standard deviation.
LLOQ of Prednisolone = 5.00 ng/mL
Source: Table 6 of Study CL003_168 PK report
Abbreviations: BID, twice daily; LLOQ, lower limit of quantification; SD, standard deviation.

Figure 51. Mean ± SD Concentration – Time Profile of Prednisolone Versus Time on Day 1 (Top Panel) and Days 8 – 85 (Bottom Panel) in Linear Scales (Study CL003_168)



Source: Figure 8 of Study CL003_168 PK report
Abbreviations: SD, standard deviation.

Conclusions:

Following the administration of an oral dose of 10 or 30 mg of CCX168 BID in subjects with ANCA-AAV, plasma concentrations of CCX168 and CCX168-M1 gradually increased.

Reviewer's comments

Prednisone is a CYP3A4 substrate, and a CYP3A4 inhibitor such as avacopan may increase the exposure of prednisone. In Study CL003_168, prednisone and prednisolone concentrations were measured using validated LC/MS assays. Since the CYP3A4 inhibitory effect of avacopan may not be reflected at early timepoint yet, PK comparison on Day 1 may not be informative. During Days 8-85, since prednisone and prednisolone concentrations in most of subjects could not be accurately quantified (below LLOQ), prednisone and prednisolone exposure could not be adequately compared among treatment groups (Table 111 and Table 111).

Table 110. The Number of Subjects With Prednisone Concentration Below the LLOQ (2 ng/mL) During Days 8-85 in Study CL003_168

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

Source: Reviewer analysis
Abbreviations: BID, twice daily; LLOQ, lower limit of quantification.

Table 111. The Number of Subjects With Prednisolone Concentration Below the LLOQ (5 ng/mL) During Days 8-85 in Study CL003_168

Treatment Arm	Day 8	Day 15	Day 22	Day 29	Day 43	Day 57	Day 71	Day 85
Avacopan 10 mg BID	3/12	1/13	3/13	5/13	5/13	4/12	4/11	7/11
Avacopan 30 mg BID	1/16	2/16	3/16	2/16	2/14	4/15	5/14	13/16
Placebo	1/13	2/11	3/12	4/13	8/13	4/13	8/13	8/13

Source: Reviewer analysis
Abbreviations: BID, twice daily; LLOQ, lower limit of quantification.

17.3.1.2.9. Phase 3 study

Trial # CL010_168

Title: A Randomized, Double-Blind, Active-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of CCX168 (Avacopan) in Patients With Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Treated Concomitantly with Rituximab or Cyclophosphamide/Azathioprine

Study period: 15 March 2017- 01 November 2019

Objective: Efficacy, safety, PK

Study design: This was a Phase 3, randomized, double-blind, double-dummy, active-controlled, multicenter international clinical study (Figure 6). Patients were randomized (1:1 ratio) to one of two study treatment groups:

- Group A: Avacopan-matching placebo plus cyclophosphamide/azathioprine or rituximab plus a full starting dose of prednisone (prednisone group)

- Group B: Avacopan (30 mg BID) plus cyclophosphamide/azathioprine or rituximab plus prednisone-matching placebo (avacopan group).

Test product: CCX168 capsules (10 mg), lot numbers: 3150014, 3158126, 3147444, 3164319, 3158127

Sampling Schedule: PK plasma samples were collected from all subjects on Day 1, and Weeks 1, 2, 4, 7, 13, 26, 39, and 52 of the study.

Results

Plasma trough concentrations (Ctrough) of avacopan and metabolite M1 for post-Day 1 visits are summarized by background medications as below.

Table 112. Summary of Plasma Trough Pharmacokinetic Concentrations of Avacopan for Post-Day 1 Visits by Background Medication (Study CL010_168)

Statistics	Scheduled Visit (Week)								Global Steady State Trough[1]
	1	2	4	7	13	26	39	52	
Avacopan (ng/mL)									
Rituximab (N = 94)									
n	68	69	53	43	59	52	40	40	34
Mean (SD)	87.5 (43.9)	124 (65.6)	179 (89.4)	187 (77.6)	235 (106)	262 (115)	269 (139)	298 (218)	272 (117)
Median	80.3	114	161	176	219	258	244	259	246
GM (GM CV%)	78.4 (51.0)	109 (57.5)	156 (64.0)	165 (70.8)	213 (48.5)	236 (50.0)	214 (113)	193 (220)	248 (45.3)
Cyclophosphamide (N = 48)									
n	29	33	37	32	33	28	23	22	21
Mean (SD)	72.5 (30.8)	118 (53.3)	144 (58.8)	187 (92.2)	217 (112)	234 (131)	244 (178)	222 (150)	228 (122)
Median	65.3	105	139	194	220	221	222	196	204
GM (GM CV%)	67.4 (39.8)	108 (45.7)	128 (61.6)	158 (80.1)	178 (103)	187 (99.6)	195 (78.1)	167 (106)	200 (56.4)
Overall (Rituximab and Cyclophosphamide Combined) (N = 142)									
n	97	102	90	75	92	80	63	62	55
Mean (SD)	83.0 (40.8)	122 (61.7)	164 (79.9)	187 (83.5)	229 (108)	252 (121)	260 (153)	271 (199)	255 (120)
Median	74.9	110	148	186	220	238	235	241	236
GM (GM CV%)	74.9 (48.2)	109 (53.6)	144 (63.7)	162 (74.2)	200 (69.7)	217 (69.3)	207 (99.6)	183 (174)	229 (50.5)

Note: The allowable time window for PK sampling was ± 3 hours (i.e. 25% of dosing interval of 12 hours). If the exact time (measured from dosing) was outside of the collection window, the compliance was outside of 80-120% range, or there was no dosing time, the corresponding concentration was excluded from trough concentration summary and mean plot preparation, but is still used in the individual plots. N is the total subject number. n is the subject number with values for specified visit.
[1] Global average steady state trough concentration was derived from the individual steady state troughs of all subjects in each treatment. Individual steady state troughs were calculated using trough concentrations from Week 13 to Week 52 for each subject.
CV = coefficient of variation; GM = geometric mean; NC = not calculable; PK = pharmacokinetic; SD = standard deviation.
Source data: Post-text Table 14.2.2.2 and Table 14.2.2.3

Source: Table 7 of Study CL010_168 PK report

Table 113. Summary of Plasma Trough Pharmacokinetic Concentrations of Metabolite M1 for Post-Day 1 Visits by Background Medication (Study CL010_168)

Statistics	Scheduled Visit (Week)								Global Steady State Trough[1]
	1	2	4	7	13	26	39	52	
Metabolite M1 (ng/mL)									
Rituximab (N = 94)									
n	68	69	53	43	59	52	40	38	34
Mean (SD)	51.5 (22.0)	66.0 (28.1)	83.6 (38.7)	81.4 (33.7)	99.3 (38.2)	105 (46.4)	105 (50.2)	110 (55.6)	106 (38.8)
Median	46.0	58.0	69.8	73.5	99.9	97.0	104	109	104
GM (GM CV%)	47.3 (43.6)	59.9 (51.9)	73.4 (68.0)	70.6 (80.8)	92.2 (41.1)	95.0 (47.5)	83.9 (122)	92.6 (76.3)	99.8 (37.6)
Cyclophosphamide (N = 48)									
n	29	33	37	32	33	28	23	22	21
Mean (SD)	46.5 (17.9)	63.1 (22.9)	68.1 (26.5)	74.1 (30.2)	89.5 (40.1)	93.3 (44.9)	88.4 (42.4)	85.4 (44.1)	88.8 (34.0)
Median	43.1	62.2	65.2	67.6	83.6	86.8	83.6	85.8	89.2
GM (GM CV%)	43.3 (40.7)	59.2 (37.6)	60.3 (68.7)	64.8 (77.7)	75.1 (102)	77.3 (94.7)	78.9 (54.2)	72.3 (73.3)	82.9 (40.1)
Overall (Rituximab and Cyclophosphamide Combined) (N = 142)									
n	97	102	90	75	92	80	63	60	55
Mean (SD)	50.0 (20.9)	65.1 (26.4)	77.3 (34.9)	78.3 (32.2)	95.8 (39.0)	101 (45.9)	99.3 (47.9)	101 (52.6)	99.6 (37.7)
Median	45.0	60.1	69.4	72.4	92.1	93.5	95.4	96.4	91.3
GM (GM CV%)	46.1 (42.7)	59.7 (47.4)	67.7 (68.8)	68.1 (79.0)	85.7 (65.8)	88.4 (65.8)	82.1 (97.1)	84.5 (75.9)	93.0 (39.4)

Note: The allowable time window for PK sampling was ± 3 hours (i.e. 25% of dosing interval of 12 hours). If the exact time (measured from dosing) was outside of the collection window, the compliance was outside of 80-120% range, or there was no dosing time, the corresponding concentration was excluded from trough concentration summary and mean plot preparation, but is still used in the individual plots. N is the total subject number. n is the subject number with values for specified visit.
[1] Global average steady state trough concentration was derived from the individual steady state troughs of all subjects in each treatment. Individual steady state troughs were calculated using trough concentrations from Week 13 to Week 52 for each subject.
CV = coefficient of variation; GM = geometric mean; NC = not calculable; PK = pharmacokinetic; SD = standard deviation.
Source data: Post-text Table 14.2.2.2 and Table 14.2.2.3

Source: Table 7 of Study CL010_168 PK report

Conclusions:
Following avacopan 30 mg BID dosing, the steady state appeared to be reached by Week 13 based on the observed Ctrough of avacopan.

17.3.2. Bioanalytical Summary

Avacopan and the active metabolite M1 concentrations in human plasma samples have been measured using fully validated high performance liquid chromatographic separation with tandem mass spectrometric (LC-MS/MS) assays in clinical pharmacology studies, except Study CL001_168 (Table 114, Table 115, Table 116, Table 117, Table 118, Table 119, Table 120, Table 121). All clinical samples were analyzed within the established stability period.

Table 114. List of LC-MS/MS Bioanalytical Methods for the Analysis of Avacopan or Metabolite M1 in Clinical Plasma Samples

Method Validation Report		ChemoCentryx/CRO Method ID	Analytes	Quantification Range	Clinical Study Using the Method	Type of Clinical Study	Study Duration (Days)
ChemoCentryx Study ID	CRO Study ID						
CLCCX1_168	NA	TM-004	Avacopan	0.2 – 100 ng/mL	CL001_168	Phase 1	29 Days
CLCCX2_168	NA	TM-011	Avacopan, M1	1 – 500 ng/mL (avacopan); 1 – 500 ng/mL (M1)	CL002_168 (Steps 1&2)	Phase 2	169 Days
					CL004_168	Phase 1	29 Days
CL-CEY-W9-383(R3)	CEY-W9-383(R3)	LAS-1716	Avacopan, M1	1 – 500 ng/mL (avacopan); 1 – 500 ng/mL (M1)	CL002_168 (Step 3)	Phase 2	169 Days
					CL003_168	Phase 2	169 Days
					CL007_168	Phase 1	14 Days
					CL008_168	Phase 1	29 Days
					CL010_168	Phase 3	421 Days
					CL014_168	Phase 1	28 Days
CL-CEY-W2-587	CEY-W2-587	LAS-1960	Avacopan, M1	0.2 – 100 ng/mL (avacopan); 1 – 100 ng/mL (M1)	CL013_168	Phase 1	18 Days
_*	CB171377	_*	Avacopan, M1	1 – 500 ng/mL (avacopan); 1 – 500 ng/mL (M1)	CCX1101	Phase 1	14 Days

*No number assigned.
Source: Table 3 of Summary of Biopharmaceutic Studies and Associated Analytical Methods
Abbreviations: LC-MS/MS: Liquid chromatographic separation with tandem mass spectrometric

Table 115. Validation Summary for Avacopan (Report CEY-W9-383 (R3))

Analytical Validation Report	CEY-W9-383(R3)	
Short description of method	Protein precipitation Reverse-phase HPLC with MS/MS detection	
Biological matrix	Human plasma	
Analyte	CCX168	
Internal standard (IS)	CCX168-d4	
Calibration concentrations	1.00 ng/mL to 500.00 ng/mL.	
QC concentrations	1.00 ng/mL, 3.00 ng/mL, 50.00 ng/mL, 250.00 ng/mL and 375.00 ng/mL.	
Specificity	No significant interference observed in the 6 blank matrix lots screened.	
Specificity in the presence of concomitantly administered compounds[1]	No significant interference observed.	
Carryover	No significant carryover observed.	
Lower limit of quantification	1.00 ng/mL Between-run accuracy 94.8% Between-run precision 9.1% Within-runs accuracy: Batches CEY383.03, CEY383.05 and CEY383.10: 84.9% - 100.6% Within-runs precision: Batches CEY383.03, CEY383.05 and CEY383.10: 2.8% - 6.8%	
Between-run accuracy	94.8% - 98.1%	
Between-run precision	2.4% -9.1%	
Within-runs accuracy	Batches CEY383.03, CEY383.05 and CEY383.10: 84.9% - 100.9%	
Within-runs precision	Batches CEY383.03, CEY383.05 and CEY383.10: 1.6% - 6.8%	
Largest batch size	180 injections	
Matrix Factor (MF) IS normalized MF C.V.% of IS normalized MF	Low QC Mean Analyte MF: 1.1145 Mean IS MF: 1.0960 Mean IS-Normalized: 1.0169 % C.V.: 1.8	High QC Mean Analyte MF: 1.1189 Mean IS MF: 1.1064 Mean IS-Normalized: 1.0112 % C.V.: 0.6
Dilution integrity	2000.00 ng/mL diluted 10-fold. Accuracy (% nominal): 93.8% Precision: 3.3%	
Recovery of analyte (P.E.Y.)	100.4% - 104.2%	
Recovery of IS (P.E.Y.)	106.1%	

[1]Refer to section 5.2.3.

Short-term stability of the stock solution and working solutions (Observed change %)	Confirmed up to 51.5 hours for CCX168 in DMSO at 200.00 µg/mL at 22°C nominal. % deviation: -1.2%. Confirmed up to 25.0 hours for CCX168 in MeOH:DMSO 75:25% v/v at 50000.00 ng/mL at 22°C nominal. % deviation: 0.6%. Confirmed up to 28.5 hours for CCX168 in MeOH:DMSO 75:25% v/v at 100.00 ng/mL at 22°C nominal. % deviation: -3.0%. Confirmed up to 23.8 hours for CCX168-d4 in DMSO at 100.00 µg/mL at 22°C nominal. % deviation: -2.5%. Confirmed up to 20.7 hours for CCX168-d4 in MeOH:DMSO 75:25% v/v at 10.00 µg/mL at 22°C nominal. % deviation: 1.1%.
Long-term stability of the stock solution and working solutions (Observed change %)	Confirmed up to 151 days for CCX168 in DMSO at 200.00 µg/mL at 4°C nominal. % deviation: 4.5%. Confirmed up to 154 days for CCX168 in MeOH:DMSO 75:25% v/v at 50000.00 ng/mL at 4°C nominal. % deviation: 4.5%. Confirmed up to 151 days for CCX168 in MeOH:DMSO 75:25% v/v at 100.00 ng/mL at 4°C nominal. % deviation: 0.1%. Confirmed up to 414 days for CCX168-d4 in DMSO at 100.00 µg/mL at 4°C nominal. % deviation: -1.0%. Confirmed up to 151 days for CCX168-d4 in MeOH:DMSO 75:25% v/v at 10.00 µg/mL at 4°C nominal. % deviation:2.5% Confirmed up to 146 days for CCX168-d4 in Cold ACN:MeOH 90:10% v/v at 60.00 ng/mL at 4°C nominal. % deviation: 4.1%.

Short-term stability in biological matrix at room temperature or at sample processing temperature. (Observed change %)	Confirmed up to 25.9 hours at 4°C nominal. Accuracy (% nominal): 102.1% for Low QCs and 99.9% for High QCs. Confirmed up to 23.3 hours at 4°C nominal in presence of Prednisone, Prednisolone Cyclophosphamide and 4-Ketocyclophosphamide. Accuracy (% nominal): 109.5% for Low QCs and 105.0% for High QCs. Confirmed up to 23.3 hours at 4°C nominal in presence of Prednisone, Prednisolone and Rituximab. Accuracy (% nominal): 112.7% for Low QCs and 104.2% for High QCs. Confirmed up to 24.3 hours at 4°C nominal in presence of Midazolam, α-Hydroxymidazolam, Celecoxib, Itraconazole and Rifampicin. Accuracy (% nominal): 101.8% for Low QCs and 94.6% for High QCs.[1]
Stability in whole blood	Confirmed up to 2.0 hours in an ice/water bath. % deviation: -0.4% for Low QCs and -1.7% for High QCs. Confirmed up to 3.0 hours at 22°C nominal and when centrifuged at 22°C nominal. % deviation: -2.6% for Low QCs and -4.4% for High QCs. Confirmed up to 3.0 hours in an ice/water bath and when centrifuged at 22°C nominal. % deviation: -1.4% for Low QCs and -3.6% for High QCs. Confirmed up to 3.0 hours in an ice/water bath (with tubes holders pre-chilled at -20°C nominal for 12 minutes) and when centrifuged at 22°C nominal. % deviation: -3.8% for Low QCs and -3.0% for High QCs. Confirmed up to 3.0 hours in an ice/water bath (with tubes holders pre-chilled at 4°C nominal for 1.1 hour) and when centrifuged at 22°C nominal. % deviation: -1.2% for Low QCs and -3.7% for High QCs.

[1] This evaluation was performed under validation project CEY-W0-774.

Freeze and thaw stability (Observed change %)	5 cycles. Accuracy (% nominal): 101.7% for Low QCs and 99.8% for High QCs. 4 cycles in presence of Prednisone, Prednisolone Cyclophosphamide and 4-Ketocyclophosphamide. Accuracy (% nominal): 106.5% for Low QCs and 101.4% for High QCs. 4 cycles in presence of Prednisone, Prednisolone and Rituximab. Accuracy (% nominal): 110.4% for Low QCs and 99.8% for High QCs. 4 cycles in presence of Midazolam, α-Hydroxymidazolam, Celecoxib, Itraconazole and Rifampicin. Accuracy (% nominal): 97.6% for Low QCs and 93.8% for High QCs.[1]
Autosampler storage stability (Observed change %)	Confirmed up to 139.5 hours at 4°C nominal. Accuracy (% nominal): 109.5% for Low QCs and 107.6% for High QCs.

[1] This evaluation was performed under validation project CEY-W0-774.

Long-term stability in biological matrix (Observed change %)	Confirmed up to 834 days at -80°C nominal using 3 QC sample tubes subjected to stability conditions. Accuracy (%Bias): -0.7% for Low Stability QC and 0.5% for High Stability QC.[1] Confirmed up to 750 days at -80°C nominal in presence of Prednisone, Prednisolone Cyclophosphamide and 4-Ketocyclophosphamide using 3 QC sample tubes subjected to stability conditions. Accuracy (% nominal): 96.2% for Low QCs and 91.5% for High QCs. Confirmed up to 752 days at -80°C nominal in presence of Prednisone, Prednisolone and Rituximab using 3 QC sample tubes subjected to stability conditions. Accuracy (% nominal): 95.1% for Low QCs and 90.1% for High QCs. Confirmed up to 221 days at -20°C nominal using 3 QC sample tubes subjected to stability conditions. Accuracy (% nominal): 97.4% for Low QCs and 99.3% for High QCs. Confirmed up to 742 days at -20°C nominal in presence of Prednisone, Prednisolone, Cyclophosphamide and 4-Ketocyclophosphamide using 3 QC sample tubes subjected to stability conditions. Accuracy (% nominal): 107.3% for Low QCs and 101.7% for High QCs. Confirmed up to 742 days at -20°C nominal in presence of Prednisone, Prednisolone and Rituximab using 3 QC sample tubes subjected to stability conditions. Accuracy (% nominal): 107.0% for Low QCs and 99.3% for High QCs.
Partial validation	NA
Cross validation(s)	NA

[1] This evaluation was performed under project CEY-L4-962.

Source: Page 6 of Report CEY-W9-383 (R3)
Abbreviations: CV%, coefficient of variation; HPLC, high performance liquid chromatography; MS-MS; tandem mass spectrometer; NA, not applicable; QC quality control.

Table 116. Validation Summary for M1 (Report CEY-W9-383 (R3))

Analytical Validation Report	CEY-W9-383(R3)	
Short description of method	Protein precipitation Reverse-phase HPLC with MS/MS detection	
Biological matrix	Human plasma	
Analyte	CCX168-M1	
Internal standard (IS)	CCX168-d4	
Calibration concentrations	1.00 ng/mL to 500.00 ng/mL.	
QC concentrations	1.00 ng/mL, 3.00 ng/mL, 50.00 ng/mL, 250.00 ng/mL and 375.00 ng/mL	
Specificity	No significant interference observed in the 6 blank matrix lots screened.	
Specificity in the presence of concomitantly administered compounds[1]	No significant interference observed.	
Carryover	No significant carryover observed.	
Lower limit of quantification	1.00 ng/mL Between-run accuracy 100.9% Between-run precision 15.7% Within-runs accuracy: Batches CEY383.03, CEY383.05 and CEY383.10: 82.7% - 99.5% Within-runs precision: Batches CEY383.03, CEY383.05 and CEY383.10: 3.8% - 10.9%	
Between-run accuracy	94.6% - 100.9%	
Between-run precision	4.2% - 15.7%	
Within-runs accuracy	Batches CEY383.03, CEY383.05 and CEY383.10: 82.7% - 100.4%	
Within-runs precision	Batches CEY383.03, CEY383.05 and CEY383.10: 1.7% - 10.9%	
Largest batch size	180 injections	
Matrix Factor (MF) IS normalized MF C.V.% of IS normalized MF	Low QC Mean Analyte MF: 1.0253 Mean IS MF: 1.0960 Mean IS-Normalized: 0.9354 % C.V.: 3.5	High QC Mean Analyte MF: 1.0339 Mean IS MF: 1.1064 Mean IS-Normalized: 0.9348 % C.V.: 2.2
Dilution integrity	1000.00 ng/mL diluted 5-fold. Accuracy (% nominal): 90.7% Precision 4.7% 2000.00 ng/mL diluted 10-fold. Accuracy (% nominal): 94.1% Precision 3.1%	
Recovery of analyte (P.E.Y.)	98.8% - 103.9%	
Recovery of IS (P.E.Y.)	106.1%	

Short-term stability of the stock solution and working solutions (Observed change %)	Confirmed up to 51.6 hours for CCX168-M1 in DMSO at 200.00 µg/mL at 22°C nominal. % deviation: -1.8%. Confirmed up to 25.0 hours for CCX168-M1 in MeOH:DMSO 75:25% v/v at 50000.00 ng/mL at 22°C nominal. % deviation: -0.1%. Confirmed up to 28.5 hours for CCX168-M1 in MeOH:DMSO 75:25% v/v at 100.00 ng/mL at 22°C nominal. % deviation: -2.6%. Confirmed up to 23.8 hours for CCX168-d4 in DMSO at 100.00 µg/mL at 22°C nominal. % deviation: -2.5%. Confirmed up to 20.7 hours for CCX168-d4 in MeOH:DMSO 75:25% v/v at 10.00 µg/mL at 22°C nominal. % deviation: 1.1%.
Long-term stability of the stock solution and working solutions (Observed change %)	Confirmed up to 151 days for CCX168-M1 in DMSO at 200.00 µg/mL at 4°C nominal. % deviation: -3.8%. Confirmed up to 154 days for CCX168-M1 in MeOH:DMSO 75:25% v/v at 50000.00 ng/mL at 4°C nominal. % deviation: 5.7%. Confirmed up to 151 days for CCX168-M1 in MeOH:DMSO 75:25% v/v at 100.00 ng/mL at 4°C nominal. % deviation: -0.6%. Confirmed up to 414 days for CCX168-d4 in DMSO at 100.00 µg/mL at 4°C nominal. % deviation: -1.0%. Confirmed up to 151 days for CCX168-d4 in MeOH:DMSO 75:25% v/v at 10.00 µg/mL at 4°C nominal. % deviation:2.5% Confirmed up to 146 days for CCX168-d4 in Cold ACN:MeOH 90:10% v/v at 60.00 ng/mL at 4°C nominal. % deviation: 4.1%.

Short-term stability in biological matrix at room temperature or at sample processing temperature. (Observed change %)	Confirmed up to 25.9 hours at 4°C nominal. Accuracy (% nominal): 111.4% for Low QCs and 107.0% for High QCs. Confirmed up to 23.3 hours at 4°C nominal in presence of Prednisone, Prednisolone Cyclophosphamide and 4-Ketocyclophosphamide. Accuracy (% nominal): 105.6% for Low QCs and 101.1% for High QCs. Confirmed up to 23.3 hours at 4°C nominal in presence of Prednisone, Prednisolone and Rituximab. Accuracy (% nominal): 107.2% for Low QCs and 101.7% for High QCs. Confirmed up to 24.3 hours at 4°C nominal in presence of Midazolam, α-Hydroxymidazolam, Celecoxib, Itraconazole and Rifampicin. Accuracy (% nominal): 98.5% for Low QCs and 93.0% for High QCs.[1]
Stability in whole blood	Confirmed up to 2.0 hours in an ice/water bath. % deviation: 4.5% for Low QCs and -0.5% for High QCs. Confirmed up to 3.0 hours at 22°C nominal and when centrifuged at 22°C nominal. % deviation: -1.9% for Low QCs and -2.2% for High QCs. Confirmed up to 3.0 hours in an ice/water bath and when centrifuged at 22°C nominal. % deviation:1.1% for Low QCs and -2.3% for High QCs. Confirmed up to 3.0 hours in an ice/water bath (with tubes holders pre-chilled at -20°C nominal for 12 minutes) and when centrifuged at 22°C nominal.. % deviation: -1.2% for Low QCs and -1.4% for High QCs. Confirmed up to 3.0 hours in an ice/water bath (with tubes holders pre-chilled at 4°C nominal for 1.1 hour) and when centrifuged at 22°C nominal. % deviation: 2.1% for Low QCs and -2.2% for High QCs.

[1] This evaluation was performed under validation project CEY-W0-774.

Freeze and thaw stability (Observed change %)	5 cycles. Accuracy (% nominal): 109.5% for Low QCs and 105.2% for High QCs. 4 cycles in presence of Prednisone, Prednisolone Cyclophosphamide and 4-Ketocyclophosphamide. Accuracy (% nominal): 102.8% for Low QCs and 101.0% for High QCs. 4 cycles in presence of Prednisone, Prednisolone and Rituximab. Accuracy (% nominal): 107.2% for Low QCs and 98.3% for High QCs. 4 cycles in presence of Midazolam, α-Hydroxymidazolam, Celecoxib, Itraconazole and Rifampicin. Accuracy (% nominal): 97.1% for Low QCs and 91.9% for High QCs.[1]
Autosampler storage stability (Observed change %)	Confirmed up to 139.5 hours at 4°C nominal Accuracy (% nominal): 109.6% for Low QCs and 110.2% for High QCs.

[1] This evaluation was performed under validation project CEY-W0-774.

Long-term stability in biological matrix (Observed change %)	Confirmed up to 834 days at -80°C nominal using 3 QC sample tubes subjected to stability conditions. Accuracy (%Bias): 2.0% for Low Stability QC and 3.7% for High Stability QC.[1] Confirmed up to 750 days at -80°C nominal in presence of Prednisone, Prednisolone Cyclophosphamide and 4-Ketocyclophosphamide using 3 QC sample tubes subjected to stability conditions. Accuracy (% nominal): 97.8% for Low QCs and 93.4% for High QCs. Confirmed up to 752 days at -80°C nominal in presence of Prednisone, Prednisolone and Rituximab using 3 QC sample tubes subjected to stability conditions. Accuracy (% nominal): 94.0% for Low QCs and 92.5% for High QCs. Confirmed up to 221 days at -20°C nominal using 3 QC sample tubes subjected to stability conditions. Accuracy (% nominal): 94.9% for Low QCs and 101.2% for High QCs. Confirmed up to 742 days at -20°C nominal in presence of Prednisone, Prednisolone, Cyclophosphamide and 4-Ketocyclophosphamide using 3 QC sample tubes subjected to stability conditions. Accuracy (% nominal): 101.2% for Low QCs and 101.4% for High QCs. Confirmed up to 742 days at -20°C nominal in presence of Prednisone, Prednisolone and Rituximab using 3 QC sample tubes subjected to stability conditions. Accuracy (% nominal): 105.5% for Low QCs and 100.0% for High QCs.
Partial validation	NA
Cross validation(s)	NA

[1] This evaluation was performed under project CEY-L4-962.
Source: Page 11 of Report CEY-W9-383 (R3)
Abbreviations: CV%, coefficient of variation; HPLC, high performance liquid chromatography; MS-MS; tandem mass spectrometer; NA, not applicable; QC quality control.

Table 117. Validation Summary for Avacopan (Report CEY-W2-587)

Analytical Validation Report	CEY-W2-587	
Short description of method	Protein precipitation Reversed-phase HPLC with MS/MS detection	
Biological matrix	Human Plasma	
Analyte	CCX168	
Internal standard (IS)	CCX168-d4	
Calibration concentrations	0.200 ng/mL to 100.000 ng/mL.	
Quality Control (QC) concentrations	0.200 ng/mL, 0.600 ng/mL, 50.000 ng/mL and 75.000 ng/mL.	
Specificity	No significant interference observed in the 10 blank matrix lots screened.	
Specificity in presence of concomitantly administered compounds	No significant interference observed.	
Carryover	No significant carryover observed.	
Lower limit of quantification	0.200 ng/mL Between-run accuracy 98.1% Between-run precision 16.2% Within-run accuracy 100.3% Within-run precision 4.5%	
Between-run accuracy	98.0% to 100.5%	
Between-run precision	5.8% to 16.2%	
Within-run accuracy	98.1% to 100.3%	
Within-run precision	1.7% to 5.4%	
Largest batch size	181 injections	
Matrix Effect (Calculation of the Matrix Factor (MF)) IS normalized MF C.V.% of IS normalized MF	Low QC Mean Analyte MF: 1.0617 Mean IS MF: 1.1540 Mean IS-Normalized: 0.9179 % C.V.: 3.8	High QC Mean Analyte MF: 1.0211 Mean IS MF: 1.0104 Mean IS-Normalized: 1.0103 % C.V.: 2.1
Dilution integrity	200.000 ng/mL diluted 5-fold (Twice the ULQ). Accuracy (% nominal): 95.9% Precision: 4.9% 1000.000 ng/mL diluted 40-fold (10 Times the ULQ). Accuracy (% nominal): 98.1% Precision: 5.5%	
Recovery of analyte (P.E.Y.)	100.3% - 103.5%	
Recovery of IS (P.E.Y.)	110.5%	

Short-term stability of the stock solution and working solutions	Confirmed up to 23.8 hours for CCX168 in DMSO at 200.00 µg/mL at 22°C nominal. % deviation: 0.7%.[1] Confirmed up to 29.3 hours for CCX168 in MeOH:DMSO 75:25% v/v at 100.00 µg/mL at 22°C nominal. % deviation:-1.8%. Confirmed up to 29.3 hours for CCX168 in MeOH:DMSO 75:25% v/v at 20.00 ng/mL at 22°C nominal. % deviation: -1.5%. Confirmed up to 23.8 hours for CCX168-d4 in DMSO at 100.00 µg/mL at 22°C nominal. % deviation: -2.5%.[1] Confirmed up to 20.7 hours for CCX168-d4 in MeOH:DMSO 75:25% v/v at 10.00 µg/mL at 22°C nominal. % deviation: 1.1%.[1]
Long-term stability of the stock solution and working solutions	Confirmed up to 151 days for CCX168 in DMSO at 200.00 µg/mL at 4°C nominal. % deviation: 4.5%.[1] Confirmed up to 91 days for CCX168 in MeOH:DMSO 75:25% v/v at 100.00 µg/mL at 4°C nominal. % deviation: 10.9%. Confirmed up to 34 days for CCX168 in MeOH:DMSO 75:25% v/v at 20.00 ng/mL at 4°C nominal. % deviation: -2.9%. Confirmed up to 151 days for CCX168-d4 in DMSO at 100.00 µg/mL at 4°C nominal. % deviation: -2.6%.[1] Confirmed up to 151 days for CCX168-d4 in MeOH:DMSO 75:25% v/v at 10.00 µg/mL at 4°C nominal. % deviation: 2.5%.[1] Confirmed up to 146 days for CCX168-d4 in Cold ACN:MeOH 90:10% v/v at 60.00 ng/mL at 4°C nominal. % deviation: 4.1%.[1]
Short-term stability in biological matrix at room temperature or at sample processing temperature	Confirmed up to 27.4 hours at 4°C nominal. Accuracy (% nominal): 85.9% for Low QCs and 97.3% for High QCs.
Stability in whole blood	Confirmed up to 2.0 hours in an Ice/Water Bath. % deviation: -3.3% for Low QCs and 1.2% for High QCs.

[1] This evaluation was performed under validation project CEY-W9-383.

Freeze and thaw stability	4 cycles. Accuracy (% nominal): 88.4% for Low QCs and 96.5% for High QCs.
Autosampler storage stability (referred to as "Processed Reconstituted Stability")	Confirmed up to 170.7 hours at 4°C nominal. Accuracy (% nominal): 107.2% for Low QCs and 108.7% for High QCs.
Long-term stability in biological matrix	Confirmed up to 84 days at -80°C nominal. Accuracy (% nominal): 94.5% for Low QCs and 99.5% for High QCs. Confirmed up to 74 days at -20°C nominal. Accuracy (% nominal): 97.4% for Low QCs and 100.2% for High QCs.
Partial validation	N/AP
Cross validation(s)	N/AP

Source: Page 4 of Report CEY-W2-587
Abbreviations: CV%, coefficient of variation; HPLC, high performance liquid chromatography; MS-MS; tandem mass spectrometer; N/AP, not applicable; ULQ, upper limit of quantification.

Table 118. Validation Summary for M1 (Report CEY-W2-587)

Analytical Validation Report	CEY-W2-587	
Short description of method	Protein precipitation Reversed-phase HPLC with MS/MS detection	
Biological matrix	Human Plasma	
Analyte	CCX168-M1	
Internal standard (IS)	CCX168-d4	
Calibration concentrations	1.00 ng/mL to 100.00 ng/mL.	
QC concentrations	1.00 ng/mL, 3.00 ng/mL, 50.00 ng/mL and 75.00 ng/mL	
Specificity	No significant interference observed in the 10 blank matrix lots screened.	
Specificity in presence of concomitantly administered compounds	No significant interference observed.	
Carryover	No significant carryover observed.	
Lower limit of quantification	1.00 ng/mL Between-run accuracy 96.7% Between-run precision 15.2% Within-run accuracy 106.5% Within-run precision 5.1%	
Between-run accuracy	96.7% to 99.5%	
Between-run precision	6.8% to 15.2%	
Within-run accuracy	97.9% to 106.5%	
Within-run precision	1.7% to 5.1%	
Largest batch size	181 injections	
Matrix Effect (Calculation of the Matrix Factor (MF)) IS normalized MF C.V.% of IS normalized MF	Low QC Mean Analyte MF: 1.0868 Mean IS MF: 1.1540 Mean IS-Normalized: 0.9464 % C.V.: 7.9	High QC Mean Analyte MF: 0.9734 Mean IS MF: 1.0104 Mean IS-Normalized: 0.9648 % C.V.: 5.2
Dilution integrity	200.00 ng/mL diluted 5-fold (Twice the ULQ). Accuracy (% nominal): 95.0% Precision: 4.2% 1000.00 ng/mL diluted 40-fold (10 Times the ULQ). Accuracy (% nominal): 92.7% Precision 8.2%	
Recovery of analyte (P.E.Y.)	97.9% - 102.0%	
Recovery of IS (P.E.Y.)	110.5%	

Short-term stability of the stock solution and working solutions	Confirmed up to 27.5 hours for CCX168-M1 in DMSO at 200.00 µg/mL at 22°C nominal. % deviation: 2.0%. Confirmed up to 25.0 hours for CCX168-M1 in MeOH:DMSO 75:25% v/v at 50000.00 ng/mL at 22°C nominal. % deviation: -0.1%.[1] Confirmed up to 28.5 hours for CCX168-M1 in MeOH:DMSO 75:25% v/v at 100.00 ng/mL at 22°C nominal. % deviation: -2.6%.[1] Confirmed up to 23.8 hours for CCX168-d4 in DMSO at 100.00 µg/mL at 22°C nominal. % deviation: -2.5%.[1] Confirmed up to 20.7 hours for CCX168-d4 in MeOH:DMSO 75:25% v/v at 10.00 µg/mL at 22°C nominal. % deviation: 1.1%.[1]
Long-term stability of the stock solution and working solutions	Confirmed up to 151 days for CCX168-M1 in DMSO at 200.00 µg/mL at 4°C nominal. % deviation: -3.8%.[1] Confirmed up to 154 days for CCX168-M1 in MeOH:DMSO 75:25% v/v at 50000.00 ng/mL at 4°C nominal. % deviation: 5.7%.[1] Confirmed up to 151 days for CCX168-M1 in MeOH:DMSO 75:25% v/v at 100.00 ng/mL at 4°C nominal. % deviation: -0.6%.[1] Confirmed up to 151 days for CCX168-d4 in DMSO at 100.00 µg/mL at 4°C nominal. % deviation: -2.6%.[1] Confirmed up to 151 days for CCX168-d4 in MeOH:DMSO 75:25% v/v at 10.00 µg/mL at 4°C nominal. % deviation: 2.5%.[1] Confirmed up to 146 days for CCX168-d4 in Cold ACN:MeOH 90:10% v/v at 60.00 ng/mL at 4°C nominal. % deviation: 4.1%.[1]

[1] This evaluation was performed under validation project CEY-W9-383.

Short-term stability in biological matrix at room temperature or at sample processing temperature	Confirmed up to 27.4 hours at 4°C nominal. Accuracy (% nominal): 94.1% for Low QCs and 96.4% for High QCs.
Stability in whole blood	Confirmed up to 2.0 hours in an Ice/Water Bath. % deviation: 2.3% for Low QCs and 3.4% for High QCs.
Freeze and thaw stability	4 cycles. Accuracy (% nominal): 95.1% for Low QCs and 93.2% for High QCs.
Autosampler storage stability (referred to as "Processed Reconstituted Stability")	Confirmed up to 170.7 hours at 4°C nominal Accuracy (% nominal): 109.6% for Low QCs and 112.2% for High QCs.
Long-term stability in biological matrix	Confirmed up to 84 days at -80°C nominal. Accuracy (% nominal): 95.0% for Low QCs and 100.5% for High QCs. Confirmed up to 74 days at -20°C nominal. Accuracy (% nominal): 92.2% for Low QCs and 100.9% for High QCs.
Partial validation	N/AP
Cross validation(s)	N/AP

Source: Page 7 of Report CEY-W2-587
Abbreviations: CV%, coefficient of variation; HPLC, high performance liquid chromatography; MS-MS; tandem mass spectrometer; N/AP, not applicable; QC, quality control; ULQ, upper limit of quantification.

Table 119. Validation Summary for Avacopan and M1 (Report CB171377)

Parameter	Result			Hyperlink
Methodology	LC/MS/MS			NA
Biological matrix	Human plasma			NA
Anticoagulant	EDTA-3K			NA
Analytes of interest	CCX168 CCX168-M1 (M1)			NA
IS	CCX168-d4			NA
Selectivity	≤20% of the LLOQ for analyte and ≤5% for IS			Table 1 and Table 2 Report text 16.1
Calibration curve range	1-500 ng/mL			Table 3 Report text 16.2
QC sample concentration	LLQC: 1 ng/mL, LQC: 3 ng/mL, MQC: 50 ng/mL, HQC: 375 ng/mL			
Within-run	CCX168	Accuracy	LLQC: 94.5% LQC: 99.7% MQC: 101.0% HQC: 101.1%	Table 4 Report text 16.3
		Precision	LLQC: 2.0% LQC: 1.3% MQC: 1.2% HQC: 1.8%	
	M1	Accuracy	LLQC: 101.0% LQC: 101.7% MQC: 102.0% HQC: 103.7%	
		Precision	LLQC: 5.9% LQC: 3.3% MQC: 2.5% HQC: 2.1%	

Parameter	Result				Hyperlink
Between-run	CCX168	Accuracy	LLQC:	98.1%	Table 4 Report text 16.3
			LQC:	101.0%	
			MQC:	101.0%	
			HQC:	101.1%	
		Precision	LLQC:	3.1%	
			LQC:	1.7%	
			MQC:	1.6%	
			HQC:	1.3%	
	M1	Accuracy	LLQC:	97.8%	
			LQC:	101.7%	
			MQC:	102.4%	
			HQC:	104.3%	
		Precision	LLQC:	4.8%	
			LQC:	3.0%	
			MQC:	2.3%	
			HQC:	2.3%	
LLOQ	1 ng/mL				Table 4 Report text 16.4
Matrix effect	CCX168	Precision: 4.0 and 4.8%			Table 5
	M1	Precision: 5.8 and 3.8%			Report text 16.5
Carry-over	≤20% of the LLOQ for analyte and ≤5% for IS				Table 6 Report text 16.6
Dilution integrity	High concentration sample: 1000 ng/mL (Dilution factor: 10)				Table 7 Report text 16.7
	CCX168	Accuracy: 105.0% Precision: 1.0%			
	M1	Accuracy: 106.0% Precision: 2.8%			

Source: Page 7 of Report CB171377
Note that the stability results refer to Validation report CEY-W9-383 (R3)
Abbreviations: HPLC, high performance liquid chromatography; LLOQ, lower limit of quantification; LLQC, lower limit of quality control; LQC, Lower quality control; MQC, middle quality control; HQC, higher quality control; MS-MS; tandem mass spectrometer; ULQ, upper limit of quantification.

Table 120. Validation Summary for Avacopan and M1 (Report TM-011)

Compounds Determined:	CCX168 and CCX168-M1	
Type of Assay:	LC-MS/MS	
Ionization	Positive Ion Electrospray	
Mode	Multiple Reaction Monitoring (MRM)	
Internal Standard:	CCX168-d_4	
Regression		
Model:	Linear	
Weighting:	CCX168: 1/x CCX168-M1: $1/x^2$	
Calibration Range:	1.00 – 500 ng/mL	
Quantitation Range:	1.00 – 50,000 ng/mL	
Matrix:	Human Plasma	
Standard Aliquot volume	50.0 µL	
Calibration Standards (K_2EDTA)	**CCX168**	**CCX168-M1**
Intra-Assay (Within-run) Precision (%CV):	≤6.50%	≤9.74%
Inter-Assay (Between-run) Precision (%CV)	≤2.31%	≤5.06%
Overall Mean Accuracy (Mean %Recovery)	95.0 – 105%	96.3 – 112%
Batch-Qualifying QC Samples (K_2EDTA) within the Calibrated Range		
Intra-Assay (Within-run) Precision (%CV):	≤2.39%	≤4.17%
Inter-Assay (Between-run) Precision (%CV)	≤1.48%	≤2.33%
Overall Mean Accuracy (Mean %Recovery)	102 – 107%	88.6 – 97.2%
Sensitivity at LLOQ (QC samples, K_2EDTA)		
Intra-Assay (Within-run) Precision (%CV):	3.68%	4.98%
Inter-Assay (Between-run) Precision (%CV)	6.50%	4.91%
Overall Mean Accuracy (%Recovery)	96.5%	92.4%
Dilution Acceptability	Analyte concentrations up to 50,000 ng/mL; samples may be diluted up to a factor of 100 (i.e., Dilution Factors ≤100)	
Stability of CCX168 and CCX168-M1 Concentrations in Plasma		

Freeze/Thaw Cycles (assisted)	6 cycles	
Ambient Temperature (Bench Top)	24 hours	
4 °C	24 hours	
Long-term, -20 °C	To 466 days	
Long-term, -80 °C	To 444 days	
Quality Control Samples (K_3EDTA) within the Calibrated Range	**CCX168**	**CCX168-M1**
Intra-Assay (Within-run) Precision (%CV):	≤4.90%	≤4.96%
Inter-Assay (Between-run) Precision (%CV)	≤1.32%	≤4.75%
Overall Mean Accuracy (Mean %Recovery)	109 – 112%	108%
Processed Sample Stability / Reinjection (Storage On-instrument; Set Point at 10 °C)		
By concurrent reinjected standard curve (full-batch reinjection)	6 days	
By originally injected standard curve (partial-batch reinjection)	6 days	
Injections from same well	3 injections	
Processed Sample Stability / Reinjection (Storage at Ambient Laboratory Conditions)		
By concurrent reinjected standard curve (full-batch reinjection)	2 days	
By originally injected standard curve (partial-batch reinjection)	2 days	
Whole Blood Collection Stability		
Ambient Temperature Storage	3.5 hours	
Wet Ice Storage	3.5 hours	
Whole Blood Centrifugation	2 – 8 °C or ambient temperature	
Hemolyzed samples	Acceptable for ≤5% hemolysis	

Note: Temperatures indicated in above table are nominal.
Source: Page 13 of Report TM-011
Abbreviations: %CV; coefficient of variation; LC-MS/MS, liquid chromatographic separation with tandem mass spectrometric; LLOQ, lower limit of quantification; QC, quality control.

Table 121. Partial Validation Summary for Avacopan (Report TM-004)

Method Parameters	Experimental	Established Validation Result
Quantification range	N/A	0.2 to 100ng/mL
Sample dilution	N/A	10×
Processed sample viability	Between 5 and 15 °C	Not established
CCX168 stock solution stability	Room temperature/4°C	6 hours[1] /31 days[1]
CCX168 intermediate solution stability[1]	4°C	25 days[1]
ISTD stock solution stability[2]	In methanol at 4°C	26 days
Short-term matrix stability – bench top stability	Room temperature	24 hours
Whole blood stability	Room temperature and in wet ice bath	Established for up to 2 hours
Freeze-thaw matrix stability	-80 °C for 3 cycles	Established for up to 3 cycles
Long term frozen matrix stability	-80 °C	14 days
Batch Size Determination	N/A	165 samples

[1] Determined under (b) (4) report PC0363_168 (8204220)
[2] Determined under ChemoCentryx Doc I.D. CLCCX2_282_Method Validation
Source: Page 5 of Report TM-004
Abbreviations: ISTD, internal standard; N/A, not applicable

17.3.3. Pharmacometrics Review

Report title (Report CMR_168_POP_PK2)

Population Pharmacokinetic Modeling and Simulations to Support Dosing of Avacopan in Healthy Subjects and Subjects with ANCA-Associated Vasculitis

Objectives:

- To characterize the population PK of avacopan to assess extrinsic and intrinsic factors that may explain variability in exposure levels of avacopan and metabolite M1
- To estimate systemic exposure to avacopan and metabolite M1 in subjects with ANCA-associated vasculitis in Phase 3 study CL010_168

Software: Dataset exploration, figures and descriptive statistics were performed using R (version 3.5 or higher). Population PK modeling and model validation were performed using Phoenix NLME Version 8.2 (Certara, Inc.) with a first-order conditional estimation (first-order conditional estimation [FOCE] with INTERACTION) algorithm.

Data source: The population PK analyses for avacopan and its metabolite M1 include data from 368 subjects enrolled in seven clinical studies (Table 122). Overall, 5682 and 5409 non-BLQ

concentrations of avacopan and M1, respectively, were included. Summaries of continuous and categorical demographic data are presented in Table 123 and Table 124, respectively.

Table 122. Summary of Studies and Data Included in the Population PK Analysis

Protocol Number	Study Description	Avacopan Regimen	Avacopan Dosage Form	Planned Numbers of Subjects	Planned PK Sampling (Avacopan and CCX168-M1 only)
CL002_168	Randomized, double-blind, placebo-controlled Phase 2 study to evaluate the safety and efficacy of CCX168 in subjects with AAV on background cyclophosphamide or rituximab treatment	30 mg BID on days 1 – 85 Subjects on active CCX168 regimens will have received a combination of some of all of cyclophosphamide, rituximab and oral/IV corticosteroids	3x10 mg CCX168 hard gelatin capsules	67 subjects (Male and Female) (44 on treatment/ 23 on placebo)	Day 1, Hour 0 (Pre-dose) and 0.5, 1, 2, 3, 4, and 6 hours post dose Days 8, 15, 22, 29, 43, 57, 71, and 85 were intended to be pre-dose trough samples (however it is assumed that actual sample times may vary with some samples being taken some time after the dose)
CL003_168	A Randomized, double-blind, placebo-controlled, dose assessment Phase 2 study to evaluate the safety and efficacy of CCX168 in subjects with AAV	Two Groups: 10 mg BID on days 1 - 85; 30 mg BID days 1 – 85 Subjects on active CCX regimens will have received a combination of some of all of cyclophosphamide, rituximab and oral/IV corticosteroids	1x10 mg CCX168 hard gelatin capsule 3x10 mg CCX168 hard gelatin capsule	39 subjects (Male and Female) (16 subjects at 30 mg BID / 13 subjects at 10 mg BID / 13 subjects at on placebo)	Day 1, Hour 0 (Pre-dose) and 0.5, 1, 2, 3, 4, and 6 hours post dose Days 8, 15, 22, 29, 43, 57, 71, and 85 were intended to be pre-dose trough samples (however it is assumed that actual sample times may vary with some samples being taken some time after the dose)
CL007_168	Phase 1 study in healthy subjects to evaluate the food-effect, dose proportionality and cardiac safety of CCX168 and M1	Crossover design with all subjects receiving: Single dose of CCX168 3 mg administered under fasted conditions Single dose of CCX168 30 mg administered under both fasted and fed conditions Single dose of CCX168 100 mg Multiple doses of CCX168 100 mg BID	3x10 mg CCX168 hard gelatin capsules (Periods 1 & 2) CCX168 mg dosing solution (Period 3) 10x10 mg CCX168 hard gelatin capsules (Period 4)	16 subjects	Period 1& 2 Hour 0 (Pre-dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, 96, 120 and 168 hours post-dose Period 3 Hour 0 (Pre-dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 and 24 hours post-dose Period 4 Hour 0 (Pre-dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, 96, 120, 144, 144.25, 144.5, 145, 145.5, 146, 146.5, 147, 148, 150, 152, 156, 162, 168, 192, 216, 264 and 312 hours after the first dose of CCX168 in Period 4 Note that doses of CCX168 were administered BID for 7 days in this period.

CL008_168	Phase 1 study in healthy subjects to evaluate the drug-drug interaction potential of CCX168	Two cohort fixed-sequence crossover design Cohort A Single PO dose of midazolam 2mg and celecoxib 200 mg on Days 1 and 13; CCX168 30 mg PO BID Days 3 – 19; Itraconazole 200 mg PO QD Days 16-19 Cohort B Single dose of CCX168 30 mg on Days 1 and 14; Rifampicin 600 mg QD Days 4-17	10 mg hard gelatin capsules	Cohort A 16 subjects Cohort B 16 subjects	Cohort A Days 15 & 9: Hour 0 (Pre-dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-dose Cohort B Day 1: Hour 0 (Pre-dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 48 and 72 hours post-dose Day 14: Hour 0 (Pre-dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 48 and 72 hours post-dose
CL013_168 (Phase 1)	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	Single dose oral dose of 30 mg avacopan at fasted state	3x10 mg CCX168 hard gelatin capsules	16 subjects with mild and moderate hepatic impairment (8 per group) 8-10 subjects in healthy control group	Hours 0 (Pre-dose) • Hours: 0.5, 1, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), 144 (Day 7), 192 (Day 9), 264 (Day 12), and 336 (Day 12) hours after the dose and at the final follow-up visit (~Day 18)
CCX1101 (Phase 1)	A Phase 1 Clinical Study of CCX168 in Japanese and Caucasian Healthy Adult Males	Four parts: Part A: single dose 10, 30 and 100 mg in Japanese adult males under fasted or fed condition (low fat meal) Part B: 30 and 50 mg BID for 7 days in Japanese adult males under fed condition Part C: single dose 10 and 30 mg in Caucasian adult males under fasted condition Part D: 30 mg BID for 7 days in Caucasian adult males under fed condition	10 mg CCX168 hard gelatin capsule 3x10 mg CCX168 hard gelatin capsule	80 male subjects (50 Japanese and 30 Caucasian)	Part A and C: Day 1-8: pre-dose, 0.25, 0.5,1, 1.5,2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72 and 168 hours Part B and D: Day 1: pre-dose, 0.25, 0.5,1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 18 hours Days 2-6: pre-dose and 12 hours
CL010_168 (Phase 3)	A Randomized, Double-Blind, Active-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of CCX168 (Avacopan) in Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Treated Concomitantly with Rituximab or Cyclophosphamide/Azathioprine	3 x 10 mg CCX168 capsules orally BID for 52 weeks preferably with food plus cyclophosphamide/ azathioprine or rituximab	Capsule	300 patients with newly diagnosed or relapsing ANCA with vasculitis	PK: Day 1 (pre-dose baseline), Weeks 1, 2, 4, 7, 13, 26, 39, and 52 in all patients and with additional sampling on Day 1 at 0.5, 1, 2, 3, 4, and 6 h after first dose for patients 12 to 17 years of age.

Source: Appendix 1 of Report CMR_168_POP_PK2
Abbreviations: ANCA, anti-neutrophilic cytoplasmic ant body; BID, twice daily; PK, pharmacokinetics; QD, once daily.

Table 123. Summary of Demographics (Continuous) Values for Subjects Included in the Population PK Analyses

Covariates	Mean (CV%) Median [Minimum, Maximum] N missing			
	Phase 1 (N=136)	Phase 2 (N=73)	Phase 3 (N=159)	Overall (N=368)
Age (years)	38.8 (35.1) 37.5 [20.0, 72.0] 0	57.3 (23.1) 59.0 [23.3, 82.1] 0	61.5 (23.7) 65.0 [13.0, 83.0] 0	52.3 (33.3) 55.0 [13.0, 83.0] 0
Body weight (kg)	73.1 (16.6) 72.1 [51.1, 117] 0	81.3 (29.7) 77.5 [40.9, 174] 0	76.6 (26.7) 74.2 [40.3, 138] 0	76.2 (24.8) 74.0 [40.3, 174] 0
Body mass index (kg/m^2)	25.1 (16.3) 24.3 [18.6, 37.5] 0	27.4 (23.7) 26.6 [16.6, 55.0] 2	26.7 (22.2) 25.6 [16.5, 46.6] 1	26.2 (21.0) 25.3 [16.5, 55.0] 3
Body surface area (m^2)	1.86 (9.01) 1.84 [1.50, 2.40] 0	1.96 (16.7) 1.92 [1.34, 3.07] 2	1.88 (15.2) 1.88 [1.28, 2.61] 1	1.89 (13.8) 1.87 [1.28, 3.07] 3
Serum Albumin (g/dL)	4.36 (7.02) 4.40 [2.90, 5.00] 0	3.80 (15.0) 3.80 [2.40, 5.00] 0	3.53 (13.7) 3.60 [2.30, 4.60] 3	3.89 (14.9) 4.00 [2.30, 5.00] 3
Alanine aminotransferase (U/L)	19.5 (71.4) 15.0 [6.00, 115] 0	25.9 (65.1) 19.0 [7.00, 83.0] 0	21.6 (77.4) 17.0 [4.00, 118] 3	21.7 (73.3) 17.0 [4.00, 118] 3
Estimated glomerular filtration rate ($mL/min/1.73\ m^2$)	104 (20.0) 101 [54.4, 156] 0	55.6 (45.8) 54.0 [18.0, 150] 0	49.1 (61.4) 40.0 [14.0, 170] 3	70.7 (51.5) 72.0 [14.0, 170] 3

Source: Table 1 of Report CMR_168_POP_PK2
Abbreviations: CV%; coefficient of variation; PK, pharmacokinetics.

Table 124. Summary of Demographics (Categorical) Values for Subjects Included in the Population PK Analyses

Covariates	Category	N (% of total)			
		Phase 1 (N=136)	Phase 2 (N=73)	Phase 3 (N=159)	Overall (N=368)
eGFR category at baseline	Normal	100 (73.5%)	7 (9.59%)	21 (13.2%)	128 (34.8%)
	Mild	35 (25.7%)	22 (30.1%)	28 (17.6%)	85 (23.1%)
	Moderate	1 (0.735%)	33 (45.2%)	56 (35.2%)	90 (24.5%)
	Severe - ESRD		11 (15.1%)	51 (32.1%)	62 (16.8%)
	Unknown			3 (1.89%)	3 (0.815%)
Age Category	<18			2 (1.26%)	2 (0.543%)
	≥18 & <50	106 (77.9%)	19 (26.0%)	25 (15.7%)	150 (40.8%)
	≥50 & <65	19 (14.0%)	32 (43.8%)	48 (30.2%)	99 (26.9%)
	≥65 & <75	11 (8.09%)	16 (21.9%)	58 (36.5%)	85 (23.1%)
	≥75		6 (8.22%)	26 (16.4%)	32 (8.70%)
BMI Category	<30 kg/m^2	114 (83.8%)	55 (75.3%)	124 (78.0%)	293 (79.6%)
	≥30 kg/m^2	22 (16.2%)	16 (21.9%)	34 (21.4%)	72 (19.6%)
	Missing		2 (2.74%)	1 (0.629%)	3 (0.815%)
Race	White	91 (66.9%)	69 (94.5%)	132 (83.0%)	292 (79.3%)
	Black	3 (2.21%)	3 (4.11%)	3 (1.89%)	9 (2.45%)
	Asian	41 (30.1%)	0	17 (10.7%)	58 (15.8%)
	Other	1 (0.735%)	1 (1.37%)	7 (4.40%)	9 (2.45%)
Sex	Female	24 (17.6%)	28 (38.4%)	62 (39.0%)	114 (31.0%)
	Male	112 (82.4%)	45 (61.6%)	97 (61.0%)	254 (69.0%)

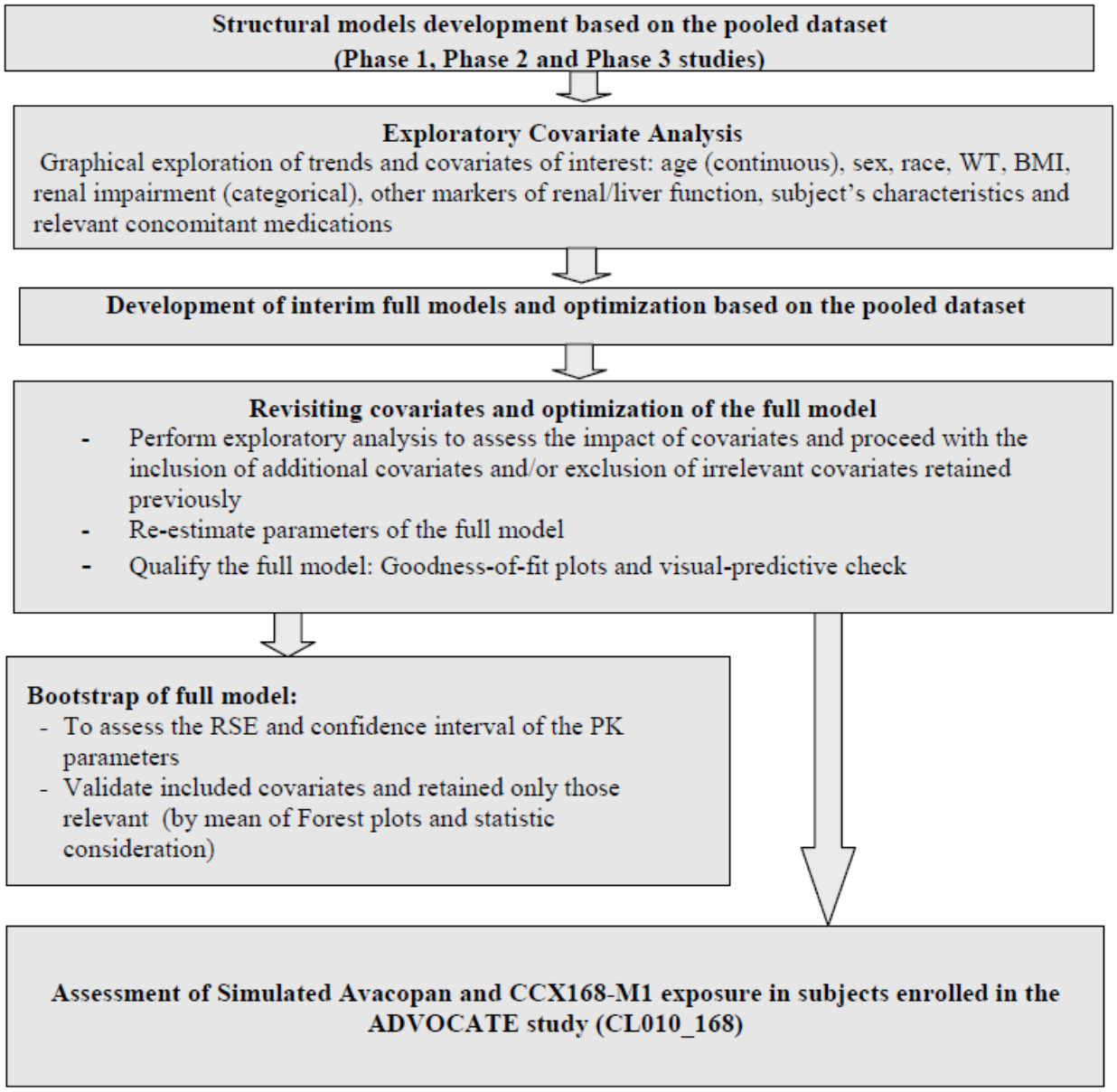
Note: Renal impairment categories were based on FDA classification[5] (i.e., normal: eGFR≥90 mL/min/1.73 m^2, mild: eGFR≥60 mL/min/1.73 m^2 and eGFR<90 mL/min/1.73 m^2, moderate: eGFR≥30 mL/min/1.73 m^2 and eGFR<60 mL/min/1.73 m^2, severe - ESRD: eGFR<30 mL/min/1.73 m^2).
BMI= body mass index; eGFR= estimated glomerular filtration rate; ESRD= end stage renal disease; N= number of subjects; PK= pharmacokinetic.
Source: Table 2 of Report CMR_168_POP_PK2

Population PK modeling: The modeling activities of avacopan and metabolite M1 were performed separately. The model development approach is as shown in Figure 52.

The evaluation of the population PK models was done using a stepwise approach: the first step was to evaluate the structural population PK models based on the combined Phase 1, 2 and 3 dataset and the second step was to conduct covariate analysis based on the covariates previously included in the models and on additional subject's characteristics. Concentration-time profiles of avacopan and metabolite M1 were previously modeled based on the PK data from five clinical trials using a NLME model. The previous final PK models without covariates were used as structural models for avacopan and M1. The relationships between covariates and PK parameters were explored graphically to obtain information on covariates likely to affect the

parameters of interest and/or that are clinically relevant. Evaluation of covariates on systemic PK parameters of avacopan and M1 was performed in Phoenix NLME using a full modeling approach. Model parameter estimates, relative standard error (RSE) and 95% non-parametric CI were obtained via non-parametric bootstrapping with stratification by study. The bootstrap analyses were conducted to evaluate the precision of the PK parameters. A covariate effect was deemed statistically significant if the bootstrap derived non-parametric 95% CI of the estimate did not contain the null value. The final models were evaluated using Goodness-of-fit plots and visual-predictive check and then used to simulate exposures of avacopan and M1 in Study CL010_168.

Figure 52. Model Development Tree: Population PK Analysis of Avacopan and Metabolite M1



Source: Figure 1 of Report CMR_168_POP_PK2
Abbreviations: BMI, body mass index; PK, pharmacokinetics; RSE, relative standard error; WT, weight.

Results:

Population PK Model for Avacopan

A three-compartment model with zero-order input and a lag time, with linear elimination, was found to best describe the PK of avacopan (Table 125). The covariates in the avacopan population PK model included body weight, ALT, estimated glomerular filtration rate (eGFR),

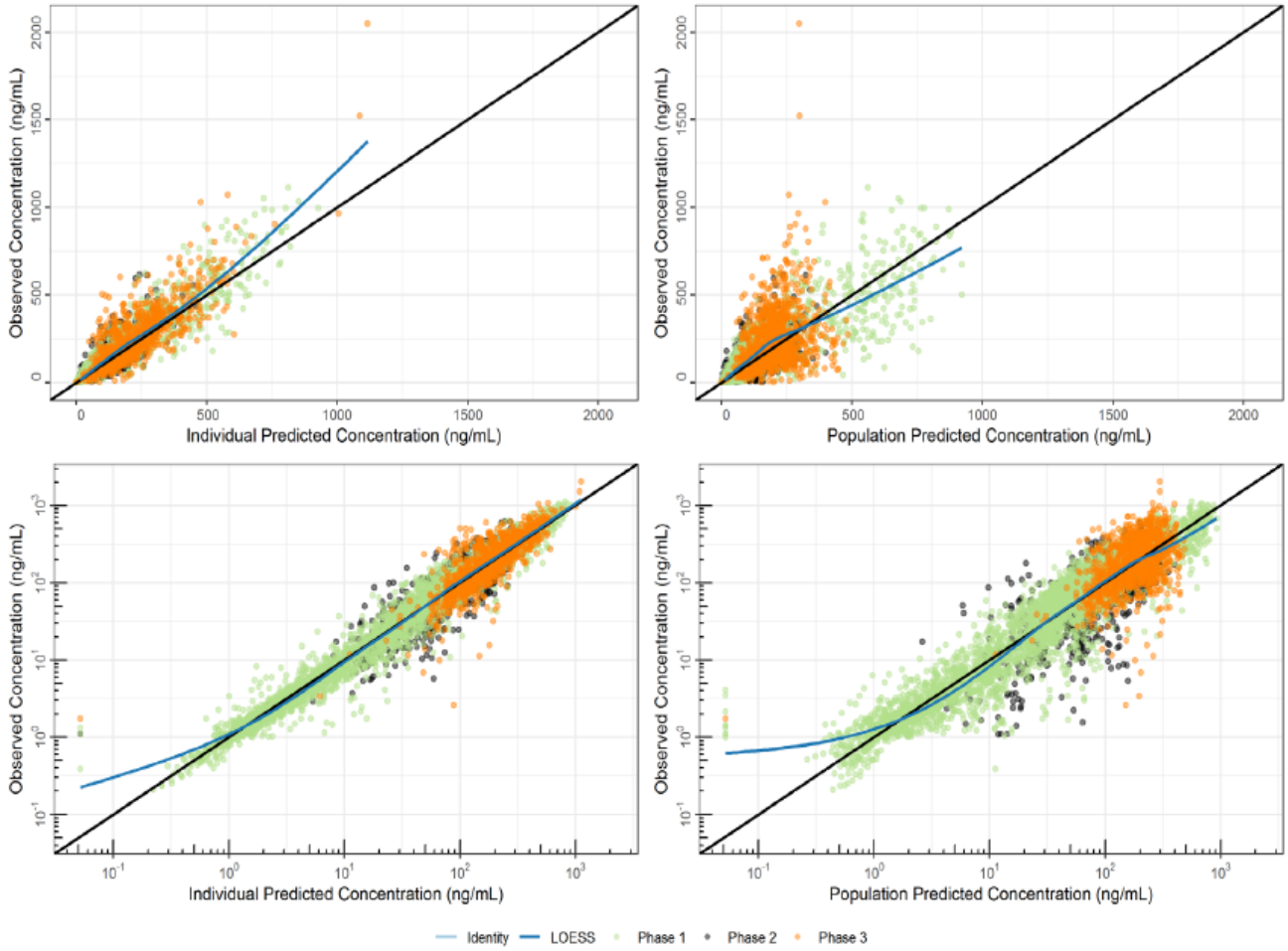
health status (patients with ANCA-associated vasculitis or healthy subjects) on clearance, and body weight, serum albumin levels, and health status on volume of distribution. Goodness of fit plots and VPCs demonstrated adequacy of the population PK model to describe avacopan PK data in subjects with ANCA-associated vasculitis (Figure 53, Figure 54).

Table 125. Typical Values of Final Model of Avacopan Based on the Data From Phase 1, Phase 2, and Phase 3

Parameter	Estimate	RSE (%)	95%CI	BSV (%) Shrinkage (%)
Relative Bioavailability				
Fasted and dose up to 50 mg	1			
Flexible or low fat fed	×1.44	6.21	[1.22-1.52]	
High fat fed	×1.30	3.62	[1.26-1.45]	
100-mg Dose*	×1.79	4.06	[1.55-1.82]	
LAG (h)	0.269	9.87	[0.208-0.315]	32.4
Flexible or low fat fed	×1.22	1.83	[1.19-1.27]	(28.5)
High fat fed	×1.77	7.36	[1.63-2.12]	
Healthy subject (fasted)	×1.34	2.13	[1.28-1.40]	
Duration (h)	1.21	6.92	[1.03-1.35]	31.9
Flexible or low fat fed	×1.21	3.04	[1.19-1.30]	(35.9)
High fat fed	×2.90	11.6	[2.61-3.95]	
Healthy subject (fasted)	×1.35	2.29	[1.26-1.41]	
Vc/F (L)	345	9.96	[290-421]	32.0
Body weight (kg)	$\times (WT/77.3)^{0.753}$	8.12	[0.621-0.878]	(41.1)
Serum albumin (g/dL)	$\times (ALB/4.3)^{-0.101}$	8.84	[-0.122--0.0846]	
Healthy subject	×0.677	4.06	[0.652-0.763]	
CL/F (L/h)	16.3	12.4	[13.1-21.1]	47.3
Body weight (kg)	$\times (WT/77.3)^{0.475}$	22.6	[0.175-0.547]	(18.9)
Age (years)	$\times (AGE/39.0)^{0.383}$	18.2	[0.183-0.441]	
Alanine aminotransferase (U/L)	$\times (ALT/15)^{-0.100}$	8.97	[-0.125--0.0840]	
eGFR (mL/min/1.73 m^2)	$\times (eGFR/94)^{0.368}$	7.3	[0.309-0.429]	
Healthy subject	×1.54	3.46	[1.43-1.63]	
V2/F (L)	$6510 \times (WT/77.3)^{0.753}$	13.1	[4611-7722]	
CL2/F (L/h)	$28.8 \times (WT/77.3)^{0.475}$	9.59	[22.0-31.3]	
V3/F (L)	$202 \times (WT/77.3)^{0.753}$	35.6	[166-473]	
CL3/F (L/h)	$11.9 \times (WT/77.3)^{0.475}$	19.4	[8.70-17.0]	
Log residual error	0.425	5.11	[0.396-0.477]	

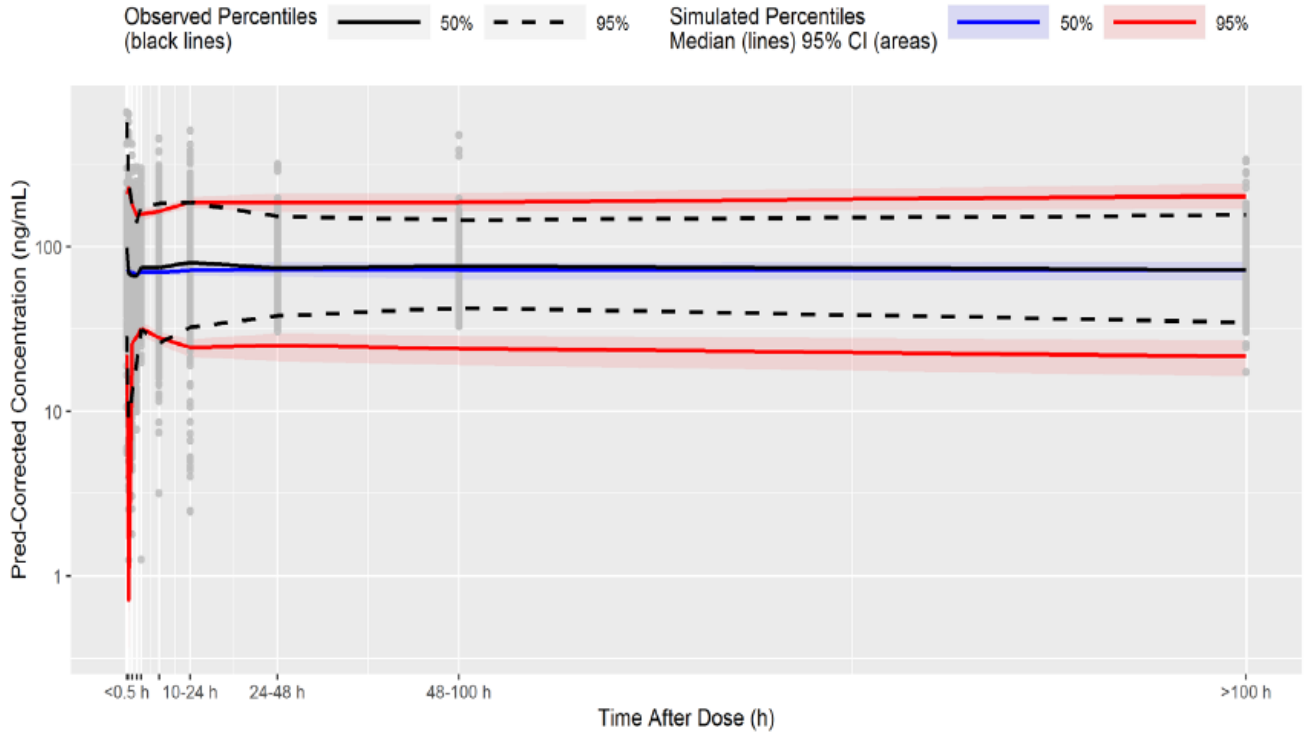
Source: Table 3 of Report CMR_168_POP_PK2
Note 1: A correlation of 0.104 was estimated between Vc/F and CL/F and a correlation of 0.153 was estimated between duration and LAG.
Note 2: The 95% confidence intervals (CI) were derived based on 474 runs of bootstrap.
Note 3: Reference subject is subject with ANCA-associated vasculitis.
* The effect was associated with multiple 100-mg dose given in multiple dose regimen.
Abbreviations: ANCA, anti-neutrophil cytoplasmic antibody; BSV, between-subject variability; CL/F, apparent systemic clearance; CL2/F, apparent peripheral inter-compartment clearance; CL3/F, apparent deep tissue intercompartment clearance; eGFR, estimated glomerular filtration rate; LAG, lag time; Vc/F, apparent central volume of distribution; V2/F, apparent peripheral volume of distribution; V3/F, apparent deep volume of distribution.

Figure 53. Goodness-of-Fit Plots for Avacopan Final PK Model



Source: Figure 3 of Report CMR_168_POP_PK2
Abbreviations: PK, pharmacokinetics.

Figure 54. Prediction-Corrected Visual Predictive Check of Final Population PK Model of Avacopan – Semi-Log Scale



Source: Figure 4 of Report CMR_168_POP_PK2
Abbreviations: PK, pharmacokinetics.

Population PK model for Metabolite M1

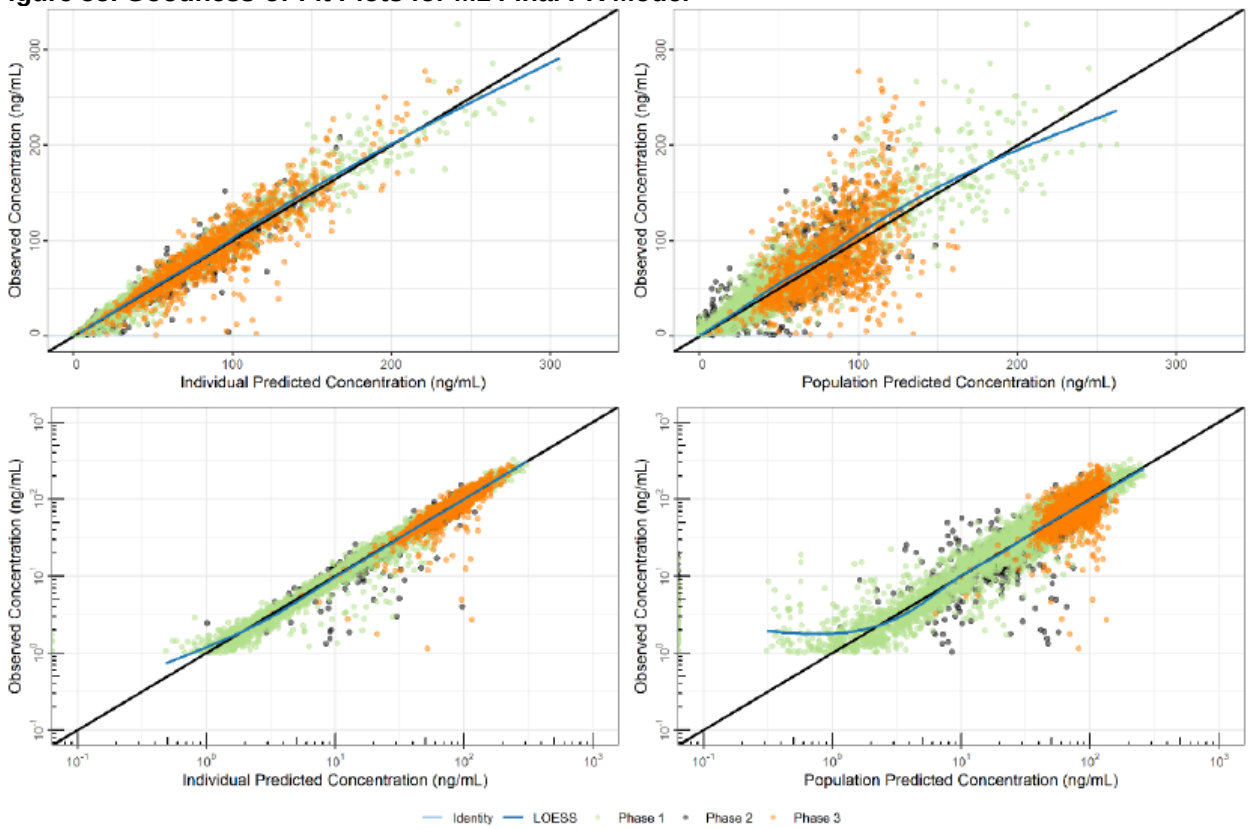
A three-compartment model with zero-order input and a lag time, with linear elimination, was found to best describe the PK of M1 (Table 126). The covariates in the population PK model for M1 included body weight, eGFR, health status (patients with ANCA-associated vasculitis or healthy subjects), and age on clearance, and body weight and health status on volume of distribution. Goodness of fit plots and VPCs demonstrated adequacy of the population PK model to describe M1 PK data in subjects with ANCA-associated vasculitis (Figure 55, Figure 56).

Table 126. Typical Values of Final Model of M1 Based on the Data From Phase 1, Phase 2, and Phase 3

Parameter	Estimate	RSE (%)	95%CI	BSV (%) Shrinkage (%)
Lag (h)	0.519	5.68	[0.452 - 0.568]	50.2
High fat fed	×5.41	14.7	[3.15 - 5.67]	(30.8)
100-mg Dose	×1.11	6.44	[0.933 - 1.19]	
Duration (h)	1.86	4.22	[1.62 - 1.90]	39.6
High fat fed	×2.73	19.8	[1.94 - 4.20]	(35.1)
100-mg Dose	×1.84	12.2	[1.47 - 2.34]	
Vc/F (L)	840	4.06	[837 - 974]	27.9
Body weight (kg)	$\times(WT/77.3)^{1.09}$	12.7	[0.846 - 1.41]	(33.5)
Healthy subject	×0.739	4.01	[0.669 - 0.782]	
Study CL013_168	×0.689	5.61	[0.596 - 0.754]	
CL/F (L/h)	28.5	3.97	[26.5 - 31.1]	34.0
Body weight (kg)	$\times(WT/77.3)^{0.334}$	19.7	[0.184 - 0.440]	(17.9)
Age (years)	$\times(AGE/39.0)^{-0.321}$	17.2	[-0.472 - -0.252]	
eGFR (mL/min/1.73 m^2)	$\times(eGFR/94)^{0.112}$	34.1	[0.0251 - 0.155]	
Healthy subject	×0.997	0.0813	[0.995 - 0.998]	
V2/F (L)	9772 $\times(WT/77.3)^{1.09}$	15.9	[7981 - 14752]	106 (31.5)
CL2/F (L/h)	23.9 $\times(WT/77.3)^{0.334}$	8.26	[20.0 - 27.4]	82.1 (18.3)
V3/F (L)	1050 $\times(WT/77.3)^{1.09}$	6.84	[995 - 1266]	
CL3/F (L/h)	64.3 $\times(WT/77.3)^{0.334}$	4.51	[59.8 - 71.3]	
Proportional error (%)	17.6	66.0	[2.43 - 121]	
Additive error (ng/mL)	0.508	53.7	[0.213 - 1.34]	

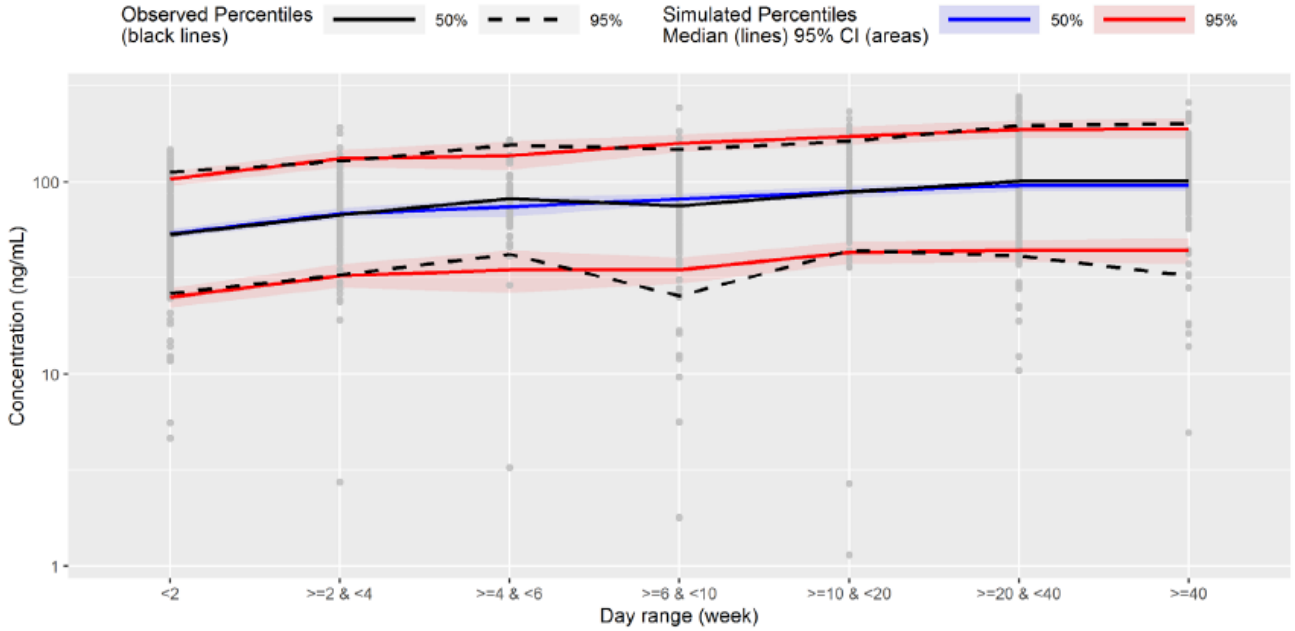
Source: Table 4 of Report CMR_168_POP_PK2
Note 1: The 95% confidence intervals (CI) were derived based on 490 runs of bootstrap
Note 2: Reference subject is subject with ANCA-associated vasculitis.
Abbreviations: BSV, between-subject variability; CL/F, apparent systemic clearance; CL2/F, apparent peripheral inter-compartment clearance; CL3/F, apparent deep tissue intercompartment clearance; eGFR, estimated glomerular filtration rate; LAG, lag time; Vc/F, apparent central volume of distribution; V2/F, apparent peripheral volume of distribution; V3/F, apparent deep volume of distribution.

Figure 55. Goodness-of-Fit Plots for M1 Final PK Model



Source: Figure 5 of Report CMR_168_POP_PK2
Abbreviations: PK, pharmacokinetics.

Figure 56. Prediction-Corrected Visual Predictive Check of Final Population PK Model of M1–Semi-Log Scale



Source: Figure 6 of Report CMR_168_POP_PK2
Abbreviations: CI, confidence interval; PK, pharmacokinetics.

Posterior Bayes Simulated Exposures of Avacopan and Metabolite M1 in Study CL010_168

Posterior Bayes parameters derived with the final population PK models for avacopan and M1 were used to generate rich concentration profiles for each subject participating in study CL010_168, assuming the actual dose history. Exposure levels estimated by NCA for Day 1, Week 4, Week 26 and Week 52 are presented in Table 127 and Table 128 for avacopan and M1, respectively. The simulated avacopan and M1 exposure at Week 26 in study CL010_168 by selected covariates, including age, body weight, sex, race, ALT, and renal impairment (eGFR) indicated that avacopan and M1 exposure are generally comparable (<25%) across subgroups and these covariates are not expected to have a clinically meaningful effect on avacopan and M1 exposure in subjects with ANCA-associated vasculitis (Figure 4, Figure 5).

Table 127. Summary of Avacopan Exposure Derived With the Posterior Bayes Parameters - Study CL010_168

Parameters	Mean (SD) Median [Minimum-Maximum]			
	Day1 (N=159; N BLQ=0)	Week 4 (N=159; N BLQ=0)	Week 26 (N=147; N BLQ=12)	Week 52 (N=129; N BLQ=30)
C_{min} (ng/mL)	0.00 (0.00) 0.00 [0.00-0.00]	150 (60.2) 147 [5.83-360]	230 (151) 218 [1.12-999]	234 (151) 205 [1.76-1069]
C_{max} (ng/mL)	136 (24.6) 133 [77.3-208]	254 (80.8) 251 [11.1-498]	322 (176) 311 [1.14-1133]	349 (169) 325 [1.81-1243]
C_{avg} (ng/mL)	57.0 (9.85) 55.8 [20.7-84.2]	190 (68.0) 184 [11.0-415]	266 (161) 252 [1.14-1053]	289 (160) 263 [1.80-1164]
AUC_{0-6} (ng.h/mL)	438 (79.7) 430 [224-664]	1268 (431) 1236 [66.2-2650]	1712 (995) 1616 [6.85-6484]	1856 (979) 1697 [10.8-7147]
AUC_{0-12} (ng.h/mL)	684 (118) 669 [249-1011]	2283 (816) 2205 [132-4983]	3193 (1929) 3021 [13.7-12640]	3466 (1921) 3154 [21.6-13963]

Source: Table 5 of Report CMR_168_POP_PK2
Abbreviations: AUC_{0-6h}, area under the curve from 0 to 6 hours; AUC_{0-12h}, area under the curve from 0 to 12 hours; BLQ, below limit of quantification; C_{avg}, average concentration; C_{max}, maximum concentration; C_{min}, minimum concentration; SD, standard deviation.

Table 128. Summary of M1 Exposure Derived With the Posterior Bayes Parameters - Study CL010_168

Parameters	Mean (SD) Median [Minimum-Maximum]			
	Day1 (N=156; N BLQ=0)	Week 4 (N=159; N BLQ=0)	Week 26 (N=146; N BLQ=13)	Week 52 (N=131; N BLQ=28)
C_{min} (ng/mL)	0.00 (0.00) 0.00 [0.00, 0.00]	66.3 (28.0) 62.6 [3.18, 159]	89.0 (44.9) 87.7 [1.03, 221]	89.5 (40.5) 86.8 [2.27, 223]
C_{max} (ng/mL)	41.4 (10.8) 39.9 [21.8, 77.8]	94.2 (35.0) 89.1 [3.23, 199]	113 (53.6) 111 [1.06, 259]	122 (49.4) 117 [2.31, 276]
C_{avg} (ng/mL)	17.7 (4.26) 17.2 [6.63, 32.3]	77.8 (30.7) 73.7 [3.22, 176]	99.1 (48.4) 97.6 [1.05, 237]	107 (45.1) 102 [2.30, 254]
AUC_{0-6} (ng.h/mL)	121 (31.2) 118 [65.6, 221]	497 (192) 470 [19.3, 1096]	621 (300) 611 [6.35, 1462]	669 (278) 632 [13.8, 1564]
AUC_{0-12} (ng.h/mL)	213 (51.1) 206 [79.6, 388]	933 (369) 884 [38.6, 2109]	1189 (581) 1172 [12.7, 2841]	1283 (541) 1221 [27.6, 3046]

Source: Table 7 of Report CMR_168_POP_PK2
Abbreviations: AUC_{0-6h}, area under the curve from 0 to 6 hours; AUC_{0-12h}, area under the curve from 0 to 12 hours; BLQ, below limit of quantification; C_{avg}, average concentration; C_{max}, maximum concentration; C_{min}, minimum concentration; SD, standard deviation.

Reviewer's comments: *The Applicant's population PK analysis for avacopan and metabolite M1 are acceptable.*

PK profiles of both avacopan and M1 were each well described with a three-compartment model with a linear clearance term. For avacopan, the absorption was best described as a zero-

order input with a lag time. The biotransformation of avacopan to M1 was best described as a zero-order process with a lag time.

For avacopan:

- The typical value of CL/F was expected to be 35% lower in subjects with ANCA-associated vasculitis compared to subjects in Phase 1 studies.
- While body weight, age, ALT, eGFR, and albumin were identified as significant covariates for clearance and volume of distribution, the impact on avacopan exposure is not expected to be clinically relevant.

For metabolite M1:

- The typical value of CL/F was expected to be similar in subjects with ANCA-associated vasculitis compared to healthy subjects.
- While body weight, age, and eGFR were identified as significant covariates for M1 clearance and volume of distribution, the impact on M1 exposure is not expected to be clinically relevant.

Concomitant administration of CYP3A4 inducers and inhibitors, cyclophosphamide, rituximab, and proton-pump inhibitors was evaluated as categorical covariates (Absence/Presence) in the population PK analysis. However, only limited number of subjects in the PK analysis were co-administered moderate CYP3A4 inhibitors (n=4), rituximab (n=3), and cyclophosphamide (n=1), and none of subjects was co-administered moderate CYP3A4 inducers. In addition, insufficient PK samples were collected during the absorption phase of avacopan with concomitant use of proton-pump inhibitors and no specific timing of dosing information was provided for these concomitant medications. Therefore, the population PK analysis alone is not considered adequate to support the related labeling claim.

17.4. Statistics

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

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

Therefore, the Applicant used the average of the lower bounds, 60.9%, as a conservative estimate of disease remission rates for a clinical trial of patients receiving cyclophosphamide plus glucocorticoids or rituximab plus glucocorticoids.

The disease remission rate with glucocorticoids alone was estimated to be 45.5% (95% CI: 28.7%, 62.3%) based on the meta-analysis of 3 published studies. The study by Hoffman et al., 1992, included 10 patients with granulomatosis with polyangiitis (GPA, Wegener granulomatosis) who received only glucocorticoids as treatment; the study by Ribi et al., 2010, included 66 patients with microscopic polyangiitis (MPA) who received only glucocorticoids; the study by Nachman et al., 1996, included patients with MPA (67%) or with necrotizing crescentic glomerulonephritis (33%) (Hoffman et al. 1992; Nachman et al. 1996; Ribi et al. 2010). None of the studies were randomized; for Ribi et al., 2010, patients were to be randomized at the time of treatment failure with glucocorticoids only regimen.

To estimate the contribution of glucocorticoids to the remission rate of the cyclophosphamide/rituximab plus glucocorticoid, the Applicant noted the following:

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

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

17.5. Additional Clinical Data

Table 129. Reasons for Use of Non-Study Supplied Glucocorticoids in Study CL010_168 by Background Therapy (Weeks 0 to 26 and Week s 27 to 52)

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

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

Table 130. Protocol-Specified Prednisone Taper in Standard of Care Arm in Study CL010_168

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

Source: CL010_168 CSR, Table 6, page 122.

Table 131. Protocol-Specified Prednisone Taper in AAV Studies

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

Source: Cortazar FB and Niles JL. The fate of plasma exchange and glucocorticoid dosing in ANCA-associated vasculitis after PEXIVAS. AJKD. 2020; 76: 595-597.
CLEAR = CL002_168
[1] prednisone was tapered to 25 mg at Week 4
Abbreviations: AAV, ANCA-associated vasculitis.

Table 132. BVAS Scoring Discrepancies Between Investigator and Adjudicator

Patients	BVAS Organ System	Manifestations	Investigator BVAS→ Adjudicator BVAS
Week 26			
Avacopan			
101-005	General	Fatigue	2 → 0
	ENT	Mastoiditis	2 → 0
126-001	Renal	Hematuria ≥10 RBCs/hpf, proteinuria >1+, rise in Cr/fall in CrCl	16 → 0
302-001	Renal	Hematuria ≥10 RBCs/hpf, proteinuria >1+	14 → 0
327-001	Renal	Proteinuria >1+	4 → 0
378-001	Chest	Infiltrate	4 → 0
429-008	ENT	Bloody nasal discharge/crust/ulcer/granulomata/ paranasal sinus involvement	6 → 0
430-001	Renal	Proteinuria >1+	4 → 0
439-001	Renal	RBC casts/GN	6 → 0
439-005	Renal	RBC casts/GN	6 → 0
451-004	Renal	Proteinuria >1+	4 → 0
	Nervous	Sensory peripheral neuropathy	6 → 0
454-007	General	Myalgia	1 → 0
460-001	Renal	Hypertension, proteinuria >1+	8 → 0
528-003	General	Fatigue	2 → 0
	Nervous	Sensory peripheral neuropathy	6 → 0
529-001	Chest	Nodules or cavities	3 → 0
652-001	Renal	Proteinuria >1+	4 → 0
751-001	Renal	Proteinuria >1+	4 → 0
751-002	Renal	Proteinuria >1+	4 → 0
764-002	Renal	Proteinuria >1+	4 → 0
958-001	Nervous	Sensory peripheral neuropathy	6 → 0
958-002	ENT	Sensorineural hearing loss	6 → 0
969-002	General	Arthralgia, myalgia	2 → 0
	ENT	Paranasal sinus involvement, sensorineural hearing loss	8 → 0
	Chest	Infiltrate, nodules or cavities, pleural infusion/pleurisy	11 → 0
Prednisone			
104-004	ENT	Bloody nasal discharge/crust/ulcer/granulomata	4 → 0
109-003	Renal	Proteinuria >1+	4 → 0
203-001	ENT	Conductive hearing loss	3 → 0
326-003	Renal	Proteinuria >1+	4 → 0
376-001	Renal	Hypertension, proteinuria >1+	8 → 0
378-005	Renal	Hematuria ≥10 RBCs/hpf	6 → 0
378-008	General	Arthralgia/arthritis	1 → 0
429-007	Renal	Proteinuria >1+	4 → 0
439-003	General	Weight loss ≥2kg	2 → 0

Patients	BVAS Organ System	Manifestations	Investigator BVAS→ Adjudicator BVAS
Week 52			
Avacopan			
302-001	Renal	HTN	4 → 0
326-002	ENT	Conductive hearing loss	0 → 3
439-001	Renal	RBC casts/GN	6 → 0
451-002	Renal	HTN, Proteinuria >1+	8 → 0
	Abdominal	Ischemic abdominal pain	0 → 6
461-005	General	Arthralgia/arthritis	1 → 0
529-003	General	Arthralgia/arthritis	1 → 0
958-001	Nervous	Sensory peripheral neuropathy	6 → 0
969-002	Chest	Infiltrate, nodules or cavities, pleural infusion/pleurisy	11 → 0
Prednisone			
104-004	ENT	Bloody nasal discharge/crust/ulcer/granulomata	4 → 0
326-003	Renal	Proteinuria >1+	4 → 0
350-002	Renal	Rise in Cr/Fall in CrCl	0 → 6
376-001	Renal	HTN	4 → 0
378-005	Renal	Hematuria ≥10 RBCs/hpf	6 → 0
429-013	Renal	Hematuria ≥10 RBCs/hpf	6 → 0
439-003	Nervous	Headache	1 → 0
460-002	Renal	HTN	4 → 0
651-002	Chest	Endobronchial involvement	4 → 0

Source: Clinical reviewer, based on ChemoCentryx Response to IR#14
Abbreviations: BVAS, Birmingham Vasculitis Activity Score; CrCl, creatinine clearance; ENT, ear, nose, throat; GN, glomerular; hpf, high power field; HTN, hypertension; RBC, red blood cells

Table 133. Examples of Case Summaries of Patients Who Required Non-Study Supplied Glucocorticoids

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

Source: Clinical reviewer, based on ChemoCentryx response to IR# 4, dated September 25, 2020
Abbreviations: BVAS, Birmingham Vasculitis Activity Score.

Table 134. Case Summaries of SAEs Associated with Hepatic Abnormalities in the Avacopan Clinical Program

Patient No./ Study No.	Reported Term	AE Start Day	Summary of Adverse Event
(b) (6) CL010_168	Elevated liver function tests	50	65-year-old female with MPA received IV CYC for induction on study day 1 (q2w through study day 93) and then started oral AZA for maintenance on study day 106-423. The patient started with normal "liver function tests" which were then noted to be elevated on study day 50 with ALT of 336 U/L, AST 163 U/L, and ALP 314 U/L. Total bilirubin was normal. Per report, this was the first and highest elevation documented. The patient received Keflex for a UTI on study day 45-49, just before these LFT elevations. The last dose of avacopan was received on study day 52 when the LFTs were already decreasing. The patient was not re-challenged, and avacopan was discontinued. Laboratory testing showed normal LFTs by study day 65. Investigators attributed the event to possibly related to study drug or IV CYC. DHN DILI team determined this case to be **possible** DILI due to avacopan. However, the DILI team noted the alternate diagnosis of Keflex liver injury.
(b) (6) CL010_168	Hepatic function disorder	114	62-year-old female with newly diagnosed GPA received RTX for induction starting on study day 1. The patient was noted to have a gradual increase in LFTs on study day 113 with the highest values on study day 161 with ALT 1933 U/L, AST 1708 U/L, and ALP 189 U/L. The highest bilirubin was 13.56 mg/dL on study day 169. Albumin increased over the course of the study, and INR remained normal. LFTs returned to normal on study day 225. Other significant laboratory results included central agranulocytosis on study day 155, which resolved without intervention. Avacopan was discontinued on study day 147. Diagnostic work-up for LFTS was conducted by GI from study day 164 to 171 – including abdominal ultrasound, abdominal CT, and liver biopsy. Viral serologies (HAV, EBV, CMV) were notable for IgG positivity. Liver biopsy was suggestive of a resolving inflammatory process, and the diagnosis was chronic and active portal and lobular hepatitis suggestive of toxic or drug-induced etiology. Investigators did not determine an etiology for either the elevated LFTs or the agranulocytosis but that the "hepatic function disorder" was possibly related to study drug. DHN DILI team determined this case to be **possible** DILI due to avacopan. This case meets Hy's Law laboratory criteria. However, the DILI team noted the alternate diagnosis of simvastatin liver injury.

Patient No./ Study No.	Reported Term	AE Start Day	Summary of Adverse Event
(b) (6) CL010_168	Hepatic cytolysis	37	80-year-old female with newly diagnosed MPA with pauci-immune GN received RTX for induction on study day 1. She was noted to have elevated in LFTs (ALT 300 U/L, AST 150 U/L) on study day 37. Avacopan and Bactrim were discontinued. LFTs subsequently decreased. The patient was re-challenged with avacopan on study day 43 when the ALT, ALP, GGT levels were not at baseline (ALT 137 U/L, ALP 22 IU/L, GGT 582 IU/L). The patient was also switched from Bactrim to pentamidine for PCP prophylaxis. On study day 51, the LFTs further increased (ALT 355 IU/L, AST 158 IU/L, TB normal, GGT elevated, ALP elevated). Avacopan was then permanently discontinued on study day 51. Pentamidine was continued. LFTs (AST, ALT, ALP) returned to normal on study day 85. Other AEs that were reported when the patient actively had elevated LFTs included diarrhea, cholestasis, and pancreatic failure. The Investigator determined the “asymptomatic hepatitis” to be possibly related to study drug, as it recurred with drug re-challenge. DHN DILI team determined this case to be **highly likely** DILI due to avacopan.
(b) (6) CL010_168	Cytolytic hepatitis, Cholestatic hepatitis	93, 93	54-year-old female with newly diagnosed MPA received IV CYC starting on study day 1 and then transitioned to oral AZA on study day 107. The patient was enrolled in the trial while hospitalized for symptoms of fatigue, GN, sinus involvement, and minimal pulmonary hemorrhage. Her hospitalization was prolonged due to nausea attributed to CYC. LFTs were normal at baseline. On study day 70, the patient was first noted to have elevated LFTs (ALT 64 U/L, AST 55 U/L). These LFTs further increased with the highest reported values at ALT 380 U/L and AST 229 U/L on study day 93. No significant increase in ALP or TB were noted. Avacopan was discontinued on study day 97. LFTs were already starting to decrease and were normal by study day 113. The Investigator attributed the severe (Grade 3) “cytolytic hepatitis” and “cholestatic hepatitis” as possibly related to study drug or IV CYC. DHN DILI team determined this case to be **probable** DILI due to avacopan.

Patient No./ Study No.	Reported Term	AE Start Day	Summary of Adverse Event
(b) (6) CL010_168	Azathioprine-induced liver toxicity	131	81-year-old female with GPA received IV CYC for induction on study day 1 and was transitioned to oral AZA on study day 114. The patient had mildly elevated LFTs during the screening period (study day -7), but these normalized by her baseline visit. On study day 131, the patient's LFTs were elevated (ALT, AST, ALP, GGT). AZA and Bactrim were discontinued, and pantoprazole was reduced. AST was decreased on study day 134, and ALT and AST normalized by study day 140. Avacopan was continued throughout the event. The Investigator attributed the severe (Grade 3) liver toxicity as probably not related to study drug, rather related to azathioprine. DHN DILI team determined this case to be **unlikely** DILI due to avacopan.
(b) (6) CL010_168	Elevated AST values >5x ULN	50	68-year-old male with newly diagnosed GPA received IV CYC for induction on study day 1 and started mycophenolate on study day 166. The patient's medical history is significant for a cholecystectomy. The patient had normal LFTs at baseline. On study day 50, the patient had elevated AST >5x ULN at 222 U/L, ALT 192 U/L, ALP 165 U/L, and normal total bilirubin. The patient underwent multiple diagnostic testing including abdominal ultrasound, abdominal nuclear magnetic resonance (NMR), and EGD, and MRCP. The patient was diagnosed with biliary sludge biliary duct dilatation. He was treated with ursodeoxycholic acid therapy on study day 113 with improvement. AST was significantly reduced by study day 120 and normal by study day 141. Avacopan was continued throughout this event, and the patient completed the study. The Investigator attributed the elevation in LFTs (AST) to cholestasis and probably not related to study drug. DHN DILI team determined this case to be **unlikely** DILI due to avacopan.

Patient No./ Study No.	Reported Term	AE Start Day	Summary of Adverse Event
(b) (6) CL010_168	Elevated liver enzymes	103	79-year-old female with newly diagnosed MPA received IV CYC for induction on study day 1 and received a total of 6 doses. At baseline, the patient had elevated LFTs (ALT 88 U/L, AST 35 U/L, normal ALP and TB) but subsequently normalized. However, from study day 49 to 74, the patient had elevated LFTs (highest on day 49 with ALT 336 U/L, AST 224 U/L, ALP 190 U/L). Avacopan and Bactrim were discontinued for this non-serious AE. LFTs normalized on study day 74. Both avacopan and Bactrim were re-started (avacopan on study day 70), and LFTs remained normal. Because of worsening AAV, the patient was treated with IV RTX on study day 96. LFTs increased on study day 103. Both avacopan and Bactrim were again discontinued and not restarted. The second elevation in LFTs was considered serious and resolved by study day 131. The Investigator considered the elevation in LFTs to be a "moderate" (Grade 2) AE and possibly related to study drug. DHN DILI team determined this case to be **probable** DILI due to avacopan.
(b) (6) CL010_168	Alcoholic hepatic enzyme elevation	23	68-year-old female with relapsed GPA was induced with IV RTX starting on study day 1. Baseline labs revealed normal LFTs. LFTs were elevated on study day 23 (AST 56 U/L, ALT 124 U/L, ALP 1035 U/L, GGT 248 U/L). Prior to this SAE, the patient admitted to vacationing in Hawaii (study days 15 to 22) and to drinking alcohol at least twice daily. Subsequent laboratory results showed decreased LFTs, and LFTs were considered resolved by study day 71. Avacopan was continued throughout this event, and the patient continued in the study. The Investigator considered this a mild (Grade 1) event of "alcoholic hepatic enzyme elevation," probably not related to study medication. DHN DILI team determined this case to be **unlikely** DILI due to avacopan.

Patient No./ Study No.	Reported Term	AE Start Day	Summary of Adverse Event
(b) (6) CL010_168	Liver dysfunction	43	81-year-old Asian female with newly-diagnosed MPA received IV CYC for induction on study day 1 (total 3 doses). She was then switched to RTX on study day 71. She had normal LFTs at baseline. HBV DNA was negative on study day 15. On study day 29 ALP rose to 213, but ALT and AST remained normal. HBV DNA was still negative on that day. Avacopan continued. On study day 43, she had elevated ALT to 207 U/L and AST 117 U/L. The ALP also rose to a peak of 1503 on study day 44. The first elevation in Total Bilirubin was still <2x ULN and noted on study day 44. Avacopan was discontinued on study day 43 and not restarted. Hepatitis B DNA was positive at low titer on study day 50 and study day 71 (serologies not provided). Rituximab started study day 71 with normal ALT and AST. ALP was down to 309. Entecavir started study day 85, and HBV DNA became negative on day 113. Liver enzymes had also fallen to normal by day 113. The Investigator considered this AE to be “severe” (Grade 3) and possibly related to study drug or IV CYC. DHN DILI team determined this case to be **probable** DILI due to avacopan. The clinical course was considered not to be consistent with acute HBV infection and the appearance of HBV DNA was considered more likely to represent HBV reactivation that was without overt liver injury.

Patient No./ Study No.	Reported Term	AE Start Day	Summary of Adverse Event
(b) (6) CL002_168	Elevated liver enzymes, elevated pancreatic enzymes	22	80-year-old male with xx and was induced with CYC and was in the treatment arm receiving avacopan 30 mg BID + no prednisone. Other concomitant medications included methylprednisolone and sulfamethoxazole/trimethoprim. His medical history was significant for “episodes of alcohol abuse” (last episode 6 months before the study). On study day 22, the patient had elevated liver enzymes (AST 201 U/L, ALT 277 U/L, GGT 356 U/L, AlkPhos 453 U/L, LDH 312 U/L) and elevated pancreatic enzymes (amylase 62 U/L). On study day 23, he experienced vomiting, fatigue, and decreased appetite. Liver and pancreatic enzymes were slightly more elevated. Abdominal ultrasound showed hepatic steatosis but was, otherwise, normal. Study medication as well as other medications were discontinued on study day 26. His laboratory values peaked with direct bili 11.31 mg/dL (study day 34), total bili 12.90 mg/dL (study day 35), AST 201 U/L, ALT 277 U/L, GGT 356 U/L, LDH 312 U/L (study day 22), alk phos 633 U/L (study day 26), p-amylase 99 U/L (study day 28). On study day 31, abdominal CT showed minimal cholangitis. Liver biopsy on study day 34 revealed a mixed pattern of injury with widely resolved hepatitis histology appearance and persistent cholangitic/cholestatic components. The laboratory values eventually returned to normal by study day 134. The Investigator considered the AE to be severe and possibly related to avacopan, probably not related to corticosteroids, and possibly related to CYC. DHN DILI team determined this case to be **possible** DILI due to avacopan. However, the DILI team noted the alternate diagnosis of Bactrim liver injury.

Patient No./ Study No.	Reported Term	AE Start Day	Summary of Adverse Event
SAE of HBV reactivation (associated with Grade 3/4 elevation in AST and ALT)			
(b) (6) CL010_168	HBV reactivation	391	79-year-old male with newly-diagnosed MPA received RTX on study day 1. On study day 50, the patient had mild hepatic enzyme elevation (ALT 90 U/L, AST 51 U/L, GGT 208 U/L). He continued study medication, and abnormal laboratory results resolved by study day 70. On study day 391, he experienced life-threatening HBV with elevated ALT and AST. Although the patient had a negative HBsAg at baseline, he did test positive for HBcAb in the past (2 years prior to study). The patient was hospitalized and received entecavir hydrate, ursodeoxycholic acid, and prednisolone. The patient completed the study on study day 432 at which time he was still hospitalized. He was discharged the following day but was re-hospitalized about 2 weeks later when another deterioration in LFTs was observed. The event of HBV was reported as resolved almost 3 months later. The Investigator and Gastroenterologist reported that HBV levels could have increased during exposure to study drug, thus, possibly related to study drug. The Applicant, on the other hand, attributed the event to RTX induction.

Source: Clinical reviewer, based on CL010_168 and CL002_168 CSR, subject narratives
TEAEs associated with Hepatic Abnormalities include AEs in the Hepatobiliary and Investigations SOCs
Abbreviations: AE, adverse events; ALT, alanine aminotransferase; ALP; alkaline phosphate; AST, aspartate aminotransferase; AZA, azathioprine; BID, twice daily; bili, bilirubin; BVAS, Birmingham Vasculitis Activity Score; CMV, cytomegalovirus; CYC, cyclophosphamide; CT, computer tomography; DILI, drug-induced liver injury; DHN, Division of Hepatology and Nutrition; EBV, Epstein-Barr virus; EGD, esophagogastroduodenoscopy; GGT, gamma-glutamyl transferase; GPA, granulomatosis with polyangiitis; HAV, hepatitis A virus; HBcAB; hepatitis B core ant body test; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LDH, lactate dehydrogenase; LFT, liver function tests; MPA, microscopic polyangiitis; MRCP, magnetic resonance cholangiopancreatography; PCP, *Pneumocystis* pneumonia; SAE, serious adverse events; TB, total bilirubin; ULN, upper limit of normal; UTI, urinary tract infection.

Table 135. Preferred Terms (PTs) of Adverse Events Potentially Associated With Glucocorticoid Toxicity (EULAR Search Terms)

SOC	Preferred Terms
Blood and lymphatic system disorders	Increased tendency to have bruise
Cardiac disorders	Acute myocardial infarction Angina pectoris Cardiac failure Cardiovascular insufficiency Congestive cardiomyopathy Myocardial infarction Myocardial ischemia
Endocrine disorders	Adrenal insufficiency Cushing's syndrome Cushingoid

SOC	Preferred Terms
Eye disorders	Cataract Cataract nuclear Glaucoma Ocular hypertension Open angle glaucoma Retinopathy hypertensive
Gastrointestinal disorders	Duodenal ulcer Gastritis Gastritis erosive Gastrointestinal disorder Pancreatitis Pancreatitis acute
General disorders and administration site conditions	Influenza like illness Edema Edema peripheral Peripheral swelling Systemic inflammatory response syndrome
Infections and infestations (only SAEs will be included)	Anal fungal infection Aspergillus infection Atypical pneumonia Bacteremia Blister infected Body tinea Breast abscess Bronchiolitis Bronchitis Campylobacter gastroenteritis Candida infection Carbuncle Catheter site infection Cellulitis Chlamydial infection Clostridium difficile infection Conjunctivitis Conjunctivitis viral Cryptococcosis Cystitis Cytomegalovirus infection Dacryocystitis Device related infection Diarrhea infectious Diverticulitis Ear infection Ear infection fungal Enteritis infectious Epstein-Barr virus infection Erysipelas Escherichia infection Escherichia urinary tract infection

SOC	Preferred Terms
	Eye infection
	Folliculitis
	Fungal infection
	Fungal skin infection
	Furuncle
	Fusobacterium infection
	Gastroenteritis
	Gastroenteritis viral
	Genital herpes
	Genitourinary tract infection
	Gingivitis
	Hepatitis B
	Herpes simplex
	Herpes zoster
	Hordeolum
	Infectious pleural effusion
	Influenza
	Laryngitis
	Latent tuberculosis
	Localized infection
	Lower respiratory tract infection
	Lower respiratory tract infection viral
	Lung infection
	Klebsiella test positive
	Meningitis
	Mucocutaneous candidiasis
	Nasopharyngitis
	Neutropenic sepsis
	Esophageal candidiasis
	Ophthalmic herpes simplex
	Oral candidiasis
	Oral fungal infection
	Oral herpes
	Otitis externa
	Otitis media
	Otitis media acute
	Otitis media chronic
	Parainfluenza virus infection
	Paronychia
	Periodontitis
	Pharyngitis
	Pharyngitis streptococcal
	Pneumonia
	Pneumonia bacterial
	Pneumonia cytomegalovirus
	Pneumonia hemophilus
	Post procedural infection
	Post procedural sepsis
	Pulpitis dental

SOC	Preferred Terms
	Pyuria
	Rash pustular
	Respiratory syncytial virus infection
	Respiratory tract infection
	Respiratory tract infection viral
	Sepsis
	Subcutaneous abscess
	Tinea cruris
	Tinea pedis
	Tinea versicolor
	Tongue fungal infection
	Tonsillitis
	Tooth abscess
	Tooth infection
	Tracheitis
	Upper respiratory tract infection
	Urethritis
	Urinary tract infection
	Urinary tract infection bacterial
	Urosepsis
	Varicella zoster virus infection
	Viral infection
	Viral rhinitis
	Viral sinusitis
	Viral upper respiratory tract infection
	Vulvovaginal candidiasis
	Vulvovaginal mycotic infection
	Vulvovaginitis
	Wound infection pseudomonas
Injury, poisoning, and procedural complications	Hip fracture
	Humerus fracture
	Lower limb fracture
	Lumbar vertebral fracture
	Spinal compression fracture
	Tendon rupture
	Wrist fracture
Investigations	Blood cholesterol increased
	Blood glucose increased
	Blood potassium decreased
	Blood pressure increased
	Intraocular pressure increased
	Low density lipoprotein increased
	Waist circumference increased
	Weight increased

SOC	Preferred Terms
Metabolism and nutrition disorders	Central obesity Diabetes mellitus Diabetes mellitus inadequate control Dyslipidemia Fluid retention Glucose tolerance impaired Hypercholesterolemia Hyperglycemia Hyperlipidemia Hypertriglyceridemia Hypervolemia Hypokalemia Type 2 diabetes mellitus
Musculoskeletal and connective tissue disorders	Muscle atrophy Muscular weakness Myopathy Osteonecrosis Osteopenia Osteoporosis
Nervous system disorders	Poor quality sleep
Psychiatric disorders	Affective disorder Agitation Anxiety Confused state Depressed mood Depression Insomnia Irritability Libido decreased Major depressed Mania Mental status changes Mood altered Nervousness
Reproductive system and breast disorders	Gynecomastia Menorrhagia Metrorrhagia
Skin and subcutaneous tissue disorders	Acne Dermatitis acneiform Ecchymosis Hirsutism Skin atrophy Skin striae
Vascular disorders	Arteriosclerosis Hypertension Hypertensive emergency

Abbreviations: SAE, serious adverse event; SOC, system organ class.

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Pharmacology and Toxicology Secondary Review for NDA 214487

TO: NDA 214487 (Avacopan, CCX-168)

FROM: Timothy W. Robison, Ph.D., D.A.B.T.
Pharmacology and Toxicology Team Leader
Division of Rheumatology and Transplant Medicine

DATE: March 15, 2021

Avacopan is a selective antagonist of the complement 5a receptor (C5aR) with a proposed indication for the treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]).

Avacopan is provided as a 30-mg capsule, which is taken twice daily with food for a total daily dose of 60 mg.

Dr. Ijeoma Uzoma's reviews dated March 8, 2021 focused on the safety assessment of the Sponsor's nonclinical pharmacology and toxicology program for Avacopan.

I concur with the recommendations of Dr. Ijeoma Uzoma's reviews dated March 8, 2021 that the nonclinical pharmacology and toxicology of Avacopan have been adequately studied and the drug product should be approved from the nonclinical perspective.

The Sponsor has a complete nonclinical development program for the Avacopan. A brief summary is provided below. Please see Dr. Ijeoma Uzoma's reviews for more details.

Pharmacology:
In vitro and in vivo pharmacology studies determined that CCX168 and its metabolite, CCX168-M1, were antagonists of C5a binding to its receptor, C5aR. Humans, monkeys, and hamsters were determined to be pharmacologically relevant species. C5aR displays a relatively low level of amino acid sequence conservation between species. The rodent versions of C5aR were only ~70% identical to human C5aR, with many amino acid changes occurring in the transmembrane and extracellular regions important for C5a binding. A tryptophan residue in transmembrane domain 5 of C5aR was identified as crucial for C5a receptor antagonist binding and appears to contribute to the species-specific activity observed with small-molecule inhibitors of C5a receptors, since the amino acid is conserved with human, cynomolgus monkey, and hamster C5aR, but not other commonly used nonclinical animal species including mice, rats, rabbits, and dogs. Mice, rats, rabbits, and dogs were determined to not be pharmacologically relevant species.

ADME:
Metabolism, rather than direct renal and biliary elimination of the intact drug, was the dominant route of CCX168 elimination. Metabolism of avacopan was comparable in rats, hamsters, monkeys, and humans. CCX168-M1 was a major metabolite of CCX168 in

nonclinical species and humans. The primary route of elimination of the metabolites was through biliary excretion into feces.

General Toxicology:
The Sponsor conducted oral toxicology studies up to 26 weeks in rats, 13 weeks in hamsters, and 44 weeks in monkeys. The hamster and monkey were pharmacologically relevant species and could assess both potential on-target and off-target toxicity. However, the rat was not a pharmacologically relevant and could only assess potential off-target toxicity.

In the 26-week oral toxicology study with rats, CCX168 was administered at doses of 0 (vehicle), 5, 15, 100, and 200 (100 mg/kg BID) mg/kg/day. The rat was not a pharmacologically relevant species. No dose-limiting toxicity or target organs of toxicity were identified. CCX168 exposure was saturated at the 100 mg/kg/day. CCX168 C_{max} and AUC_{0-24} were not markedly increased with a dose of 100 mg/kg BID (200 mg/kg/day) relative to the dose of 100 mg/kg/day. Based upon the observed saturation, the NOAEL was 100 mg/kg/day, the lowest dose where the saturation was first observed.

In the 13-week toxicology study in hamster, CCX168 was administered at doses of 0 (vehicle), 10, 30, 100 and 1000 (500 mg/kg BID) mg/kg/day. No dose-limiting toxicity or target organs of toxicity were identified. The highest exposure was observed at 100 mg/kg/day for both the parent drug and M1 metabolite. The NOAEL for general toxicity of CCX168 was identified at 100 mg/kg/day.

In the 44-week oral toxicology with monkeys, CCX168 was administered at doses of 0 (vehicle), 5, 15 and 30 (15 mg/kg BID) mg/kg/day over the first 25 weeks of the study. Doses were increased to 7.25, 22.5, and 45 (22.5 mg/kg BID) mg/kg/day, respectively, from Weeks 26-44. No dose-limiting toxicity or target organs of toxicity were identified. The NOAEL was considered as the high dose.

Genetic Toxicology:
Avacopan was negative in all assays including the *in vitro* bacterial mutagenicity study (Ames test), *in vitro* mouse lymphoma forward-mutation assay, and *in vivo* rat bone marrow micronucleus study. Metabolite CCX168-M1 was judged negative for mutagenicity in the Ames test for bacterial gene mutation based on confirmation that CCX168-M1 was formed upon incubation of CCX168 with S9.

Carcinogenicity:
Dr. Uzoma presented the results of the Sponsor's 2-year carcinogenicity studies in Sprague Dawley rats and hamsters to the Executive Carcinogenicity Assessment Committee (ECAC) on February 23, 2021 (see meeting minutes dated February 25, 2021). The ECAC judged that both studies were adequate, noting prior concurrence for doses used in the studies, and that no treatment-related neoplastic findings were identified in males and females of either species.

Phototoxicity:

CCX168 absorbed UV light at 290 nm with a molar extinction coefficient of 2989 L mol^{-1} cm^{-1}. However, CCX168 was negative in a Neutral Red Uptake Phototoxicity Assay with BALB/c 3T3 Mouse Fibroblasts. This assay has a high false positive rate, so the negative assay indicated that there was minimal concern for potential phototoxicity.

Reproductive Toxicology:
A complete battery of reproductive toxicity studies were conducted with Avacopan.

Fertility and reproductive performance were unaffected in a fertility and early embryonic development study with male and female hamsters that received oral doses of CCX168 up to 1000 mg/kg/day.

In embryofetal development studies with hamsters and rabbits, no fetal harm or malformations were observed with oral doses of CCX168 up 1000 and 200 mg/kg/day. An increase in a skeletal variation described as supernumerary ribs was noted in hamsters at the dose of 1000 mg/kg/day. This finding was considered a developmental delay as supernumerary ribs can resolve into the vertebral arch later in development. An increased incidence of abortions was observed in rabbit does at 200 mg/kg/day.

In a pre- and post-natal development study with hamsters, there were no effects of CCX168-treatment of the F0 mothers at doses up to 1000 mg/kg/day on growth, physical, and neurological development as well as reproductive performance of the F1 generation.

Labeling:
A labeling review was in preparation at the time of this review. From the nonclinical perspective, there appears to be adequate evidence for the Established Pharmacological Class (EPC) for Avacopan as a selective antagonist of the complement 5a receptor (C5aR). A final decision is pending discussion with the Review Team.

Recommendation: From the nonclinical perspective, approval of the application is recommended. No further nonclinical studies are required at this time. There are no outstanding nonclinical issues.

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/s/

TIMOTHY W ROBISON
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 214487
Supporting document/s:	SDN #16
Applicant's letter date:	December 2, 2020
CDER stamp date:	December 2, 2020
Product:	Avacopan "Complement 5a receptor (C5aR) Antagonist"
Indication:	Treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA])
Applicant:	ChemoCentryx, Inc.
Review Division:	Division of Rheumatology and Transplant Medicine (DRTM) Division of Pharm/Tox for Immunology and Inflammation (DPT-II)
Reviewer:	Ijeoma Uzoma, PhD
Supervisor/Team Leader:	Timothy W. Robison, Ph.D., D.A.B.T.
Division Director:	Nikolay Nikolov, MD
Project Manager:	Susie Choi, PharmD

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 214487 are owned by ChemoCentryx Inc. or are data for which ChemoCentryx Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 214487 that ChemoCentryx Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 214487.

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1 Executive Summary

1.1 Introduction

ChemoCentryx Inc. submitted NDA 214487 on July 7, 2020 in support of marketing approval for Avacopan (CCX168). CCX168 is a small molecule inhibitor of complement component 5a receptor (C5aR), that is being developed as an oral treatment for adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis.

This review evaluates the results of a 2-year oral carcinogenicity study conducted in Sprague Dawley rats (Study No. PC0675_168) and a 2-year oral carcinogenicity study conducted in hamsters (Study No. PC0674_168).

1.2 Brief Discussion of Nonclinical Findings

2-year carcinogenicity study in Sprague Dawley rats:
The Sponsor conducted a 2-year carcinogenicity study in Sprague Dawley rats. In the 2-year carcinogenicity study, Sprague Dawley rats received CCX168 (avacopan) by oral gavage at doses of 10, 30, and 100 mg/kg/day. These doses received concurrence from the FDA Executive Carcinogenicity Assessment Committee (IND 120784, see ECAC meeting minutes dated November 9, 2017). Treatment with CCX168 had no effects on survival for male or female rats. The carcinogenicity study was terminated for female groups after reaching the termination criteria of 20 animals for Group 1 (vehicle-control) females during Week 92 and for male groups after reaching the termination criteria of 20 animals for Group 2 (water control) males during Week 97. Study termination was in accordance with FDA ECAC recommendations. There were no statistically significant test article-related tumor findings in male or female rats. Toxicokinetic analysis conducted on Day 28 indicated that the highest systemic exposures (AUC) and C_{max} were achieved in mid-dose group at 30 mg/kg/day. The C_{max} and AUC_{0-24} exposure decreased from 30 to 100 mg/kg/day resulting in 0.68- and 0.65-fold reduction in C_{max} and AUC_{0-24}, respectively. Therefore, to assess the relationship of findings to treatment with CCX168, the 30 mg/kg group was also analyzed as the high dose group. Collectively, CCX168 was not tumorigenic in rats at doses up to 30 or 100 mg/kg/day in males and females.

The ECAC concurred that the 2-year rat carcinogenicity study was adequate and that there were no drug-related neoplasms in males or females.

2-year carcinogenicity study in hamsters (see Appendix 1):
Using doses of CCX-168 at 10, 30, and 100 mg/kg/day, per agreement with ECAC recommendations, female hamsters were treated for periods up to 92 weeks and male hamsters were treated for periods up to 98 weeks. There were no CCX-168-related neoplastic findings in either male or female hamsters.

Females were terminated during or after Week 92 when survival in the water-control group declined to 20 (20/65 = 30.7%) animals in the group. Males were terminated

during or after Week 98 when survival in the vehicle-control group declined to 20 (20/65 = 30.7%) animals in the group.

For male hamsters, survival was comparable for vehicle-control and drug-treated groups. However, survival for the male water-control group (41/65 = 63.1%) was significantly higher relative to the male vehicle-control and drug-treated groups (20/65 [30.7%] to 26/65 [40%]). The vehicle was Polyethylene glycol (b) (4) [(b) (4) v:v]. A potential vehicle-related effect on survival occurred for male vehicle-control and drug-treated groups. For female hamsters, survival was comparable for the vehicle-control, water-control, and drug-treated groups. The severity of chronic progressive nephropathy (CPN) was increased for male and female vehicle-control and drug-treated groups relative to male and female water-control groups. However, overall incidences of CPN across all male or female groups were not different. There were corresponding increases in CPN as the cause of death for male and female vehicle-control and drug-treated groups relative to male and female water-control groups. The severity of CPN led to increases in mortality for male vehicle-control and drug-treated groups relative to the male water-control group. This did not appear to impact the ability of the study to assess the carcinogenic potential of CCX-168 as males were treated up to Week 98 and females up to Week 92.

There were no CCX-168-related neoplastic findings in either male or female hamsters.

Non-neoplastic findings were evident in ovaries, kidneys, rectum, spleen, mesenteric lymph nodes, liver, colon, cecum, and liver. Mineralization was noted in the ovaries of females administered 30 or 100 mg/kg/day; a corresponding increase in this finding was also noted in females administered 100 mg/kg/day that survived to the terminal sacrifice. This finding was characterized by small foci of basophilic, crystalline, or granular material within the ovarian interstitium.

Administration of the vehicle-control (Polyethylene glycol (b) (4)), regardless of CCX168 dose, resulted in higher incidence and/or severity of chronic progressive nephropathy (CPN) in the kidneys, cystic glands in the rectum, pigment in the spleen, mesenteric lymph nodes, liver, colon, and cecum, and pigmented macrophages in the liver compared to the water-control group.

The ECAC concurred that the 2-year hamster carcinogenicity study was adequate and that there were no drug-related neoplasms in males or females.

2 Drug Information

2.1 Drug

CAS Registry Number 1346623-17-3

Generic Name Avacopan

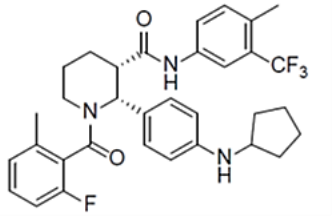
Code Name (CCX-168)

Chemical Name 3-Piperidinecarboxamide, 2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]-, (2R,3S)-

Molecular Formula/Molecular Weight $C_{33}H_{35}F_4N_3O_2$ / 581.6435 Da

Structure or Biochemical Description

Avacopan Drug Substance Structural Formula



Pharmacologic Class Complement 5a receptor (C5aR) Antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 120784

2.3 Drug Formulation

Table 1 Composition of Avacopan 10 mg Hard Capsule

Table 1: Composition of Avacopan 10 mg Hard Capsule

Component	Function	Quality Standard	10 mg Capsule	
			(mg)	% w/w
Avacopan	Drug Substance	In-House	10.0	(b) (4)
Polyoxyl-40 hydrogenated castor oil (b) (4)				(b) (4)
Polyethylene glycol 4000 (PEG-4000) (b) (4)				(b) (4)
Hard gelatin capsule, light orange opaque/ yellow opaque, Size 0				
Gelatin sealing band				
Total				(b) (4)

(b) (4)

Table 2 Composition of Size 0 Light Orange Opaque and Yellow Opaque Bicolor Hard Gelatin Capsule Shell

Table 2: Composition of Size 0 Light Orange Opaque and Yellow Opaque Bicolor Hard Gelatin Capsule Shell

Component	Function	Quality Standard	Quantity per Empty Capsule Cap or Body	
			(mg)	% (w/w)
				(b) (4)

Table 3 Composition of Clear Gelatin Sealing Solution

Table 3: Composition of Clear Gelatin Sealing Solution

Component	Function	Quality Standard	10 mg Capsule	
			(mg)	% (w/w)
Gelatin				(b) (4)
Polysorbate 80				

2.6 Proposed Clinical Population and Dosing Regimen

Avacopan (CCX168) has been developed for treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) at a dose of 30 mg BID. The Sponsor's target AUC concentration for the 30 mg BID dose for CCX168 is 2 x $AUC_{0\text{-}12hr}$ = 6932 ng*hr/mL and for CCX168-M1 is 2 x $AUC_{0\text{-}12hr}$ = 2566 ng*hr/mL.

2.7 Regulatory Background

A Pre-IND meeting was held with the Sponsor. See preliminary comments and final meeting minutes dated April 17, 2014 and May 20, 2014, respectively.

3 Studies Submitted

3.1 Studies Reviewed

1. CCX168: 104 Week Oral (Gavage) Administration Carcinogenicity Study in the Rat (Study No. PC0675-168)

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

Application	Reviewer	Date in DARRTS	Notes
IND 120784	Matthew Whittaker	11-09-2017	Review of 6-month toxicology study with rats
IND 120784	Stephanie J Quinn	11-09-2017	ECAC meeting minutes

IND 120784	Matthew Whittaker	08-22-2019 (Comments were conveyed on 08-13-2019)	Early termination criteria for 104-week carcinogenicity study with rats

8 Carcinogenicity

Study title: CCX168: 104 Week Oral (Gavage) Administration Carcinogenicity Study in the Rat

Study no.:	PC0675_168
Study report location:	EDR
Conducting laboratory and location:	(b) (4) [redacted]
Date of study initiation:	December 5, 2017
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	D-17-043/98.2%; D-16-013/98.2%; D-19-049/98.3%
CAC concurrence:	Yes

Key Study Findings

- In the 2-year carcinogenicity study, Sprague Dawley rats received CCX168 (avacopan) by oral gavage at doses of 10, 30, and 100 mg/kg/day. The highest systemic CCX168 exposures were achieved in the 30 mg/kg/day group due to an apparent saturation of exposure. Therefore, analysis was conducted separately using the 30 and 100 mg/kg groups as the high dose group.

- Treatment with CCX168 had no effects on survival of male or female rats. The Sponsor terminated all female groups starting at Week 92 due to the female vehicle-control group reaching pre-defined termination criteria of 20 survivors (i.e., 20 of 57 [35% survival] females). All male groups were terminated starting at Week 97 due to the male water-control group reaching pre-defined termination criteria of 20 survivor (i.e., 20 of 57 [35% survival] males). Study termination at these time points was supported by ECAC study termination criteria which states that if the number of animals of a sex within the control group declines to 20, then all groups of that sex including drug-treated groups should be terminated.

- There were no treatment related changes of absolute body weights during the treatment period for drug-treated male or female rats relative to vehicle-control groups.

- There were no statistically significant test article-related tumor findings in male or female rats.

- There were no test article related non-neoplastic findings in male or female rats. The incidences of focal C-cell hyperplasia in the thyroid gland for male drug-treated groups were within the historical control range. There was no clear dose relationship for incidences of focal C-cell hyperplasia in the thyroid gland of female drug-treated groups.

- Toxicokinetic analysis conducted on Day 28 indicated that the highest systemic exposures (AUC) and C_{max} were achieved in mid-dose group at 30 mg/kg/day. The C_{max} and AUC_{0-24} exposure decreased from 30 to 100 mg/kg/day resulting in 0.68- and 0.65-fold reductions of C_{max} and AUC_{0-24}, respectively. Therefore, to assess the relationship of findings to of treatment with CCX168, the 30 mg/kg group was also analyzed as the high dose group. Sex-related differences in CCX168 C_{max} and AUC_{0-24} values were minor and generally less than 2-fold.

- The study was judged to be adequate, noting prior ECAC concurrence for dose selection and study design, and negative for test article-related tumor findings in male or female rats.

Adequacy of Carcinogenicity Study

- No treatment groups were retained for the full planned duration of the study (104 weeks); however, the time of sacrifice used were considered acceptable based on established ECAC guidelines for study termination.
- Concurrence for all doses in males and females was obtained from the ECAC (see meeting minutes dated November 9, 2017).

Appropriateness of Test Models

- Sprague Dawley rats are a standard model for assessment of carcinogenic potential. The oral gavage route of administration models the clinical route of administration.

Evaluation of Tumor Findings

There were no treatment-related neoplastic findings based on the lack of statistical significance for both trend and pair-wise statistical analysis separately using the 30 mg/kg or 100 mg/kg as the high dose group.

Methods

Doses:	0, 10, 30, and 100 mg/kg/day
Frequency of dosing:	Daily
Dose volume:	2.5 mL/kg

Route of administration:	Oral
Formulation/Vehicle:	Group 1- Vehicle control -Polyethylene glycol (b) (4) (b) (4) v:v] Group 2- Water control- purified water
Basis of dose selection:	Doses used in the 26-week oral toxicology study in SD rats were used as the basis for dose selection. In the 26-week rat study (No. PC0655-168), animals received CCX168 at doses (mg/kg) of 5 mg/kg QD, 15 mg/kg QD, 100 mg/kg QD, and 100 mg/kg BID. The rat is not a pharmacologically relevant species for CCX168 as CCX168 has no activity toward its target, complement C5a receptor, in rats. There were no test article related deaths during the study. There was no effect of CCX168 treatment on mean absolute body weights in males or females at any time point during the dosing period. Systemic CCX168 exposure and its M1 metabolite were saturated at the dose of 100 mg/kg/day. CCX168 C_{max} and AUC_{0-24} were not markedly increased in animals that received 100 mg/kg BID (total daily dose of 200 mg/kg) relative to those that received 100 mg/kg once per day. Based upon the observed saturation, the NOAEL was 100 mg/kg/day, the lowest dose where the saturation was first observed. Rats dosed at 100 mg/kg/day CCX168 were expected to achieve a systemic CCX168-M1 (major human metabolite) exposure level approximately equal to that in humans at the maximum recommended human dose For the design of the 2-year rat carcinogenicity study, the Sponsor proposed oral doses of 10, 30, and 100 mg/kg/day in males and females. The high dose was based on saturation of exposure of CCX168 at doses ≥ 100

	mg/kg/day. The ECAC agreed with the proposed high dose based on saturation of exposure. Separation of dose at 10, 30, and 100 mg/kg/day in the 26-week rat study was noted to be approximately 2-fold. The mid- and low-doses for both sexes were selected based on adequate spacing of AUC. The Committee concurred with vehicle-control (PEG (b) (4) (b) (4) and water-only control groups. (See meeting minutes dated November 9, 2017).
Species/Strain:	Sprague Dawley/CRL:CD rats from (b) (4)
Number/Sex/Group:	Carcinogenicity animals: 57/sex/group for controls and CCX168 treatment groups TK: 3/sex/group for vehicle control group and 9/sex/group for CCX168 treatment groups
Age:	6 to 7 weeks old at the start of dosing
Animal housing:	Animals were housed in cages with groups of up to three.
Paradigm for dietary restriction:	5LF2 EU Rodent Diet and water were provided *ad libitum*
Dual control employed:	Yes (water and vehicle control groups were included)
Interim sacrifice:	No
Satellite groups:	Health Screen animals: were not dosed and retained on study for viral analysis only
Deviation from study protocol:	These study deviations neither affected the overall interpretation of study findings nor compromised the integrity of the study. Five animals were replaced after either being found dead or moribund during the first 4 weeks of the study. There was no dose relationship among the animals that necessitated replacement. One carcinogenicity animal from Group

1, Group 2, Group 4 and Group 5 were replaced, as well as one toxicokinetic animal from Group 5. See description of animals that were removed and replaced in the footnote (a) of Table 1.

Table 4: Experimental Design

			Animal numbers			
			Carcinogenicity (Subgroup 1)		Toxicokinetics (Subgroup 2)	
Group number	Group description	Dose level (mg/kg/day)	Male n=25 or 57	Female n=25 or 57	Male n=0, 3 or 9	Female n=0, 3 or 9
1	Control I	0	R0001-R0002, R0004-R0057, R0061[a]	R0601-R0657	R0058-R0060	R0658-R0660
2	Control II	0	R0101-R0157	R0701-R0725, R0727-R0758[a]	-	-
3	Low	10	R0201-R0257	R0801-R0857	R0258-R0266	R0858-R0866
4	Intermediate	30	R0301-R0312, R0314-R0357, R0367[a]	R0901-R0957	R0358-R0366	R0958-R0966
5	High	100	R0401-R0457	R1001-R1015, R1017-R1057, R1067[a]	R0458-R0466	R1058, R1060-R1066, R1068[a]
6	Health Screen[b]	Not dosed	R0501-R0525[c]	R1101-R1125[c]	-	-

Control I = polyethylene glycol (b) (4) [(b) (4) v:v]
Control II = Purified water

a Five animals necessitated premature sacrifice or were found dead in the first 4 weeks of study; therefore, these animals were replaced with spare animals.
Animal R0003 (Group 1 carcinogenicity male) was replaced with Animal R0061
Animal R0313 (Group 4 carcinogenicity male) was replaced with Animal R0367
Animal R0726 (Group 2 carcinogenicity female) was replaced with Animal R0758
Animal R1016 (Group 5 carcinogenicity female) was replaced with Animal R1067
Animal R1059 (Group 5 toxicokinetics female) was replaced with Animal R1068

b Health Screen animals were not dosed and were retained on study for viral analysis only; all analysis was for information only and included only as information in the Annex.

c Group 6 health screen animals bled at pre-treatment and during Weeks 26 and 52 of the dosing phase were killed and discarded following completion of sampling, but animals bled during Week 78 were retained to ensure five animals were available for sampling at the end of the dosing phase.

(Excerpted from Study Report)

Observations and Results

Mortality

All animals were observed at the beginning and end of each working day for signs of ill health or overt toxicity.

Survival:

Treatment with CCX168 had no effects on survival of male or female rats.

The Sponsor terminated all female groups starting at Week 92 due to the female vehicle-control reaching pre-defined termination criteria of 20 survivors (i.e., 20 of 57 [35%] females). All male groups were terminated starting at Week 97 due to the male water-control group reaching pre-defined termination criteria of 20 survivors (i.e., 20 of 57 [35% survival]).

Termination of females occurred over the period from Day 646 to 660 (15 days). Males were terminated over the period from Days 686 and 697 (12 days). All carcinogenicity animals that died or were sacrificed following initiation of the scheduled terminal necropsy process were marked as a terminal sacrifice. Scheduled necropsies were carried out by controlled randomization (i.e., one cage of animals from Groups 1, 4, 2, 5 then 3 and repeated in the same sequence until all animals terminated).

There were no test article related effects on male or female survival relative to vehicle control and water control groups. Survival in the treatment group was comparable to the survival in either the water control or vehicle control groups for each sex.

Table 5: Survival Analysis in the 2-Year Rat Carcinogenicity Study

Rat Survival Data	**Males**		**Females**	
n=57 per group	# Early Deaths	# At terminal necropsy	# Early Deaths	# At terminal necropsy
Vehicle Control	31 (54%)	26 (46%)	37 (65%)	**20 (35%)**
Water Control	37 (65%)	**20 (35%)**	28 (49%)	29 (51%)
Low Dose	36 (63%)	21 (37%)	29 (51%)	28 (49%)
Mid Dose	36 (63%)	21 (37%)	31 (54%)	26 (46%)
High Dose	30 (53%)	27 (47%)	31 (54%)	26 (46%)

The most common microscopic cause of demise was skin tumors/lesions for males, mammary gland tumors for females, and pituitary tumors for both sexes.

There were no test article related effects on male or female survival relative to vehicle control and water control groups. Survival in the treatment group was comparable to the survival in either the water control or vehicle control groups for each sex.

The Sponsor conducted a statistical survival analysis and generated Kaplan-Meier survival curves (below) for male and female animals.

No statistically significant results of the survival analyses were noted in males or females.

Table 6: Sponsor's Statistical Analysis of Survival in Males in the 2-Year Rat Carcinogenicity Study

		Unadjusted Survival Incidence Rate				
Group	Trend	1	2	3	4	5
Dose Level(mg/kg/day)	(1,3,4,5)	0	0	10	30	100
Group Size		57	57	57	57	57
Terminal Sacrifice		26	20	21	21	27
Deaths		31	37	36	36	30
Log-Rank P-value (v1)	0.2095	N/A	0.3238	0.4843	0.5997	0.4513
Wilcoxon P-value (v1)	0.1152	N/A	0.4518	0.5357	0.9398	0.2903

Figure 1: Sponsor's Survival Curves for Males in the 2-Year Rat Carcinogenicity Study

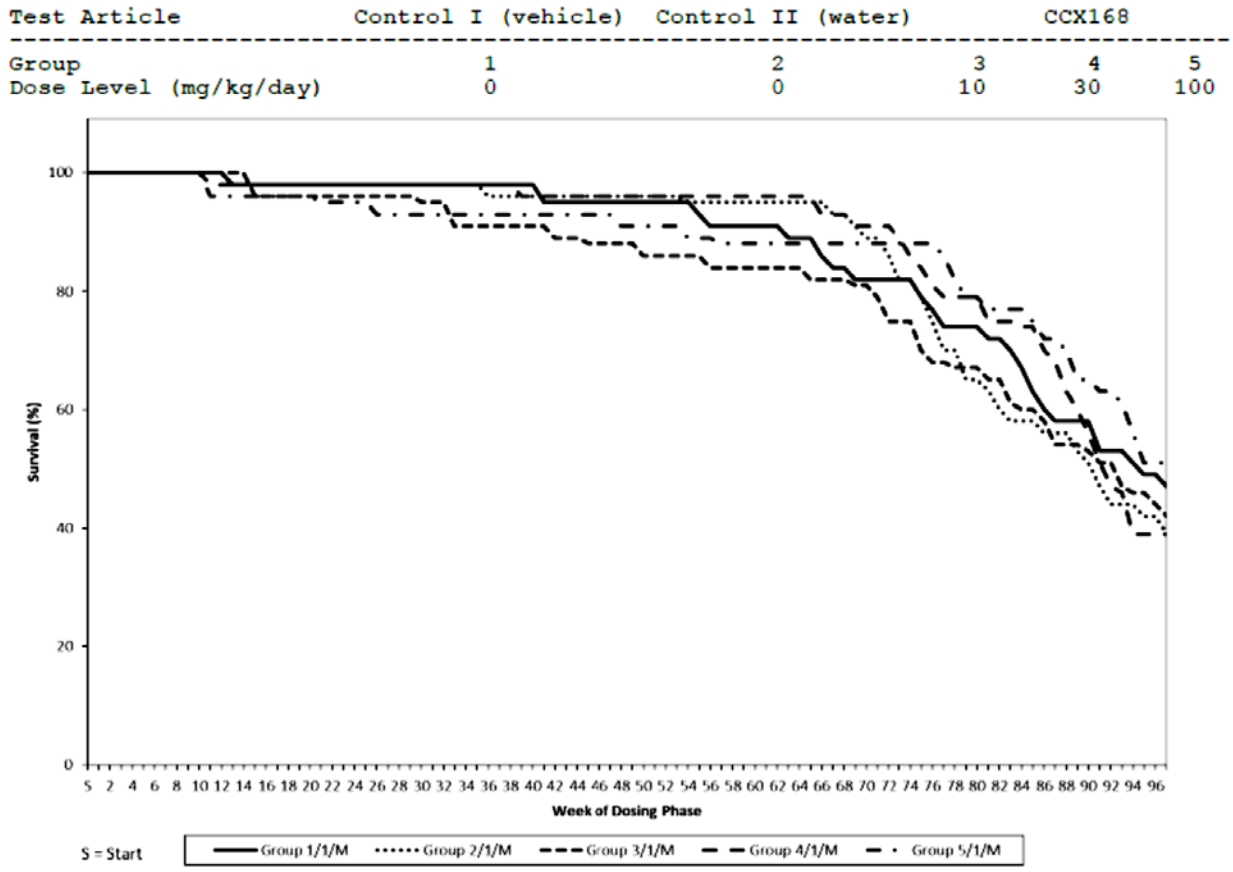
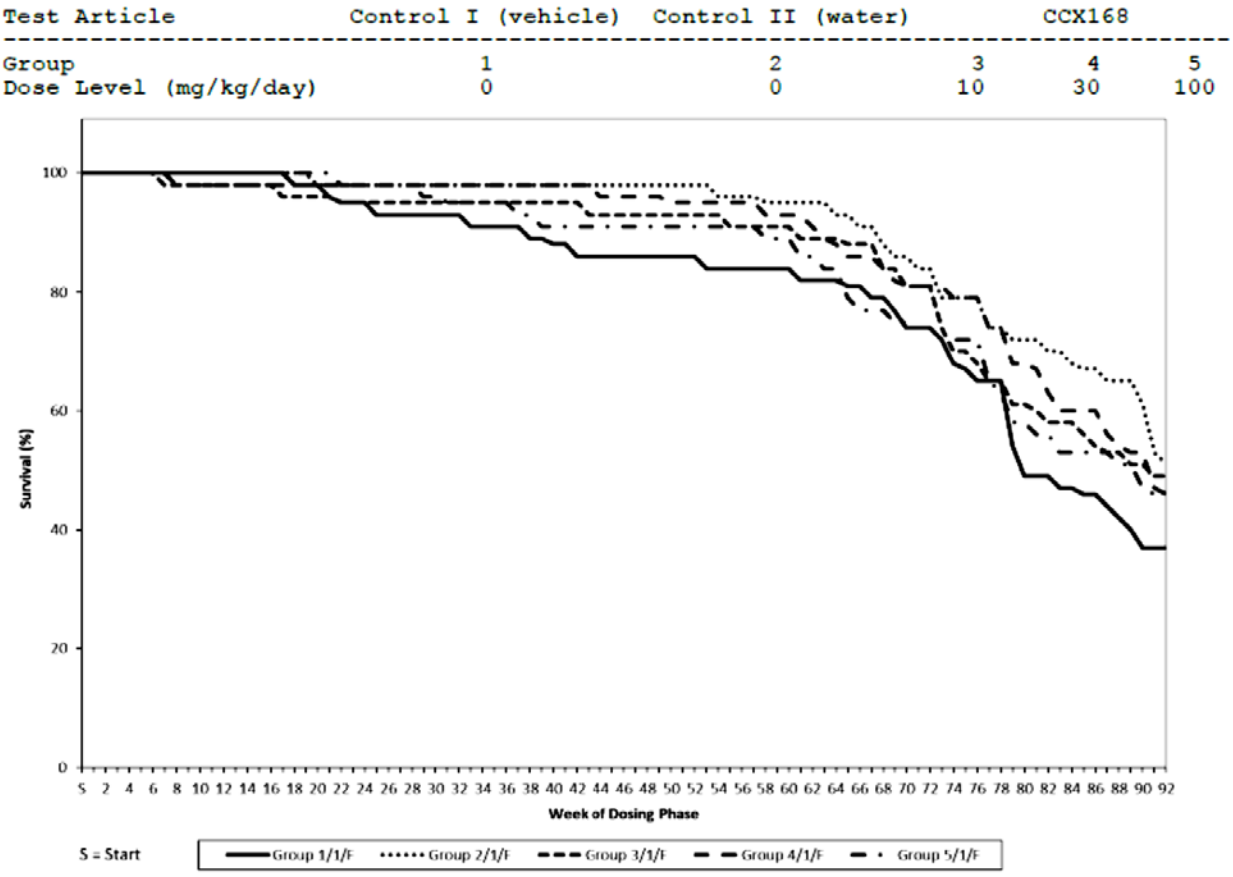


Table 7: Sponsor's Statistical Analysis of Survival in Females in the 2-Year Rat Carcinogenicity Study

		Unadjusted Survival Incidence Rate				
Group	Trend	1	2	3	4	5
Dose Level(mg/kg/day)	(1,3,4,5)	0	0	10	30	100
Group Size		57	57	57	57	57
Terminal Sacrifice		20	29	28	26	26
Deaths		37	28	29	31	31
Log-Rank P-value (v1)	0.7803	N/A	0.1169	0.2442	0.2293	0.4464
Wilcoxon P-value (v1)	0.9214	N/A	0.1073	0.3185	0.1827	0.5871

Figure 2: Sponsor's Survival Curves for Females in the 2-Year Rat Carcinogenicity Study



Clinical Signs

All animals were observed at the beginning and end of each working day for signs of ill health or overt toxicity. Each animal was given a detailed physical examination, including palpation for tissue masses, once weekly and on the day of terminal sacrifice. During Week 1 of the dosing phase, the first 12 carcinogenicity animals/group/sex were observed once daily, on return to the home cage after dosing.

On occasion from Day 620 of the dosing phase onwards, animals with sore feet were treated with Isaderm (fusidic acid hemihydrate 0.5% w:w and betamethasone valerate 0.1% w:w).

No treatment-related clinical signs were noted during the treatment period.

Body Weights

Individual body weights of all animals were recorded on Day 1 of the predose phase; once weekly from Day 1 (predose) through Week 16, once every 4 weeks from the start of Week 17, once weekly from the start of Week 69 of the dosing phase; on the day prior to terminal sacrifice; and before each necropsy.

There were no treatment related changes of absolute body weights for male and female drug-treated groups, relative to controls at Day 169, Day 365, Day 533, and Day 680/Day 645 (final measurements for male and females).

Table 8: Body Weight Changes and Body Weight Gains Males and Females in the 2-year Carcinogenicity Study in Rats

Body Weights Rat (g)	Males					Females				
	Veh Control	Water	Low Dose	Mid Dose	High Dose	Veh Control	Water	Low Dose	Mid Dose	High Dose
PreDose Day 1	136.6	132.4	139.3	134.7	136.3	126.9	120.6	121.9	126.6	126.4
Day 169	603.7	617.3	607.0	602.5	604.0	309.6	317.0	300.6	325.4	316.1
Absolute BW, % Control	100.0	102.3	100.5	99.8	100.0	100.0	102.4	97.1	105.1	102.1
Δ, g	467.1	484.9	467.7	467.8	467.7	182.7	196.4	178.7	198.8	189.7
BW gain, % control	100.0	103.8	100.1	100.1	100.1	100.0	107.5	97.8	108.8	103.8
Day 365	716.3	750.3	709.1	713.3	707.6	369.8	383.2	355.1	390.2	380.3
Absolute BW, % Control	100.0	104.7	99.0	99.6	98.8	100.0	103.6	96.0	105.5	102.8
Δ, g	579.7	617.9	569.8	578.6	571.3	242.9	262.6	233.2	263.6	253.9
BW gain, % control	100.0	106.6	98.3	99.8	98.6	100.0	108.1	96.0	108.5	104.5
Day 533	761.0	804.5	750.0	766.7	783.2	450.3	445.7	425.9	461.8	442.0
Absolute BW, % Control	100.0	105.7	98.6	100.7	102.9	100.0	99.0	94.6	102.6	98.2
Δ, g	624.4	672.1	610.7	632.0	646.9	323.4	325.1	304.0	335.2	315.6
BW gain, % control	100.0	107.6	97.8	101.2	103.6	100.0	100.5	94.0	103.6	97.6
Day 680 (M)/ Day 645 (F)	748.3	832.0	771.2	781.2	776.9	486.8	454.4	457.3	483.0	463.5
Absolute BW, % Control	100.0	111.2	103.1	104.4	103.8	100.0	93.3	93.9	99.2	95.2
Δ, g	611.7	699.6	631.9	646.5	640.6	359.9	333.8	335.4	356.4	337.1
BW gain, % control	100.0	114.4	103.3	105.7	104.7	100.0	92.7	93.2	99.0	93.7

Figure 3: Body Weight Changes in Males in the 2-Year Carcinogenicity Study in Rats

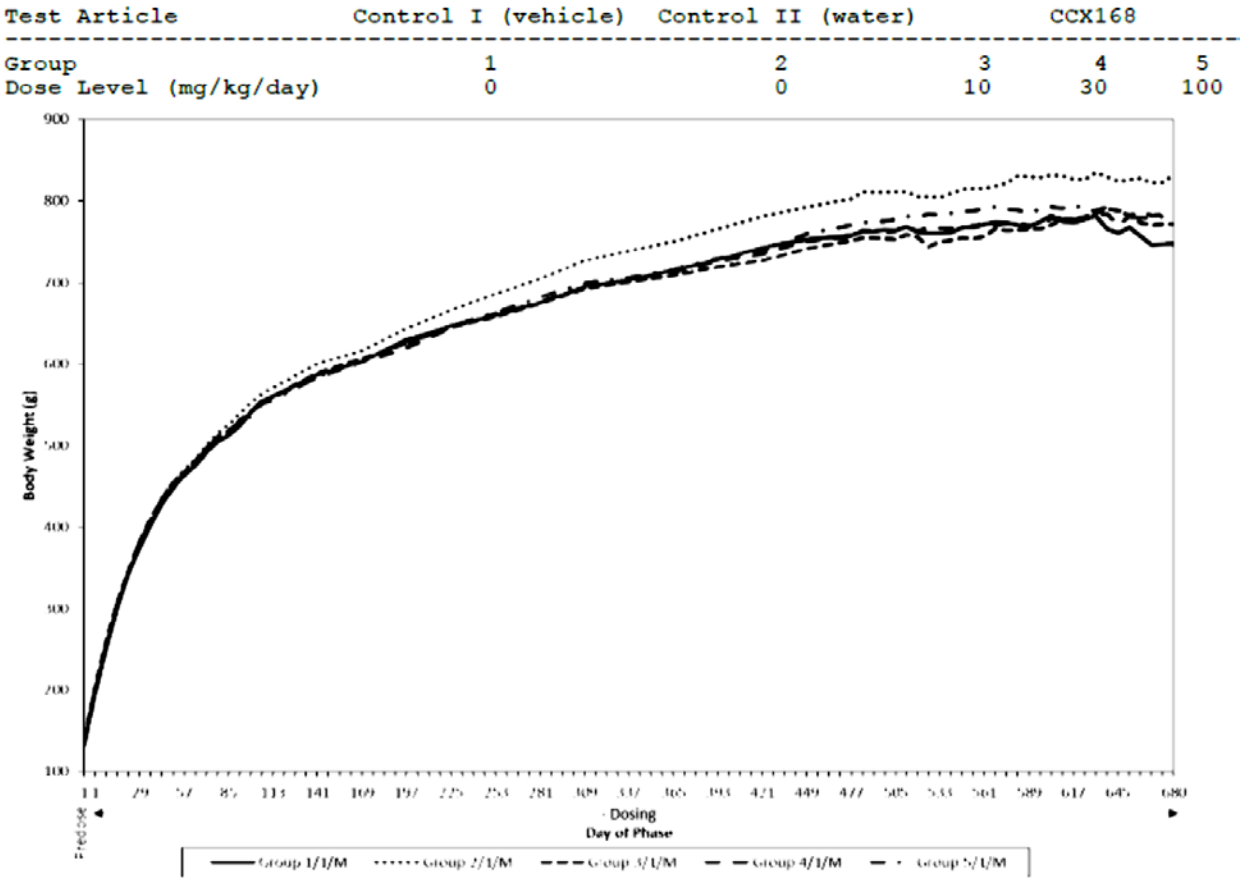
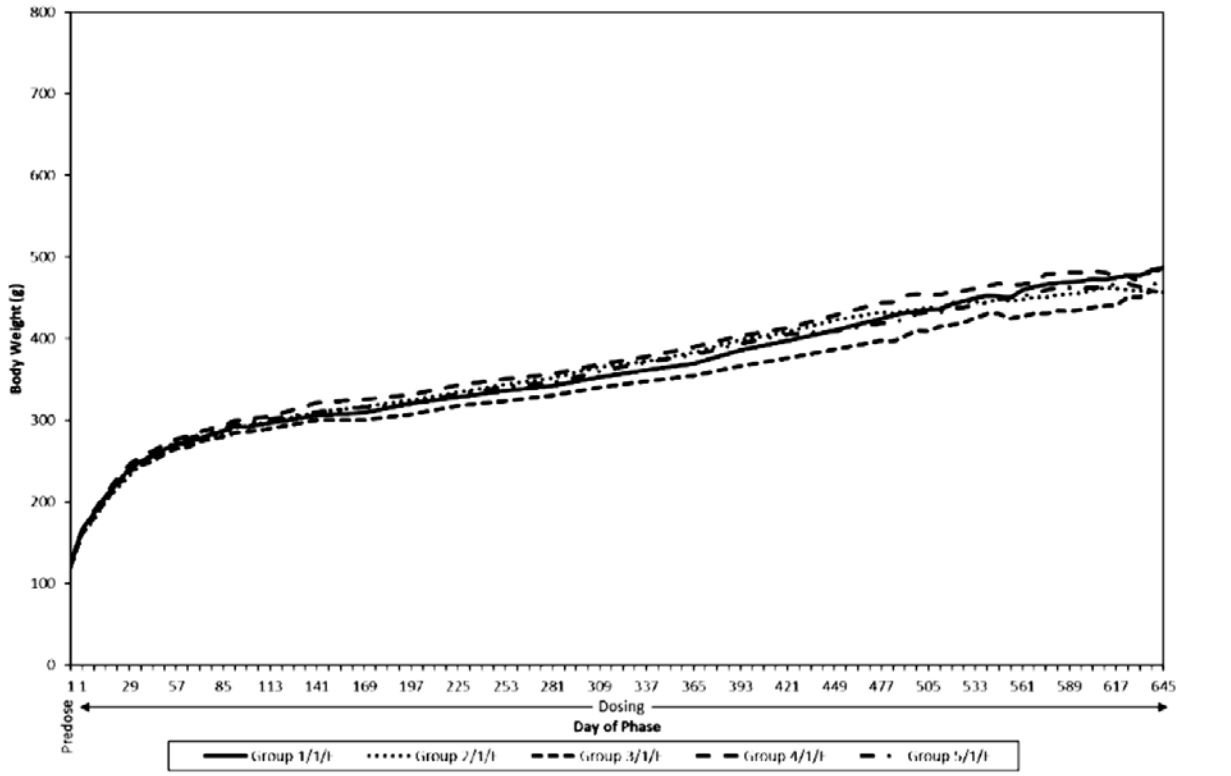


Figure 4: Body Weight Changes in Females in the 2-Year Carcinogenicity Study in Rats

Test Article	Control I (vehicle)	Control II (water)	CCX168		
Group	1	2	3	4	5
Dose Level (mg/kg/day)	0	0	10	30	100



Feed Consumption

The amount of food consumed per cage of carcinogenicity animals was assessed twice weekly from Week 1 through Week 16 of the dosing phase, and once every 4 weeks thereafter.

There were no treatment-related changes in food consumption.

Hematology

Blood samples for hematology (0.5 mL preserved in EDTA) were withdrawn from the abdominal aorta of all carcinogenicity animals at the terminal necropsy. Samples were collected from animals after fasting overnight. Blood samples were also taken from animals sacrificed at an unscheduled interval. No samples were obtained from animals that were dead on arrival at the necropsy exam. Blood smears were prepared from each hematology specimen and used when necessary to confirm results produced by the analyzer.

hemoglobin	mean cell hemoglobin concentration
red blood cell count	reticulocyte count
packed cell volume	red cell distribution width
mean cell volume	total and differential white cell count
mean cell hemoglobin	platelet count[a]

a Includes platelet clump assessment. Clump counts below 100 were considered *none detected*; clump counts over 100 were considered *platelet clumps present* and were confirmed by review of Advia cytogram or blood film examination.

Potential dose-related reductions in reticulocyte counts were noted in females at 30 mg/kg (↓ -21.5%) and 100 mg/kg (↓ -22.3%), relative to the vehicle control group. Reductions in neutrophil counts were noted in the 30 mg/kg (↓ -14.2%) and 100 mg/kg (↓ -20.2%) groups in males and in the 100 mg/kg group in females (↓ -37.1%).

Table 9: Hematology Changes in Males (Days 686-697) and Females (Days 646-660) at the Terminal Necropsy in the 2-Year Carcinogenicity Study

Hematology	Males (Days 686-697)					Females (Days 646-660)				
	Veh Ctrl	Water	Low Dose	Mid Dose	High Dose	Veh Ctrl	Water	Low Dose	Mid Dose	High Dose
Abs Reticulocytes 10^9/L	182.2	217.1	209.9	210.9	199.1	223.6	236.8	213.6	175.5	173.7
% Change of Control	0.0	19.2	15.2	15.8	9.3	0.0	5.9	-4.5	**-21.5**	**-22.3**
Neutrophils 10^9/L	2.53	1.9	2.7	2.17	2.02	1.7	1.63	1.57	1.61	1.07
% Change of Control	0.0	-24.9	6.7	**-14.2**	**-20.2**	0.0	-4.1	-7.6	-5.3	**-37.1**

Gross Pathology

All carcinogenicity animals, and all unscheduled deaths/sacrifices, were subjected to necropsy. Toxicokinetic animals, upon completion of blood sampling, were discarded and not subjected to necropsy. The terminal sacrifice commenced on Day 646 or Day 686 for females and males, respectively. All carcinogenicity animals that died or were sacrificed following initiation of the scheduled terminal necropsy were marked as a terminal sacrifice. Animals were weighed before necropsy. Each animal was administered isoflurane anesthesia and was exsanguinated by severing its major blood vessels. If urgent euthanasia of an animal in extremis was necessary, the animal was sacrificed by intraperitoneal injection of sodium pentobarbitone (overdose), and death was confirmed by cervical dislocation and/or exsanguination. A full macroscopic examination was performed under the general supervision of a pathologist, and all lesions were recorded.

The following tissues from each animal were preserved in 10% neutral-buffered formalin, unless otherwise indicated.

Table 10: Organs and Tissues Collected and Preserved for Macroscopic and Microscopic Examination in the 2-Year Carcinogenicity Study in Rat

Organ/Tissue		Organ/Tissue	
adrenal	E	nerve, optic	E
animal identification		nerve, sciatic	E
aorta	E	nose/nares	
bone marrow smear (femur)[a,b]		ovary	E
brain	E	oviduct	
cecum	E	pancreas	E
colon	E	pituitary	E
duodenum	E	preputial/clitoral gland	E
epididymis[c]	E	prostate	E
esophagus	E	rectum	E
eye[d]	E	seminal vesicle with coagulating glands	E
femur with bone marrow and femorotibial joint	E	skin and subcutis	E
gut-associated lymphoid tissue (GALT)/Peyer's patch	E	spinal cord, cervical	E
gross lesions	E	spinal cord, lumbar	E
Harderian gland[e]		spinal cord, thoracic	E
head (not processed)		spleen	E
heart	E	sternum with bone marrow	E
ileum	E	stomach	E
jejunum	E	sublingual salivary gland	E
kidney	E	testis[c]	E
liver	E	thymus	E
lungs with main stem bronchi and bronchioles	E	thyroid with parathyroid	E
lymph node, mandibular	E	tissue masses	E
lymph node, mesenteric	E	tongue	E
mammary gland	E	trachea	E
mandibular salivary gland	E	urinary bladder	E
muscle, biceps femoris	E	uterus with cervix	E
nasal cavity		vagina	E
nasopharynx		Zymbal's gland	

E = Processed and examined microscopically.
Note: Bone designated for microscopic examination was decalcified using Kristenson's fluid.
Primary neoplasms involving hemopoietic or lymphoid tissue and the mononuclear phagocyte system (reticular tissue) are recorded by the pathologist as *Hemolympho-reticular system*.

a Methanol fixative.
b See Bone Marrow Smear Evaluation (see Protocol Deviations).
c Modified Davidson's fixative.
d Davidson's fluid fixative.
e Preserved with the head (*in situ*).

No treatment related gross pathology changes were noted.

Histopathology

All tissues denoted by “E” in the tissue list (above) from each carcinogenicity animal were embedded in paraffin wax, sectioned at a thickness of 5 µm, and stained with hematoxylin and eosin. These tissues were examined microscopically by the Contributing Scientist for Anatomic Pathology.

Peer Review No.

Neoplastic

Potential treatment related neoplastic findings in rats were noted in the thyroid gland. Dose-related increased incidences of C-cell adenoma and the combination of C-cell adenoma and carcinoma were observed in males. Incidences of C-cell carcinoma alone were low and showed no dose-response relationship. The incidence of C-cell adenoma and combination of C-cell adenoma and carcinoma were within historical control ranges for males (2.2-25.5% and 2.2-32.2%, respectively). The incidences of C-cell adenoma and the combination of C-cell adenoma and carcinoma relative to the vehicle-control group did not reach statistical significance.

Clear dose responses for incidences of C-cell adenoma and the combination of C-cell adenoma and carcinoma in females were not evident; however, the highest incidences were noted in the MD group. TK data indicated that the MD group achieved the highest systemic exposures (AUC) among all treatment groups. The highest incidences of C-cell adenoma and the combination of C-cell adenoma and carcinoma occurred in the MD group, which suggested a potential relationship to treatment. Incidences of C-cell carcinoma alone were low and showed no dose-response relationship. The incidences of benign C-cell adenoma (17.5%) and the combination of C cell adenoma and carcinoma in the female MD group exceeded historical control ranges for females of 0-13.3% for C-cell adenoma and 0-18.1% for the combination of C-cell adenoma and carcinoma, but the incidences did not achieve statistically significant positive trends or statistically significant pairwise comparisons.

Table 11: Neoplastic Findings in the 2-Year Carcinogenicity Study in Male Rats

Organ (Neoplastic findings)	**Males (mg/kg/day)**					
Thyroid	Veh Ctrl	Water	Low Dose	Mid Dose	High Dose	Hist Control
	NA	NA	10	30	100	
Total examined	55	57	57	57	57	1766
M- Carcinoma, C-cell	1	1	0	1	2	0 - 6.7%
B-Adenoma, C-cell	7	6	9	9	13	2.2 - 25.5%
Combined Adenoma and Carcinoma, C-cell tumor number	**8**	**7**	**9**	**10**	**15**	**2.2-32.2%**

Table 12: Neoplastic Findings in the 2-Year Carcinogenicity Study in Female Rats

Organ (Neoplastic findings)	**Females (mg/kg/day)**					
Thyroid	Veh Ctrl	Water	Low Dose	Mid Dose	High Dose	Hist Control
	NA	NA	10	30	100	
Total examined	56	57	57	57	57	1748
M- Carcinoma, C-cell	0	0	1	0	1	0 - 4.8%
B-Adenoma, C-cell	5	5	8	10	4	0 - 13.3%
Combined Adenoma and Carcinoma, C-cell tumor number	**5**	**5**	**9**	**10**	**5**	**0-18.1%**

Non-Neoplastic

Potential treatment related non-neoplastic findings in rats were noted in the thyroid gland during the study period. Focal C-cell hyperplasia increased in a dose proportional manner in males (vehicle control-6 [11%], water control- 6 [11%], LD-6 [11%], MD-7[12%], HD- 11[19%]). The incidences focal C-cell hyperplasia in males were within the historical control range for males (up to 21.7%) based on the data provided (b) (4)

A clear dose response for focal C-cell hyperplasia in females was not evident, however, the highest incidence was noted in the MD group (vehicle control-14 [25%], water control- 11 [19%], LD-10 [18%], MD- 7[28%], HD- 10[18%]). TK data indicated that the MD group received the highest systemic exposures (AUC) among all treatment groups. The highest incidence occurred in the MD group, which appeared to be consistent with

the highest drug exposure and could suggest a potential relationship to treatment. The incidences of focal C-cell hyperplasia in the MD (28%), the vehicle control (25%), and water control (19%) were outside the range of the historical control (0-18.3%). The incidence of focal C-cell hyperplasia at the MD is similar to the incidence in the vehicle control and overall, the data do not suggest a clear relationship to treatment with CCX168.

Findings of diffuse C-cell hyperplasia were unrelated to treatment with CCX168.

Table 13: Non-neoplastic Findings in the 2-Year Carcinogenicity Study in Male Rats

Organ (Non-neoplastic)	Males (mg/kg/day)					
Thyroid	**Veh Ctrl**	**Water**	**Low Dose**	**Mid Dose**	**High Dose**	**Hist Control**
	NA	NA	10	30	100	
Total examined	55	57	57	57	57	1766
Hyperplasia, C-cell, focal	6	6	6	7	11	21.70%
Hyperplasia, C-cell, diffuse	21	22	17	23	21	73.30%

Table 14: Non-neoplastic Findings in the 2-Year Carcinogenicity Study in Female Rats

Organ (Non-neoplastic)	Females (mg/kg/day)					
Thyroid	**Veh Ctrl**	**Water**	**Low Dose**	**Mid Dose**	**High Dose**	**Hist Control**
	NA	NA	10	30	100	
Total examined	56	57	57	57	57	1748
Hyperplasia, C-cell, focal	14	11	10	16	10	18.30%
Hyperplasia, C-cell, diffuse	40	40	31	40	39	71.70%

Toxicokinetics

Blood samples (0.6 mL nominal) were collected from 3 toxicokinetic animals per sex/group/time point at 0 (predose), 0.5, 1, 2, 4, and 7 hours postdose during Week 4 (Day 28) of the dosing phase. In addition, blood samples were collected from all surviving carcinogenicity animals from Groups 1, 3, 4, and 5 at 2 hours postdose during Week 27 of the dosing phase. Plasma samples were analyzed for CCX168 and CCX168-M1 for C_{max}, T_{max}, AUC_{0-24}, and half-life ($t_{1/2}$). The Sponsor noted that AUC_{0-24} was calculated instead of AUC_{0-7}. As the final sampling time point was 7 hours it was assumed that steady state had been achieved by Day 28 and, therefore, the predose values were used as the 24-hour time point.

	No. of TK Animals		Dose Level
Group	Male	Female	(mg/kg/day)
1 (Control 1)	3	3	0
3 (Low)	9	9	10
4 (Intermediate)	9	9	30
5 (High)	9	9	100

CCX168 (parent)

On Day 28, C_{max} and AUC_{0-24} values increased in a dose proportional manner to the from 10 to 30 mg/kg/day. Conversely, C_{max} and AUC_{0-24} exposure decreased from 30 to 100 mg/kg/day resulting in 0.68- and 0.65-fold reduction in C_{max} and AUC_{0-24}, respectively. Due to the observed saturation effect, the highest systemic exposures were achieved in mid-dose group at 30 mg/kg/day.

Sex-related differences in CCX168 C_{max} and AUC_{0-24} values were minor and generally less than 2-fold. T_{max} values ranged from 1 to 4 hours. The half-life range from 5.48 to 9.85 hours.

Table 15: Sponsor's Summary of the CCX168 Toxicokinetic Parameters in Rat Plasma on Day 28

Dose Group	Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$ (h)
3	10	M	1270	1.00	11500	5.48
		F	1670	2.00	13600	NC
		MF	1320	2.00	12600	9.85
4	30	M	2710	2.00	25600	5.90
		F	3310	2.00	33400	7.12
		MF	3010	2.00	29500	6.52
5	100	M	1890	1.00	17400	NC
		F	2350	4.00	21400	NC
		MF	2050	1.00	19400	9.48

NC = Not calculated.

Note: Combined male and female (MF) parameters were calculated by combining concentration data for all animals (male and female) at each dose level and using these data as a separate composite profile for toxicokinetic analysis. These parameters are not an average of the values calculated for males and females separately.

As the final sampling time point was 7 hours, it was assumed that steady state had been achieved by Day 28 and, therefore, the predose values were used as the 24-hour time point.

CCX168-M1

Concentrations (C_{max}) and exposures (AUC_{0-24hr}) of the CCX168-M1 metabolite increased in a less than dose proportional manner in males. In females it appears that saturation occurred at the low dose as the highest AUC_{0-24hr} was at 10 mg/kg. An approximate 50% reduction in exposure was noted from 10 mg/kg to 30 and 100 mg/kg. The changes in C_{max} in females did not change in a dose proportional manner.

Sex related differences in CCX168-M1 C_{max} and AUC_{0-24} were evident and were generally higher in females than in males. The largest difference was noted at the low dose where an 8-fold difference in exposure was calculated. The t_{max} ranged from 2 to 7 hours and half-life was not calculated.

Table 16: Sponsor's Summary of the CCX168-M1 Toxicokinetic Parameters in Rat Plasma on Day 28

Dose Group	CCX168 Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng·h/mL)	$t_{1/2}$ (h)
3	10	M	36.7	4.00	445	NC
		F	303	0.00	3670	NC
4	30	M	97.7	4.00	1140	NC
		F	125	7.00	1830	NC
5	100	M	157	2.00	1440	NC
		F	346	4.00	1970	NC

NC = Not calculated.
Note: As the final sampling time point was 7 hours, it was assumed that steady state had been achieved by Day 28 and, therefore, the predose values were used as the 24-hour time point.

Dosing Solution Analysis

Homogeneity and Achieved Concentration

For homogeneity analysis/concentration analysis, samples were removed in duplicate from the top, middle, and bottom of each formulation and were analyzed. A single sample was taken from the middle of the control formulation and was analyzed.

For achieved concentration analysis, triplicate samples were taken from the middle of the test article formulations and were analyzed. A single sample was taken from the middle of the control formulations and was analyzed.

Formulations prepared for use on Week 1 (Day 1) of the dosing phase were analyzed to determine homogeneity and achieved concentrations. Samples were removed in duplicate from the top, middle, and bottom of each formulation and were analyzed. A single sample was taken from the middle of the control formulation and was analyzed. The mean of the homogeneity results was used as the achieved concentration result.

Formulations prepared for use during Weeks 4, 13, 26, 27 (Group 4 repeats and from residue formulations after completion of dosing), 39, 52, 65, 78, and 91 of the dosing phase were analyzed to determine the achieved concentration. Triplicate samples were taken from the middle of the test article formulations and were analyzed. A single sample was taken from the middle of the control formulations and was analyzed.

The test article was not detected in the Group 1 and 2 control samples.

The formulations from Week 1 were judged to be acceptable as the mean percent nominal concentrations were within the target ranges of 90 to 110% with an RSD of ≤5.0%. All other samples, with the exception of those from Week 13 Group 5 male, Week 26 Group 4 female, Week 27 Group 5 male and Group 3 female, and Week 78

Group 3 male samples were acceptable. The samples with out-of-specification results were reanalyzed. Upon reanalysis, most samples were within specification and all values with within ± 15% of the expected mean which were judged to be valid and did not affected the integrity of the study.

11 Integrated Summary and Safety Evaluation

ChemoCentryx Inc. submitted NDA 214487 on July 7, 2020 in support of marketing approval for Avacopan (CCX168). CCX168 is a small molecule inhibitor of complement component 5a receptor (C5aR), that is being developed as an oral treatment for adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis.

This review evaluates the results of a 2-year oral carcinogenicity study conducted in Sprague Dawley rats (Study No. PC0675_168).

Nonclinical Findings

The rat is not a pharmacologically relevant species for CCX168 as CCX168 has no activity toward its target C5aR in rats. However, based upon in vitro studies in liver microsomes as well as in vivo studies, the metabolism and pharmacokinetic properties of CCX168 appear to be comparable between rats and humans. Orally administered CCX168 is highly bioavailable in rats and humans. Tmax, Vd, and $T_{1/2}$ values are all similar between both species. CCX168 is highly protein bound in both rat and human plasma (>99.9%). CCX168-M1, a hydroxylated metabolite of the parent compound, is the major human metabolite. CCX168-M1 is also a major metabolite in rats. The proportion of CCX168-M1 formed in humans is greater than in rats (Humans: CCX168-M1: 21.9% of CCX168; Rats: CCX168-M1: 3 - 15% of CCX168).

CCX168 was negative in a standard genetic toxicology battery including the in vitro bacterial reverse mutation assay, in vitro mouse lymphoma assay, and in vivo rat micronucleus assay. CCX168-M1 was demonstrated to be present under the conditions of the in vitro bacterial reverse mutation assay and in vivo rat micronucleus assay and could be concluded to be negative for genotoxicity.

Carcinogenicity

The Sponsor conducted a 2-year carcinogenicity study in Sprague Dawley rats. In the 2-year carcinogenicity study, Sprague Dawley rats received CCX168 (avacopan) by oral gavage at doses of 10, 30, and 100 mg/kg/day. These doses received concurrence from the FDA Executive Carcinogenicity Assessment Committee (IND 120784, see ECAC meeting minutes dated November 9, 2017). Treatment with CCX168 had no effects on survival for male or female rats. The carcinogenicity study was terminated for female groups after reaching the termination criteria of 20 animals for Group 1 (vehicle-control) females during Week 92 and for male groups after reaching the termination criteria of 20 animals for Group 2 (water control) males during Week 97. Study termination was in accordance with FDA ECAC recommendations. There were no treatment related changes in absolute body weight during the treatment period in male or female rats.

There were no statistically significant test article-related tumor findings in male or female rats. There were no test article related non-neoplastic findings in male or female rats. Toxicokinetic analysis conducted on Day 28 indicated that the highest systemic exposures (AUC) and C_{max} were achieved in mid-dose group at 30 mg/kg/day. The C_{max} and AUC_{0-24} exposure decreased from 30 to 100 mg/kg/day resulting in 0.68- and 0.65-fold reduction in C_{max} and AUC_{0-24}, respectively. Therefore, to assess the relationship of findings to treatment with CCX168, the 30 mg/kg group was also analyzed as the high dose group. Collectively, CCX168 was not tumorigenic in rats at doses up to 30 or 100 mg/kg/day in males and females.

The ECAC concurred that the 2-year rat carcinogenicity study was adequate and that there were no drug-related neoplasms in males or females.

Safety margins for the proposed clinical dose 30 mg BID of CCX168 are calculated for the low dose, mid dose, and high dose in the 2-year rat carcinogenicity study.

Table 17: Exposure Margins for Clinical Dose of 30 mg BID CCX168 and CCX168-M1 based on the 2-Year Carcinogenicity Study in Rats

Sex	CCX168 (mg/kg/day)	CCX168		CCX168-M1	
		AUC_{0-24} (ng*hr/mL)	Exposure Margin[a]	AUC_{0-24} (ng*hr/mL)	Exposure Margin[b]
Males	10	11,500	1.66	445	0.17
	30	25,600	3.7	1140	0.44
	100	17,400	2.51	1440	0.56
Females	10	13,600	1.96	3670	1.43
	30	33,400	4.8	1830	0.71
	100	21,400	3.09	1970	0.77

[a] Steady state human CCX681 2x AUC_{0-12}: 6932 ng*hr/mL for the 30 mg BID dose from Study No. CL010_168

[b] Steady state human CCX681-M1 2x AUC_{0-12}: 2566 ng*hr/mL for the 30 mg BID dose from Study No. CL010_168

12 Appendix/Attachments

12.1 Appendix I: Review of the 2-year oral (gavage) carcinogenicity study in Hamsters

12.2 Appendix II: ECAC Final Study Meeting Minutes for the 2-year rat and hamster CCX168 carcinogenicity studies (Dated February 25, 2021).

Appendix I

Review of the 2-year oral (gavage) carcinogenicity study in hamsters
(Reviewer: Dr. Timothy Robison, PhD, DABT)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA ASSESSMENT AND EVALUATION

Application Number*:	214487
Supporting Document Number/s:	016
CDER Receipt Date:	December 2, 2020
Sponsor:	ChemoCentryx, Inc.
Product:	Avacopan
Pharmacologic Class:	"Complement 5a receptor (C5aR) Antagonist"
Indication:	Treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA])
Therapeutic area:	Rheumatology
Clinical Review Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Pharm/Tox Division	Division of Pharm/Tox for Immunology and Inflammation (DPT-II)
Reviewer/Team Leader:	Timothy W. Robison, Ph.D., D.A.B.T.
Project Manager:	Susie Choi
Purpose of Review:	Other Review of 2-year carcinogenicity study with hamsters
Alternative Assays:	Click here to enter text.
Reviewer Completion Date:	March 8, 2021

Template Version: Sep 11, 2020

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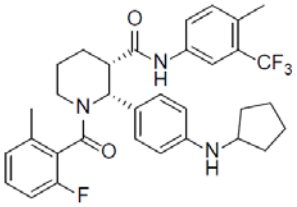
Nonclinical Summary

Drug Information[+]

Type of Product:	Small molecule
Code/ Generic Name:	Avacopan (CCX-168)
Chemical Name (optional):	3-Piperidinecarboxamide, 2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]-, (2R,3S)-
CAS# or UNII (if available):	CAS:1346623-17-3 UNII:Click here to enter text.
Structure or Biochemical Description:	**Avacopan Drug Substance Structural Formula** 
Molecular Formula/ Molecular Weight:	$C_{33}H_{35}F_4N_3O_2$ / 581.6435 Da

Clinical Information

Indication:	Treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA])
Dose:	30 mg BID
Patient Population:	Adults
Sponsor's Maximum Recommended Human Dose/ Target AUC or Cmax (if applicable):	30 mg BID CCX168, 2 x $AUC_{0\text{-}12hr}$ = 6932 ng*hr/mL CCX168-M1, 2 x $AUC_{0\text{-}12hr}$ = 2566 ng*hr/mL

Pharmacology (primary & secondary/ MoA)

Key Findings:

The hamster is a pharmacologically relevant species as CCX168 inhibits hamster C5aR with potencies similar to that observed with human whole blood. CCX168 and CCX168-M1 inhibited C5aR function in human, cynomolgus monkey, and hamster whole blood samples with A2 values less than 18 nM (A2 = concentration required for 2-fold rightward shift of C5a dose response curve). Both CCX 168 and M1 were found to be inactive or minimally active (A2 > 1,000 nM) at rat, mouse, and rabbit C5aRs.

Table 1 In vitro potency of CCX168 and its M1 metabolite for inhibition of C5a mediated chemotaxis in leukocytes of multiple species. Note that the numbers in

brackets refer to the specific study number that the data were derived from. A2 values are reported. This value generally corresponds to the IC50 when the agonist is present at its Kd value.

		A_2 value (nM)	
Species	Sample	CCX168	M1
Human	whole blood	1.7 [PC0346]	3 [PC0463]
Cynomolgus	whole blood	18 [PC0347]	1 [PC0484]
Hamster	whole blood	10 [PC0627]	6 [PC0627]
Rabbit	whole blood	1,400 [PC0627]	1,400 [PC0627]
Mouse	peritoneal cells in Mouse plasma	> 10,000 [PC0347]	> 10,000 [PC0484]
Rat	peritoneal cells in Rat plasma	> 10,000 [PC0347]	>1,000 [PC0484]

C5aR amino acid sequence alignment performed by the sponsor identified a potential key residue located within the 5th transmembrane region (TM-5) of C5aR with regard to species specific binding of CCX168 or M1. The amino acid sequences for human, cynomolgus, and hamster C5aR all contain a tryptophan residue at this location, while other species have variable amino acid residues here (Figure 1).

Figure 1 Amino acid sequence alignment of the C5a receptor for 10 species shows a potential key residue in the TM-5 region that may influence CCX168 and M1 binding.

PK/ ADME/ TK:

Key Findings:

The extent of plasma protein binding for CCX168 or its metabolite CCX168-M1 were measured in humans as well as other six species including Syrian hamsters. Both CCX168 and its metabolite CCX168-M1 were protein bound reversibly at >99.9% in plasma of all species tested. The major metabolite CCX168-M1, identified in human

plasma in clinical studies, constituted approximately 12% of total plasma exposure in humans and was also detected in nonclinical species including Golden Syrian hamster.

Genotoxicity
Key Findings:
Genotoxicity studies evaluating CCX168 were reviewed previously and the test item was negative in all assays including in vitro bacterial mutagenicity study (Ames test), in vitro mammalian cell mutagenicity study (mouse lymphoma forward-mutation assay), and in vivo rat bone marrow micronucleus study.

Carcinogenicity
Key Findings:
Using doses of CCX-168 at 10, 30, and 100 mg/kg/day, per agreement with ECAC recommendations, female hamsters were treated for periods up to 92 weeks and male hamsters were treated for periods up to 98 weeks. There were no CCX-168-related neoplastic findings in either male or female hamsters.

Females were terminated during or after Week 92 when survival in the water-control group declined to 20 (20/65 = 30.7%) animals in the group. Males were terminated during or after Week 98 when survival in the vehicle-control group declined to 20 (20/65 = 30.7%) animals in the group.

For male hamsters, survival was comparable for vehicle-control and drug-treated groups. However, survival for the male water-control group (41/65 = 63.1%) was significantly higher relative to the male vehicle-control and drug-treated groups (20/65 [30.7%] to 26/65 [40%]). The vehicle was Polyethylene glycol (b) (4) (b) (4) v:v]. A potential vehicle-related effect on survival occurred for male vehicle-control and drug-treated groups. For female hamsters, survival was comparable for the vehicle-control, water-control, and drug-treated groups. The severity of chronic progressive nephropathy (CPN) was increased for male and female vehicle-control and drug-treated groups relative to male and female water-control groups. However, overall incidences of CPN across all male or female groups were not different. There were corresponding increases in CPN as the cause of death for male and female vehicle-control and drug-treated groups relative to male and female water-control groups. The severity of CPN led to increases in mortality for male vehicle-control and drug-treated groups relative to the male water-control group. This did not appear to impact the ability of the study to assess the carcinogenic potential of CCX-168 as males were treated up to Week 98 and females up to Week 92.

There were no CCX-168-related neoplastic findings in either male or female hamsters.

Non-neoplastic findings were evident in ovaries, kidneys, rectum, spleen, mesenteric lymph nodes, liver, colon, cecum, and liver.

Mineralization was noted in the ovaries of females administered 30 or 100 mg/kg/day; a corresponding increase in this finding was also noted in females administered 100

mg/kg/day that survived to the terminal sacrifice. This finding was characterized by small foci of basophilic, crystalline, or granular material within the ovarian interstitium.

Administration of the vehicle-control (Polyethylene glycol (b) (4)), regardless of CCX168 dose, resulted in higher incidence and/or severity of chronic progressive nephropathy (CPN) in the kidneys, cystic glands in the rectum, pigment in the spleen, mesenteric lymph nodes, liver, colon, and cecum, and pigmented macrophages in the liver compared to the water-control group.

The ECAC judged the study to be adequate, noting prior concurrence for dose selection and study design, and negative for test article-related tumor findings in male or female hamsters.

Table 2: Exposure Margins for Clinical Dose of 30 mg BID CCX168 and CCX168-M1 based on the 2-Year Carcinogenicity Study in Rats

Sex	CCX168 mg/kg/day	CCX168		CCX168-M1	
		AUC0-24, ng*hr/mL	Exposure Margins(a)	AUC0-24, ng*hr/mL	Exposure Margins(b)
Males	10	5560	0.8	363	0.1
	30	21600	3.1	1550	0.6
	100	42000	6.1	2850	1.1
Females	10	4290	0.6	283	0.1
	30	24500	3.5	1750	0.7
	100	35600	5.1	2500	1.0

a. steady state human CCX168, 2 x AUC_{0-12} = 6932 ng*hr/mL for the 30 mg BID dose from Study No. CL010_168
b. Sponsor's projected steady state human CCX168-M1, 2 x AUC_{0-12} = 2566 ng*hr/mL for the 30 mg BID dose from Study No. CL010_168

1 Background

1.1 Regulatory History

A Pre-IND meeting was held with the Sponsor. See preliminary comments and final meeting minutes dated April 17, 2014 and May 20, 2014, respectively.

1.2 Relevant INDs, NDAs, BLAs or DMFs

IND 120784

1.3 Previous Reviews Referenced

Application	Reviewer	Date in DARRTS	Notes
IND 120784	Matthew Whittaker	11-09-2017	Review of 6-month toxicology study with rats
IND 120784	Dong Zhao	11-14-2017	Review of 13-week toxicology study with hamsters
IND 120784	Stephanie J Quinn	11-09-2017	ECAC meeting minutes
IND 120784	Matthew Whittaker	08-22-2019 (Comments were conveyed on 08-13-2019)	Early termination criteria for 104-week carcinogenicity study with rats

2 Supplemental Drug Information

2.1 Drug Formulation

Table 3 Composition of Avacopan 10 mg Hard Capsule

Table 1: Composition of Avacopan 10 mg Hard Capsule

Component	Function	Quality Standard	10 mg Capsule	
			(mg)	% w/w)
Avacopan	Drug Substance	In-House	10.0	(b) (4)
Polyoxyl-40 hydrogenated castor oil (b) (4)				(b) (4)
Polyethylene glycol 4000 (PEG-4000) (b) (4) (b) (4)				
Hard gelatin capsule, light orange opaque/ yellow opaque, Size 0				
Gelatin sealing band				
Total				(b) (4) (b) (4)

Table 4 Composition of Size 0 Light Orange Opaque and Yellow Opaque Bicolor Hard Gelatin Capsule Shell

Table 2: Composition of Size 0 Light Orange Opaque and Yellow Opaque Bicolor Hard Gelatin Capsule Shell

Component	Function	Quality Standard	Quantity per Empty Capsule Cap or Body	
			(mg)	% (w/w)
				(b) (4)

Table 5 Composition of Clear Gelatin Sealing Solution

Table 3: Composition of Clear Gelatin Sealing Solution

Component	Function	Quality Standard	10 mg Capsule	
			(mg)	% (w/w)
Gelatin				(b) (4)
Polysorbate 80				
				(b) (4)

3 Studies Submitted

3.1 Studies Reviewed

1. CCX168: 104 Week Oral (Gavage) Administration Carcinogenicity Study in the Hamster

8 Carcinogenicity

8.1 Study Title+: CCX168: 104 Week Oral (Gavage) Administration Carcinogenicity Study in the Hamster

Study no.: PC0674_168
Study report location: EDR
Study initiation date: December 21, 2017
Conducting laboratory and location: (b) (4)

GLP compliance: Yes
Drug, lot #, and % purity:

Test Article[a]	Storage[c]	Lot Number	Expiration/ Review Date	Purity[b]
CCX168	Sealed container, 15 to 25°C, protected from light, with desiccant	D-17-043	17 September 2020	98.2%
CCX168	Sealed container, 15 to 25°C, protected from light, with desiccant	D-16-013	17 September 2020	98.2%
CCX168	Sealed container, 15 to 25°C, protected from light, with desiccant	D-18-049	17 September 2020	98.3%

a See Certificates of Analysis.
b Purity is potency by high-performance liquid chromatography.
c Test Article lot D-17-043 stored at 2 to 8°C on receipt and moved to room temperature storage 1 week later. Storage with desiccant was not recorded for all lots until Day 459 of the dosing phase (see Protocol Deviations).

Prior Exec CAC Dose Concurrence: Y

Basis for Dose Selection: Saturation of systemic exposure for parent drug and M1 metabolite (see meeting minutes dated 11/09/2017).

Notable comments:

- The Committee concurred with doses of 10, 30 and 100 mg/kg/day for males and females, with the high dose based on saturation of systemic exposure.
- The Committee concurred with vehicle-control (PEG (b) (4)) and water-only control groups.
- The Committee noted that the 2-year carcinogenicity study will be performed in a different facility with a different source of animals than used in the 13-week oral toxicity study. The carcinogenicity study may not be acceptable if toxicity is significantly different due to these changes such that dose selection would have been altered.

Reviewer Carcinogenicity Conclusion (negative/ positive): Negative
ECAC Carcinogenicity Conclusion (negative/ positive): Negative

Tumor Findings: Using doses of CCX-168 at 10, 30, and 100 mg/kg/day, per agreement with ECAC recommendations, female hamsters were treated for periods up to 92 weeks and male hamsters were treated for periods up to 98 weeks.

There were no CCX-168-related neoplastic findings in either male or female hamsters.

Non-neoplastic findings were evident in ovaries, kidneys, rectum, spleen, mesenteric lymph nodes, liver, colon, cecum, and liver. Only findings in the ovaries were attributed to CCX-168. Findings in the kidneys, rectum, spleen, mesenteric lymph nodes, liver, colon, cecum, and liver appeared to be primarily associated with the vehicle.

Methods

Doses:	0 (Vehicle), 0 (Purified water), 10, 30, and 100 mg/kg/day
Frequency of dosing:	Daily
Number/Sex/Group:	65
Dose volume:	5 mL/kg
Formulation/Vehicle:	Polyethylene glycol (b) (4) [(b) (4) v:v]
Route of administration:	ORAL GAVAGE
Species:	HAMSTER
Strain:	SYRIAN
Age:	Male and female HsdHan:AURA (Syrian Golden) hamsters were obtained (b) (4) (b) (4) (b) (4) in order to provide 367 healthy animals of each sex plus spare animals for use as replacements. 375 animals of each sex were originally ordered from (b) (4) however, insufficient females were received and one male and one female were found dead on arrival at the test facility. Therefore, additional animals were ordered (b) (4) Animals were ordered as weanlings of approximately 3 to 4 weeks of age upon arrival. Males weighed between 65.9 and 120.3 g, and females weighed between 71.1 and 117.3 g; animals were approximately 5 to 7 weeks old at the start of dosing.

Comment on Study Design and Conduct: Hamsters were determined to be a pharmacologically relevant species during the Pre-IND meeting (see meeting minutes dated May 20, 2014). The rat was not a pharmacologically relevant species. The Sponsor proposed to use hamsters in reproductive toxicity and carcinogenicity studies.

During the first 4 weeks of the study, 7 animals, from drug-treated group, in moribund condition or found dead were replaced as shown in the table below. The group incidences did not display a dose-response relationship. Over the course of the study, there were no drug treatment-related effects on survival.

Group/ Subgroup/Sex	Replaced Animal	Day of Death/ Sacrifice	Replacement Animal	First Day of Dosing for Replacement Animal
4/1/M	H0340	4	H0378	4
3/1/M	H0227	5	H0278	5
4/1/F	H0811	4	H0878	5
4/2/F	H0872	10	H0879	11
4/2/F	H0874	10	H0880	11
5/1/M	H0402	24	H0478	24
5/1/F	H0943	26	H0978	26

The test article was administered by oral gavage. Males and females were dosed once daily for up to 694 or 657 days, respectively, excluding the day of necropsy (682 or 643 days, respectively, prior to the first terminal sacrifice).

Dosing Comments (Dose Adjustments or Early Termination): Criteria for study termination were conveyed to the Sponsor on October 11, 2019 following communication with the ECAC by email to obtain concurrence.

Dosing Solution Analysis: Formulations prepared for use in Week 1 (Day 1) of the dosing phase were analyzed to determine homogeneity and achieved concentration. Samples were removed in duplicate from the top, middle, and bottom of each formulation and were analyzed. A single sample was taken from the middle of the control article (vehicle) and water control formulations and was analyzed. The mean of the homogeneity results was used as the achieved concentration result. Formulations prepared for use in Weeks 4, 13, 26, 39, 52, 65, 78, 91, and 98 of the dosing phase were analyzed to determine the achieved concentration. Triplicate samples were taken from

the middle of the test article formulations and were analyzed. A single sample was taken from the middle of the control article (vehicle) and water control formulations and was analyzed.

Table 6 Design of the 104-week oral gavage carcinogenicity study with hamsters

3.1.5 Study Design

Group number	Group description	Dose level (mg/kg/day)	Animal numbers: Carcinogenicity (Subgroup 1) Male n=65	Carcinogenicity (Subgroup 1) Female n=65	Toxicokinetics (Subgroup 2) Male n=0, 6 or 12	Toxicokinetics (Subgroup 2) Female n=0, 6 or 12
1	Control I	0	H0001-H0065	H0501-H0565	H0066-H0071	H0566-H0571
2	Control II	0	H0101-H0165	H0601-H0665	-	-
3	Low	10	H0201-H0226, H0228-H0265, H0278[a]	H0701-H0765	H0266-H0277	H0766-H0777
4	Intermediate	30	H0301-H0339, H0341-H0365, H0378[a]	H0801-H0810, H0812-H0865, H0878[a]	H0366-H0377	H0866-H0871, H0873, H0875-H0877, H0879-H0880[a]
5	High	100	H0401, H0403-H0465, H0478[a]	H0901-H0942, H0944-H0965, H0978[a]	H0466-H0477	H0966-H0977

Control I = polyethylene glycol (b) (4) [(b) (4) v:v]
Control II = Purified water

a Seven animals necessitated premature sacrifice or were found dead during the first 4 weeks of the study; therefore, these animals were replaced with spare animals.
Animal H0340 (Group 4 carcinogenicity male) was replaced with Animal H0378.
Animal H0227 (Group 3 carcinogenicity male) was replaced with Animal H0278.
Animals H0811 (Group 4 carcinogenicity female), and H0872 and H0874 (Group 4 toxicokinetics females) were replaced with Animals H0878, H0879, and H0880, respectively.
Animal H0402 (Group 5 carcinogenicity male) was replaced with Animal H0478.
Animal H0943 (Group 5 carcinogenicity female) was replaced with Animal H0978.

Observations and Results

Mortality: All animals were observed at the beginning and end of each working day (nominal) for signs of ill health or overt toxicity.

Females were terminated during or after Week 92 when survival in the water-control group declined to 20 (20/65 = 30.7%) animals in the group. Males were terminated during or after Week 98 when survival in the vehicle-control group declined to 20 (20/65 = 30.7%) animals in the group.

For male hamsters, survival was comparable for vehicle-control and drug-treated groups. However, survival for the male water-control group (41/65 = 63.1%) was significantly higher relative to the male vehicle-control and drug-treated groups (20/65 [30.7%] to 26/65 [40%]). The vehicle was Polyethylene glycol (b) (4) [(b) (4) v:v]. A

potential vehicle-related effect on survival occurred for male vehicle-control and drug-treated groups. For female hamsters, survival was comparable for the vehicle-control, water-control, and drug-treated groups. The severity of chronic progressive nephropathy (CPN) was increased for male and female vehicle-control and drug-treated groups relative to male and female water-control groups. However, overall incidences of CPN were not different for male and female groups. There were corresponding increases in CPN as the cause of death for male and female vehicle-control and drug-treated groups relative to male and female water-control groups. The severity of CPN led to increases in mortality for male vehicle-control and drug-treated groups relative to the male water-control group. This did not appear to impact the ability of the study to assess the carcinogenic potential of CCX-168 as males were treated up to Week 98 and females up to Week 92.

In control and CCX168-treated groups, the most common cause of death was chronic progressive nephropathy (CPN) for males and CPN or a cardiovascular lesion, most commonly atrial thrombosis, for females.

Administration of the vehicle-control (Polyethylene glycol (b) (4)), regardless of CCX168 dose, resulted in higher incidence and/or severity of chronic progressive nephropathy (CPN) in the kidneys, cystic glands in the rectum, pigment in the spleen, mesenteric lymph nodes, liver, colon, and cecum, and pigmented macrophages in the liver compared to the water-control group. However, only CPN appear to have an effect on survival.

Table 7 Summary of Animal Fate

Table 8.1: Summary of Animal Fate

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Test Article	Control I (vehicle)	Control II (water)	CCX168		
Group	1	2	3	4	5
Dose Level (mg/kg/day)	0	0	10	30	100

Phase: Dosing

Fate Status / Group/Subgroup/Sex: Number in Group:	1/1/M 65	2/1/M 65	3/1/M 65	4/1/M 65	5/1/M 65	1/1/F 65	2/1/F 65	3/1/F 65	4/1/F 65	5/1/F 65
Terminal Sacrifice 1	20	41	26	26	26	0	0	0	0	0
Terminal Sacrifice 2	0	0	0	0	0	22	20	26	18	20
Accidental	0	0	0	1	1	0	0	0	0	0
Found Dead	6	3	5	15	8	10	8	6	12	11
Moribund Sacrifice	39	21	34	23	30	33	37	33	35	34

Table 8 Statistical Analysis of Survival for Male Hamsters

Text Table 4.17: Results of Statistical Analysis of Survival - Males

		Unadjusted Survival Incidence Rate				
Group	Trend	1	2	3	4	5
Dose Level(mg/kg/day)	(1,3,4,5)	0	0	10	30	100
Group Size		65	65	65	65	65
Terminal Sacrifice		20	41	26	26	26
Deaths		45	24	39	39	39
Log-Rank P-value (v1)	0.3994	N/A	0.0002*	0.4752	0.2186	0.2763
Wilcoxon P-value (v1)	0.4566	N/A	0.0002*	0.6140	0.2405	0.3653

* = Significant at 5% level

Table 9 Statistical Analysis of Survival for Female Hamsters

Text Table 4.18: Results of Statistical Analysis of Survival - Females

		Unadjusted Survival Incidence Rate				
Group	Trend	1	2	3	4	5
Dose Level(mg/kg/day)	(1,3,4,5)	0	0	10	30	100
Group Size		65	65	65	65	65
Terminal Sacrifice		22	20	26	18	20
Deaths		43	45	39	47	45
Log-Rank P-value (v1)	0.3024	N/A	0.4900	0.6368	0.4048	0.4541
Wilcoxon P-value (v1)	0.2417	N/A	0.3642	0.8206	0.4413	0.3361

Table 10 Survival curves the male vehicle-control, water-control, and drug-treated groups

Figure 7.1: Summary of Survival - Males

Test Article	Control I (vehicle)	Control II (water)	CCX168		
Group	1	2	3	4	5
Dose Level (mg/kg/day)	0	0	10	30	100

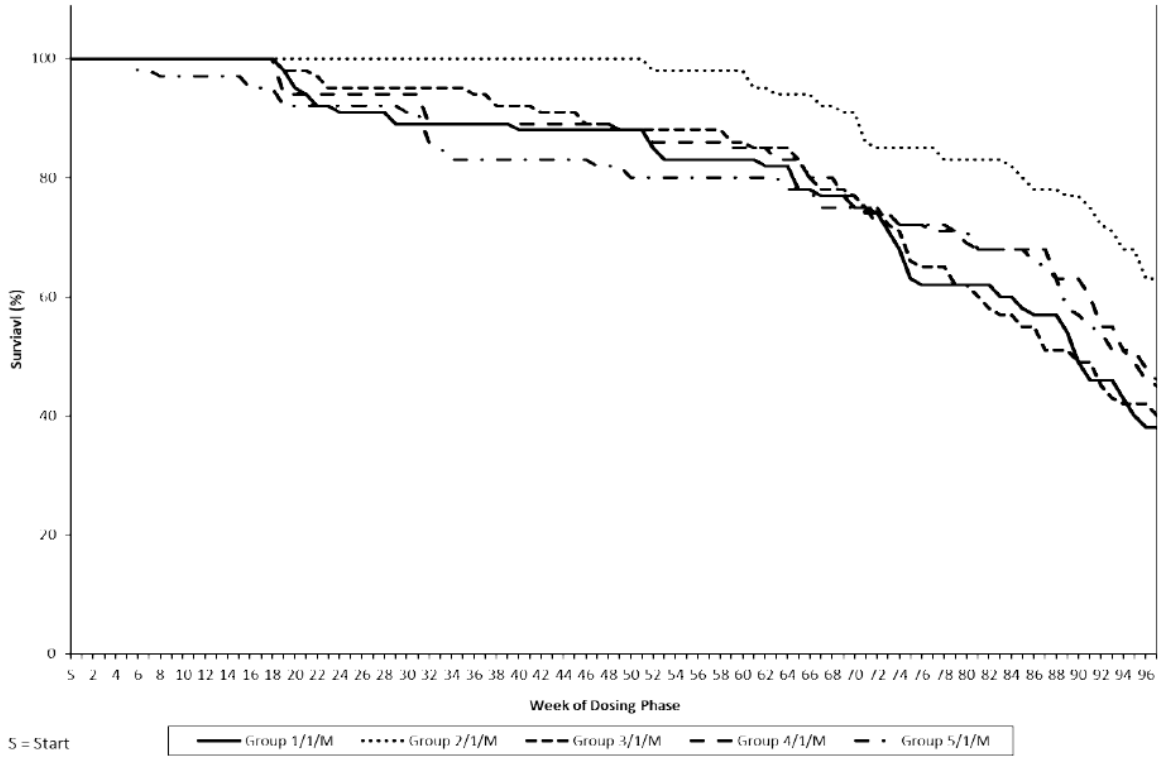


Table 11 Survival curves the female vehicle-control, water-control, and drug-treated groups

Figure 7.2: Summary of Survival - Females

Test Article	Control I (vehicle)	Control II (water)	CCX168		
Group	1	2	3	4	5
Dose Level (mg/kg/day)	0	0	10	30	100

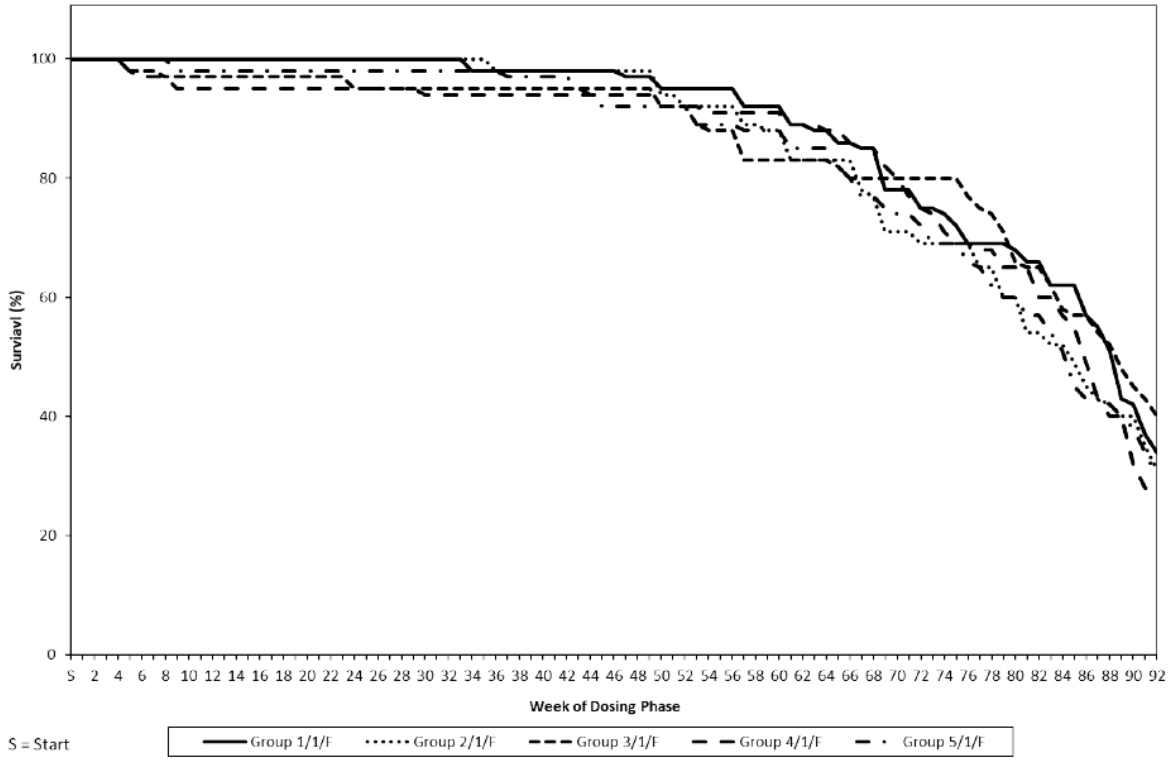


Table 12 Incidences of chronic progressive nephropathy for male and female vehicle-control, water-control, and drug-treated groups

Text Table 3.5: Incidence of Chronic Progressive Nephropathy: Kidneys - All Carcinogenicity Animals; and the Incidence of Chronic Progressive Nephropathy as the Cause of Demise - Decedent Carcinogenicity Animals

		Males					Females				
		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Tissue and finding	Level (mg/kg/day)	0	0[a]	10	30	100	0	0[a]	10	30	100
Kidney	No. examined:	65	65	65	65	65	65	65	65	65	65
nephropathy, chronic progressive	Grade -	5	6	2	5	8	2	3	3	4	1
	1	9	22	7	2	1	7	17	7	3	5
	2	15	27	16	19	14	23	35	20	19	27
	3	20	9	23	23	17	23	9	24	29	21
	4	15	1	14	15	22	10	1	9	8	8
	5	1	0	3	1	3	0	0	2	2	3
	Total Incidence	60	59	63	60	57	63	62	62	61	64
Cause of Demise	No. examined:	45	24	39	39	39	43	45	39	47	45
nephropathy, chronic progressive	Grade -	27	23	20	25	22	36	45	25	39	34
	Present	18	1	19	14	17	7	0	14	8	11

- = finding not present; 1 = Minimal; 2 = Slight; 3 = Moderate; 4 = Marked; 5 = Severe.
F = Female; M = Male.
a = Water control group.

Clinical Signs: Each animal was given a detailed physical examination, including palpation for tissue masses, once weekly and on the day of terminal sacrifice. Twelve carcinogenicity animals/group/sex were observed once daily, upon return to the home cage after dosing, during Week 1 of the dosing phase

Increased incidences of swollen mouth, loss of hair, and various sores and lesions were observed across all groups, including both controls. These findings appeared to be unrelated to treatment with CCX168.

Treatment with CCX168 had no apparent effects on the incidence, multiplicity, or size of palpable masses.

Body Weights: Individual body weights of all animals were recorded on Day 1 of the predose phase (replacement animals were weighed once weekly during the predose phase until allocated to the dosing phase), once weekly from Day 1 (predose) through Week 16 of the dosing phase, once every 4 weeks from the start of Week 17 of the dosing phase, and once weekly from the start of Week 69 of the dosing phase; on the day prior to terminal sacrifice, and a terminal body weight was recorded before each necropsy.

Body weights were comparable for vehicle-control and drug-treated groups. Body weights were slightly higher for the control (water) groups relative to the vehicle-control groups.

Table 13 Body weights as a percent of control on Day 680 for males and Day 638 for females

Body weights	Males					Females				
	Vehicle-Control	Control	10 mg/kg	30 mg/kg	100 mg/kg	Vehicle-Control	Control	10 mg/kg	30 mg/kg	100 mg/kg
Day 1	94.6	98.3	94.9	98.0	97.4	92.9	95.0	93.0	93.6	94.8
Day 680 (M)/ 638 (F)	146.6	161.8	146.6	150.4	153.0	167.0	174.5	165.3	158.4	169.8
BW, % of Control	100.0	110.4	100.0	102.6	104.4	100.0	104.5	99.0	94.9	101.7

Figure 2 Body weights for male control and drug-treated groups

Figure 7.3: Summary of Body Weight - Males

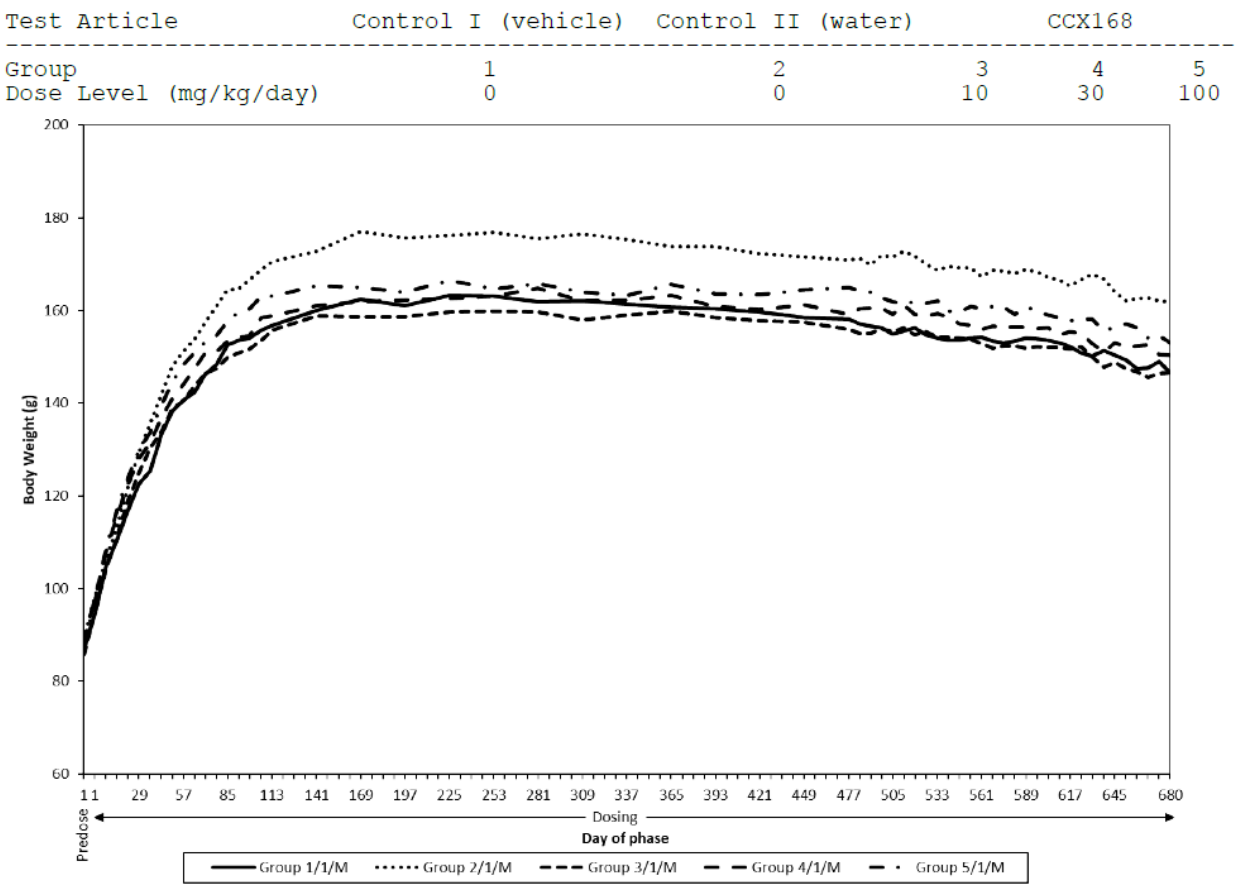
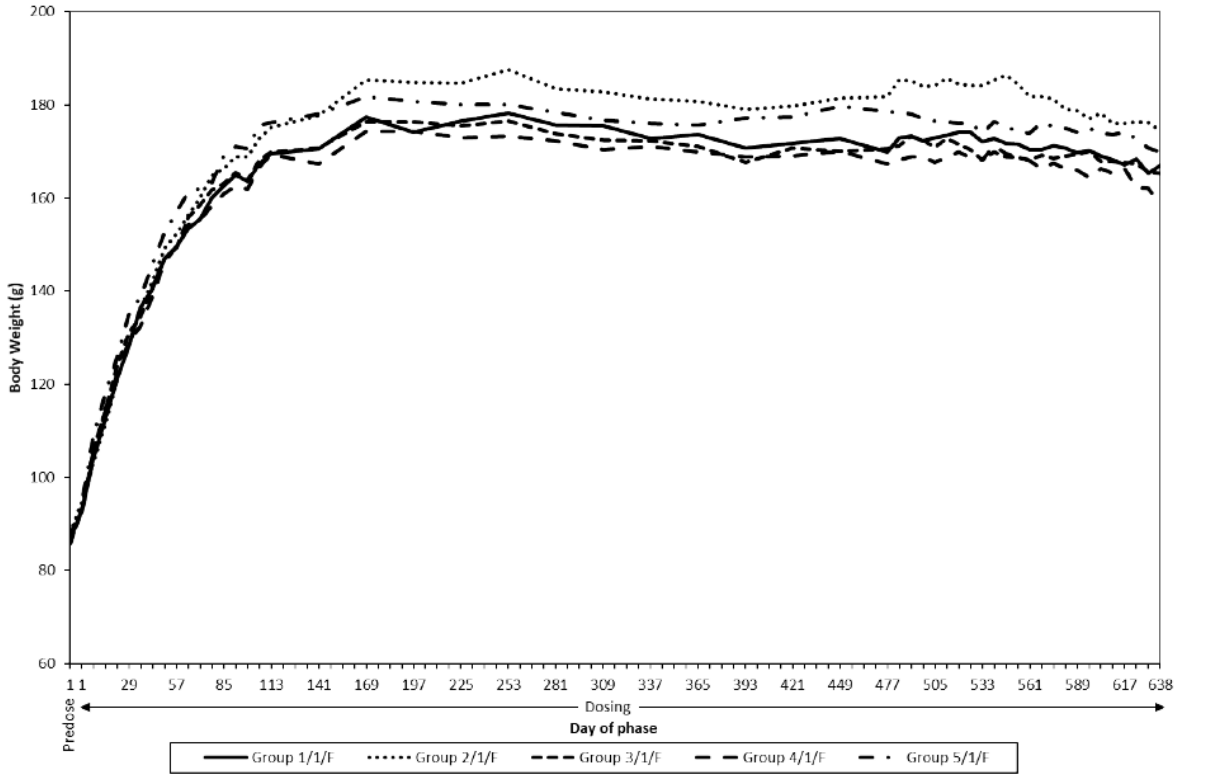


Figure 3 Body weights for female control and drug-treated groups

Figure 7.4: Summary of Body Weight - Females

Test Article	Control I (vehicle)	Control II (water)	CCX168		
Group	1	2	3	4	5
Dose Level (mg/kg/day)	0	0	10	30	100



Feed Consumption: The amount of food consumed by each cage of carcinogenicity animals was determined twice weekly during Weeks 1 through 4, once weekly during Weeks 5 through 16 of the dosing phase, and once every 4 weeks thereafter.

Overall, there were no treatment-related effects on food consumption. As noted above, absolute body weights were unaffected for females treated up to 92 weeks and males treated up to 98 weeks.

Clinical Pathology: Blood samples (1 x 0.5 mL [EDTA], nominal) were withdrawn from the abdominal aorta of all carcinogenicity animals at terminal necropsy for measurements of hematology parameters.

Hematology parameters at the time of the terminal sacrifice were unaffected by treatment with CCX-168 at doses up to 100 mg/kg/day.

Gross Pathology: The terminal sacrifice commenced on Day 644 or 683 of the dosing phase for females and males, respectively. All carcinogenicity animals that died or were

sacrificed following commencement of the scheduled necropsy were marked as a terminal sacrifice. The scheduled necropsies were performed on Days 645 through 658 or Days 683 through 695 of the dosing phase for females and males, respectively, after an overnight period without food. Animal H0912 (Group 5 carcinogenicity female) was sacrificed in a moribund condition on Day 644 of the dosing phase, but was marked as a terminal sacrifice. Scheduled necropsies were carried out by controlled randomization (i.e., one cage of animals from Group 1, 4, 2, 5, and then 3 and repeated in the same sequence until all animals had been terminated). Animals were weighed before necropsy. Each animal was administered isoflurane anesthesia. Once a suitable deep plane of anesthesia was established, the animal was exsanguinated by severing its major blood vessels. If urgent sacrifice of an animal in extremis was necessary, the animal was sacrificed by intraperitoneal injection of sodium pentobarbitone (overdose) and death was confirmed by cervical dislocation and/or exsanguination. A full macroscopic examination was performed under the general supervision of a Pathologist, and all lesions were recorded.

Gross pathological findings were not remarkable and did not generally correlate with neoplastic and non-neoplastic findings listed below.

Histopathology:
Adequacy of tissue examination: An adequate panel of organs and tissues was submitted for histopathological examination. All tissues denoted by E in the previous tissue list from each carcinogenicity animal were embedded in paraffin wax BP (block stage), sectioned at a nominal 5 µm, and stained with hematoxylin and eosin. All tissues denoted by E in the previous tissue list from all carcinogenicity animals were examined microscopically by the Contributing Scientist for Anatomic Pathology.

Table 14 List of tissues examined

7.4 Tissue list							
Tissue / organ				**Tissue / organ**			
Bone Marrow Smear (femur)				Skin/Subcutis (x1)	P		E
Brain (x6)	P		E	Mammary Gland (x1)	P		E
Spinal Cord, Cervical (x1)	P		E	Heart (x1)	P		E
Spinal Cord, Thoracic (x1)	P		E	Aorta (x1)	P		E
Spinal Cord, Lumbar (x1)	P		E	Muscle, Biceps Femoris (x2)	P		E
Adrenal (x2)	P		E	Kidney (x2)	P		E
Pituitary (x1)	P		E	Urinary Bladder (x1)	P		E
Nerve, Sciatic (x1)	P		E	Testis (x2)	P[4]		E
Eye (x2)	P[1]		E	Epididymis (x2)	P[4]		E
Nerve, Optic (x2)	P		E	Ovary (x2)	P		E
Harderian Gland (x2)	P[2]			Oviduct (x2)	P		
Thyroid (x2) and Parathyroid	P		E	Seminal Vesicle (x2)	P[5]		E
Trachea (x1)	P		E	Prostate (x1)	P		E
Oesophagus (x1)	P		E	Uterus (x3)	P[6]		E
Lung (x2)	P[3]		E	Vagina (x1)	P		E
Spleen (x1)	P		E	Femur + Marrow (x1)	P[7]		E
Thymus (x1)	P		E	Sternum + Marrow (x1)	P		E
Lymph Node, Mesenteric (x1)	P		E	Larynx (x1)			
Liver (x 2)	P		E	Lacrimal Gland (x2)			
Pancreas (x1)	P		E	Zymbal's Gland (x2)	P		
Stomach (x1)	P		E	Lymph Node, Bronchial (x1)			
Duodenum (x2)	P		E	Head (not processed)	P		
Jejunum (x1)	P		E	Nasal Cavity (x4)	P		
Colon (x1)	P		E	Nasopharynx (x2)	P		
Ileum (x1)	P		E	Nose/Nares (x1)	P		
GALT/Peyers patch (x1)	P		E	Lymph Node, Popliteal (x2)			
Caecum (x1)	P		E	Ureter (x2)			
Rectum (x1)	P		E	Dosing sites (variable)			
Mandibular Salivary Gland (x2)	P		E	Untreated skin site (x3)			
Sublingual Salivary Gland (x2)	P		E	Animal identification	P		
Parotid Salivary Gland (x1)				Gross lesions (variable)	P		E[8]
Lymph Node, Mandibular (x1)	P		E	Tissue masses (variable)	P		E
Tongue (x1)	P		E	Lymph Node, Axillary			
Gall Bladder	P		E	Preputial/clitoral gland (x1)	P		E
Legend:							
P = Tissues preserved; E = Tissues processed and examined microscopically.							
(xN) = number of sections for histopathology.							
Footnotes:							
1: Tissue taken into Davidson's fixative.							
2: Preserved with the head (*in situ*) unless histopathological processing is required.							
3: Tissue includes mainstem bronchi and bronchioles.							
4: Tissue taken into Modified Davidsons fixative and processed to at least the block stage.							
5: Tissue includes coagulating glands.							
6: Tissue includes cervix.							
7: Tissue includes femorotibial joint.							
8: Gross lesions processed in accordance with current Histology Standard Operating Procedure							
Additional information:							
Fixative will be neutral buffered 10% formalin unless specified otherwise.							
Left and right organs will be weighed together.							
Bone tissue designated for histopathological examination will be decalcified using Kristenson's fluid.							

(excerpted from the Sponsor's submission)

Peer Review Conducted: An external peer review was not conducted.
Historical Control Provided for Tumor Incidence: No

Neoplastic:
There were no CCX-168 treatment-related neoplastic findings in female hamsters treated up to 92 weeks or male hamsters treated up to 98 weeks.

Neoplastic findings in female hamsters:
The incidences of squamous cell papilloma and combined squamous cell papilloma and carcinoma in the vagina were statistically significantly increased for females in the 100 mg/kg/day group relative to vehicle-control group; however, statistical significance was not present when compared to the water-control group. There were no differences in survival between the vehicle-control and water-control groups.

There was a positive trend test for the dose-response relationship for incidences of malignant lymphoma-pleomorphic in female drug-treated groups; however, pairwise comparisons were not statistically significant.

The trend test for the dose-response relationship for incidences of adenoma in the uterus of female drug-treated groups did not achieve statistical significance. Further, pairwise comparisons were not statistically significant.

The incidence of adenoma in the parathyroid gland was increased for the female water-control group relative to the female vehicle-control group, although statistical significance was not achieved.

The trend test for the dose-response relationship for incidences of benign pheochromocytoma in the uterus of female drug-treated groups did not achieve statistical significance. Further, pairwise comparisons were not statistically significant. The combined incidences of benign and malignant pheochromocytoma in the vehicle-control group were comparable to the incidence in the high dose CCX-168 group.

Table 15 Neoplastic findings in female hamsters following treatment with CCX-168 for periods up to 92 weeks

Females	Vehicle-Control	Water-Control	10 mg/kg	30 mg/kg	100 mg/kg	
VAGINA						
Squamous cell papilloma	0/65 (34) 0.0610	2/65 (32) 0.2312	3/65 (34) 0.1194	2/65 (33) 0.2388	4/65 (32) **0.0499***	
Squamous cell carcinoma	0/65 (34) 0.7405	0/65 (31) NC	1/65 (34) 0.5000	0/65 (32) NC	0/65 (31) NC	
Combined squamous cell papilloma and carcinoma	0/65 (34) 0.0972	2/65 (32) 0.2312	4/65 (35) 0.0606	2/65 (33) 0.2388	4/65 (32) **0.0499***	
HEMOLYMPHO-RETICULAR SYSTEM						

Malignant Lymphoma-Pleomorphic	0/65 (34) 0.0172*	3/65 (33) 0.1139	0/65 (34) NC	1/65 (33) 0.4925	3/65 (33) 0.1139	
UTERUS						
B-Adenoma	1/65 (34) 0.0406@	0/65 (31) 1.0000	1/65 (34) 0.7537	1/65 (33) 0.7463	4/65 (33) 0.1686	
PARATHYROID GLAND						
B-Adenoma	9/62 (35) 0.4391	18/59 (37) 0.0382@	16/62 (38) 0.1096	17/61 (38) 0.0729	12/60 (34) 0.2735	
ADRENAL						
Benign Pheochromocytoma	3/65 (35) 0.0227@	3/65 (33) 0.6347	0/65 (34) 1.0000	2/65 (33) 0.8031	6/65 (35) 0.2386	
Malignant pheochromocytoma	3/65 (35) 0.7687	1/65 (32) 0.9317	1/65 (34) 0.9394	1/65 (33) 0.9357	1/65 (32) 0.9317	
Combined benign and malignant pheochromocytoma	6/65	4/65	1/65	3/65	7/65	

X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed
*: Statistically significant (compared to the vehicle-control group) at 0.005 and 0.025 levels for common and rare tumors or 0.01 and 0.05 level for common and rare tumors for tests of dose response relationship and pairwise comparison, respectively.
(Partially excerpted from Dr. Malick Mbodj's Statistical Review)

Neoplastic findings in male hamsters:
There were no CCX-168 treatment-related tumors for male hamsters.

There was a statistically significant increase of the dose-response relationships across the male vehicle control and the treated groups for the incidence of benign squamous cell papilloma in the stomach; however, pairwise comparisons were not statistically significant.

The incidence of cortical adenoma was significantly increased for the male water-control group; however, significance was not present for the combination of cortical adenoma and carcinoma.

Table 16 Neoplastic findings in male hamsters following treatment with CCX-168 for periods up to 98 weeks

Males	Vehicle-Control	Water-Control	10 mg/kg	30 mg/kg	100 mg/kg	
Stomach						
Squamous cell papilloma	0/65 (35) 0.0164*	3/64 (46) 0.1779	1/65 (36) 0.5070	1/65 (39) 0.5270	4/65 (38) 0.0678	
ADRENAL						
Cortical adenoma	5/65 (37) 0.5392	21/65 (51) 0.0042*	13/65 (41) 0.0498	7/65 (40) 0.4350	8/65 (39) 0.3079	
Cortical carcinoma	5/65 (37) 0.8578	2/65 (47) 0.9736	3/65 (37) 0.8694	3/65 (40) 0.8924	2/65 (38) 0.9503	

Combined cortical adenoma and carcinoma	10/65 (38) 0.8031	23/65 (52) 0.0634	15/65 (41) 0.2305	10/65 (41) 0.6758	9/65 (39) 0.7235	

X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed
*: Statistically significant (compared to the vehicle-control group) at 0.005 and 0.025 levels for common and rare tumors or 0.01 and 0.05 level for common and rare tumors for tests of dose response relationship and pairwise comparison, respectively.
(Partially excerpted from Dr. Malick Mbodj's Statistical Review)

Non-neoplastic:
Mineralization was noted in the ovaries of females administered 30 or 100 mg/kg/day; a corresponding increase in this finding was also noted in females administered 100 mg/kg/day that survived to the terminal sacrifice. This finding was characterized by small foci of basophilic, crystalline, or granular material within the ovarian interstitium.

Administration of the vehicle-control (Polyethylene glycol (b) (4)), regardless of CCX168 dose, resulted in higher incidence and/or severity of chronic progressive nephropathy (CPN) in the kidneys, cystic glands in the rectum, pigment in the spleen, mesenteric lymph nodes, liver, colon, and cecum, and pigmented macrophages in the liver compared to the water-control group.

The severity (grade) of chronic progressive nephropathy was higher in all groups administered the vehicle, regardless of CCX168 dose, compared to the water-control group. However, the overall incidence was similar across all control and CCX168-treated groups. Increased severity of CPN was linked to decreased survival in the male vehicle-control and drug-treated groups relative to the water-control group; however, there were no such findings for female groups.

Cystic glands were observed in the rectum of some animals from all groups administered control article (vehicle), with or without CCX168, compared to water controls. A minor overall increase in the severity of cystic glands was noted for males administered 100 mg/kg/day and the overall incidence and grades were higher in vehicle control and CCX168-treated females. Cystic glands were characterized by glands with large lumens without associated inflammation, luminal secretion, or debris.

An increase in specific findings in the spleen, mesenteric lymph nodes, liver, cecum, colon, rectum, and kidneys was noted in animals administered the vehicle (Polyethylene glycol (b) (4)), compared to water-controls. The incidences of these findings were generally similar across the CCX168-treated groups, which indicated no additional effect occurred due to drug. Pigment was higher in the spleen, mesenteric lymph nodes, liver, colon, and cecum of animals administered the vehicle-control, compared with water-control groups, regardless of CCX168 dose. Similarly, pigmented macrophages in the liver were higher in animals in the vehicle-control and CCX168-treated groups compared to the water-control group.

Incidences of distention in the cecum were higher for animals in the vehicle-control and CCX168-treated groups compared to the water-control group.

Table 17 Non-neoplastic findings in hamsters following treatment with CCX-168 for periods up to 92 weeks in females and 98 weeks in males

Organ/Tissue	Males					Females				
	VC	WC	10 mg/kg	30 mg/kg	100 mg/kg	VC	WC	10 mg/kg	30 mg/kg	100 mg/kg
Ovary -mineralization	-	-	-	-	-	2/64	4/64	5/64	15/64	32/65
Kidney -nephropathy, chronic, progressive	60/65	59/65	63/65	60/65	57/65	63/65	62/65	62/65	61/65	64/65
G1	9	22	7	2	1	7	17	7	3	5
G2	15	27	16	19	14	23	35	20	19	27
G3	20	9	23	23	17	23	9	24	29	21
G4	15	1	14	15	22	10	1	9	8	8
G5	1	0	3	1	3	0	0	2	2	3
Rectum -cystic glands	17/64	0/64	17/64	23/65	30/64	52/65	0/65	56/65	55/64	51/65
Spleen -pigment	39/64	3/65	39/65	37/65	33/65	48/65	20/65	44/65	43/65	36/65
Mesenteric LN -pigment	45/54	0/59	48/58	37/55	42/57	44/55	4/62	40/59	41/58	38/59
Liver -pigment macrophages	54/65	35/65	53/65	49/65	48/65	61/65	21/65	51/65	47/65	48/65
-pigment, hepatocellular	41/65	19/65	32/65	33/65	35/65	25/65	7/65	23/65	15/65	19/65
Colon -pigment	55/65	1/64	57/64	50/64	53/64	63/65	21/65	58/65	55/64	58/65
Cecum -pigment	47/64	0/65	43/65	39/64	37/65	52/65	2/65	49/65	45/65	38/65
-distension	12/64	0/65	20/65	18/64	15/65	21/65	3/65	14/65	20/65	15/65

Toxicokinetics: Blood samples were collected from 3 TK animals/sex/group/time point from Groups 3, 4, and 5 during Week 4 (Day 23) at approximately 2 hr postdose and during Week 26 (Day 182) predose and at approximately 1, 2, 4, and 7 hr postdose. Blood samples were also collected from the control group (Group 1) from 3 TK animals/sex on Days 23 and 182 at approximately 2 hr postdose. The TK report contained transcription errors. The incorrect day number was documented for the Week 4 sampling occasion; Day 28 was documented, instead of Day 23. The data confirmed all samples were collected on Day 23. Blood samples were processed to plasma and were analyzed for CCX168, CCX168-M1, and CCX168-M6 (Day 182 only) (b) (4) The method involved protein precipitation extraction followed by analysis using high

performance liquid chromatography followed by tandem mass spectrometric detection (LC-MS/MS).

All concentration values of CCX168, CCX168-M1 and CCX168-M6 in the vehicle control group were below the lower limit of quantitation (<2.00 ng/mL for CCX168 and <1.00 ng/mL for CCX168-M1 and CCX168-M6) with the exception of a measurable concentration of CCX168 on Day 182 (Animal H0070, Male, 2.80 ng/mL). Plasma concentrations of CCX168 observed in this control animal could not be explained by the conduct of the in-life procedures or the validated method used in sample analysis. However, this finding was unlikely to affect the inferences or conclusions drawn for the toxicokinetic analysis for this study as the value was slightly higher than the lower limit of quantitation (2.00 ng/mL) and greater than 200-fold lower than the mean concentration observed in the low dose group at 2 hours postdose.

For $AUC_{0\text{-}24hr}$ values, predose values were used in place of 24-hr time points, which were not collected, using the assumption that steady-state had been achieved (e.g., trough values were assumed to be roughly constant at steady state, although the TK data was complicated by saturation of exposure).

On Day 182, C_{max} values for CCX-168 increased in an approximate dose proportional manner. $AUC_{0\text{-}7hr}$ and $AUC_{0\text{-}24hr}$ for CCX-168 from 10 to 30 mg/kg/day increased in an approximate dose proportional manner; however, increases from 30 to 100 mg/kg/day were less than dose proportional. C_{max} and AUC values for CCX-168 were comparable in male and female hamsters. Exposures were relatively comparable to those observed in the 13-week dose range finding study with hamsters (Study # PC0677_168; see Review dated November 14, 2017); saturation was noted between doses of 100 mg/kg/day and 1000 mg/kg/day (500 mg/kg BID).

C_{max} and AUC values for CCX-168-M1 from 10 to 30 mg/kg/day increased in an approximate dose proportional manner; however, increases from 30 to 100 mg/kg/day were less than dose proportional. C_{max} and AUC values for CCX-168-M1 were comparable in male and female hamsters. C_{max} and AUC values for CCX-168 M1 were generally less than 7% of values for CCX-168.

C_{max} and AUC values for CCX-168-M6 from 10 to 30 mg/kg/day increased in a greater than dose proportional manner; however, increases from 30 to 100 mg/kg/day were less than dose proportional. C_{max} and AUC values for CCX-168-M6 were greater in females than males. C_{max} and AUC values for CCX-168 M6 were generally less than 3 to 7% of values for CCX-168.

Table 18 Summary of mean concentrations (ng/mL) of CCX168 in hamster plasma on Day 28 at 2 hours postdose

Summary of Mean Concentrations (ng/mL) of CCX168 in Hamster Plasma on Day 28 at 2 Hours Postdose

Dose Group	Dose Level (mg/kg/day)	Sex		CCX168 Concentration (ng/mL)
3	10	M	Mean	482
			SD	411
		F	Mean	285
			SD	71.8
		MF	Mean	384
			SD	285
4	30	M	Mean	2010
			SD	596
		F	Mean	854
			SD	224
		MF	Mean	1430
			SD	750
5	100	M	Mean	3260
			SD	429
		F	Mean	3240
			SD	774
		MF	Mean	3250
			SD	560

Table 19 Summary of CCX168 toxicokinetic parameters in hamster plasma on Day 182

Summary of the CCX168 Toxicokinetic Parameters in Hamster Plasma on Day 182

Dose Group	Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-7} (h*ng/mL)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (h)
3	10	M	689	2.00	2950	5560	5.44
		F	458	1.00	2380	4290	7.80
		MF	568	2.00	2670	4920	6.47
4	30	M	1780	2.00	10100	21600	7.36
		F	1820	1.00	8810	24500	9.97
		MF	1540	1.00	9470	23100	8.38
5	100	M	5650	2.00	20900	42000	8.53
		F	3540	2.00	16200	35600	NC
		MF	4600	2.00	18600	39300	NC

NC Not calculated due to the lack of a distinct elimination phase.

Notes: Combined male and female (MF) parameters were calculated by combining concentration data for all animals (male and female) at each dose level on each interval and using these data as a separate composite profile for TK analysis. These parameters are not an average of the values calculated for males and females separately.

AUC_{0-t} is equivalent to AUC_{0-24}. The 24 hour was set to be equal to the predose concentration as steady-state was assumed.

Table 20 Summary of mean concentrations (ng/mL) of CCX168-M1 metabolite in hamster plasma on Day 28 at 2 hours postdose

Summary Mean Concentrations (ng/mL) of Metabolite CCX168-M1 in Hamster Plasma on Day 28 at 2 Hours Postdose

Dose Group	CCX168 Dose Level (mg/kg/day)	Sex		CCX168-M1 Concentration (ng/mL)
3	10	M	Mean	19.8
			SD	9.22
		F	Mean	16.4
			SD	0.907
		MF	Mean	18.1
			SD	6.15
4	30	M	Mean	81.5
			SD	22.7
		F	Mean	52.6
			SD	14.2
		MF	Mean	67.0
			SD	23.2
5	100	M	Mean	129
			SD	9.45
		F	Mean	142
			SD	23.6
		MF	Mean	135
			SD	17.6

Table 21 Summary of metabolite CCX168-M1 toxicokinetic parameters in hamster plasma on Day 182

Summary of Metabolite CCX168-M1 Toxicokinetic Parameters in Hamster Plasma on Day 182

Dose Group	CCX168 Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-7} (h*ng/mL)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (h)
3	10	M	25.7	4.00	152	363	NC
		F	23.1	2.00	127	283	9.12
		MF	24.1	2.00	140	323	7.32
4	30	M	94.1	7.00	547	1550	NC
		F	118	7.00	514	1750	NC
		MF	106	7.00	530	1650	NC
5	100	M	173	7.00	971	2850	NC
		F	175	4.00	974	2500	NC
		MF	158	4.00	985	2720	NC

NC Not calculated due to the lack of a distinct elimination phase.

Notes: Combined male and female (MF) parameters were calculated by combining concentration data for all animals (male and female) at each dose level on each interval and using these data as a separate composite profile for TK analysis. These parameters are not an average of the values calculated for males and females separately.

AUC_{0-t} is equivalent to AUC_{0-24}. The 24 hour was set to be equal to the predose concentration as steady-state was assumed.

Table 22 Summary of metabolite CCX168-M6 toxicokinetic parameters in hamster plasma on Day 182

Summary of Metabolite CCX168-M6 Toxicokinetic Parameters in Hamster Plasma on Day 182

Dose Group	CCX168 Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-7} (h*ng/mL)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (h)
3	10	M	17.7	4.00	98.0	227	NC
		F	24.2	4.00	141	353	NC
		MF	20.9	4.00	119	290	NC
4	30	M	42.7	4.00	252	712	NC
		F	121	7.00	552	1890	NC
		MF	80.4	7.00	402	1300	NC
5	100	Male	90.5	2.00	453	1220	NC
		Female	154	4.00	927	2570	NC
		MF	119	2.00	716	1980	NC

NC Not calculated due to the lack of a distinct elimination phase.

Notes: Combined male and female (MF) parameters were calculated by combining concentration data for all animals (male and female) at each dose level on each interval and using these data as a separate composite profile for TK analysis. These parameters are not an average of the values calculated for males and females separately.

AUC_{0-t} is equivalent to AUC_{0-24}. The 24 hour was set to be equal to the predose concentration as steady-state was assumed.

11 Nonclinical Discussion

There were no CCX-168-related neoplastic findings in either male or female hamsters.

The ECAC judged the study to be adequate, noting prior concurrence for dose selection and study design, and negative for test article-related tumor findings in male or female hamsters.

Appendix II

ECAC Final Study Meeting Minutes for the 2-year rat and hamster CCX168 carcinogenicity studies

(Dated February 25, 2021)

Executive CAC Final Study Minutes
Date of Meeting: February 23, 2021

Committee: Karen Davis Bruno, PhD, OND IO, Chair
Paul Brown, PhD, OND IO, Member
Tim McGovern, PhD, OND IO, Member
Ron Wange, PhD, OND IO, Member
Eleni Salicru, PhD, DPT-II, Alternate Member
Timothy Robison, PhD, DABT, DPT-II, Pharm/Tox Team Leader
Ijeoma Uzoma, PhD, DPT-II, Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

Application Type and Number(s): NDA 214487
Drug Name: Avacopan (CCX168) capsule
Sponsor: ChemoCentryx

Background
CCX168 is a small molecule antagonist of complement component 5a receptor (C5aR), that is being developed as an oral treatment for adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis.

CCX168 was negative in all genotoxicity assays including in vitro bacterial mutagenicity study (Ames test), in vitro mammalian cell mutagenicity study (mouse lymphoma forward-mutation assay), and in vivo rat bone marrow micronucleus study.

The Applicant conducted 2-year oral rat and hamster carcinogenicity studies with CCX168.

Hamster Carcinogenicity Study
In the 2-year carcinogenicity study, Syrian Golden hamsters received CCX168 (avacopan) by oral gavage at doses of 0 (vehicle control: PEG [(b) (4) v:v]), 0 (water control), 10, 30, and 100 mg/kg/day.

Hamsters were determined to be a pharmacologically relevant species.

Prior concurrence for doses used in this study was obtained from the Executive Carcinogenicity Assessment Committee.

A potential vehicle-related effect on survival occurred for male vehicle-control and drug-treated groups. This did not appear to impact the ability of the study to assess the carcinogenic potential of CCX168 as males were treated up to Week 98 and females up to Week 92.

There were no CCX168-related neoplastic findings in either male or female hamsters.

Rat Carcinogenicity Study
In the 2-year carcinogenicity study, Sprague Dawley rats received CCX168 (avacopan) by oral gavage at doses of 0 (vehicle control: PEG [redacted] [redacted] v:v]), 0 (water control), 10, 30, and 100 mg/kg/day.

The rat is not a pharmacologically relevant species.

Prior concurrence for doses used in this study was obtained from the Executive Carcinogenicity Assessment Committee.

Treatment with CCX168 had no effects on survival in male or female rats up to 97 and 92 weeks, respectively.

There were no CCX168-related neoplastic findings in either male or female rats.

Toxicokinetic analysis conducted on Day 28 indicated that the Cmax and AUC0-24 exposure decreased from 30 (MD) to 100 mg/kg/day (HD) such that the highest systemic exposures were achieved in the mid-dose group at 30 mg/kg/day. Therefore, to assess the relationship of findings to treatment with CCX168, the 30 mg/kg/day group was also analyzed as the high dose group.

Executive CAC Conclusions
Hamster:

- The Committee concurred that the two-year hamster study was adequate, noting prior Exec CAC approval of the protocol.
- The Committee determined that there were no drug-related neoplasms in the 2-year hamster study in either males or females.

Rat:

- The Committee concurred that the two-year rat study was adequate, noting prior Exec CAC approval of the protocol.
- The Committee determined that there were no drug-related neoplasms in the 2-year rat study in either males or females.

Karen Davis Bruno, PhD
Chair, Executive CAC

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROBEENA M AZIZ
02/25/2021 11:12:38 AM

KAREN L DAVIS BRUNO
02/25/2021 11:24:21 AM

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

IJEOMA K UZOMA
03/08/2021 09:54:32 AM

TIMOTHY W ROBISON
03/08/2021 10:01:27 AM
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

APPENDICES FOR PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	214487
Supporting document/s:	SDN #1
Applicant's letter date:	July 7, 2020
CDER stamp date:	July 7, 2020
Product:	Avacopan (CCX168)
Indication:	Treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA])
Applicant:	ChemoCentryx, Inc.
Review Division:	Division of Rheumatology and Transplant Medicine (DRTM) Division of Pharm/Tox for Immunology and Inflammation (DPT-II)
Reviewer:	Ijeoma Uzoma, Ph.D.
Supervisor/Team Leader:	Timothy W. Robison, Ph.D., D.A.B.T.
Division Director:	Nikolay Nikolov, MD
Project Manager:	Susie Choi, PharmD

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 214487 are owned by ChemoCentryx Inc. or are data for which ChemoCentryx Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 214487 that ChemoCentryx Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 214487.

Appendix

1. IND 120784: 30 Day Safety Review; Review of 13-week rat and 20-week monkey toxicology studies (Dr. Matthew Whittaker, Dated in DARRTS July 15, 2014)

2. IND 120784: Review of 6-month toxicology study with rats and genetic toxicology studies (Dr. Matthew Whittaker, Dated in DARRTS November 9, 2017)

3. IND 120784: Review of 13-week toxicology study with hamster (Dr. Dong Zhao, Dated in DARRTS November 14, 2017)

4. IND 120784: ECAC meeting minutes (Dr. Karen Davis-Bruno, Dated in DARRTS November 9, 2017)

5. IND 120784: Early termination criteria for 104-week carcinogenicity study with rats (Dr. Matthew Whittaker, Comments were conveyed on 08-13-2019, Dated in DARRTS August 22, 2019)

6. NDA 214487: ECAC meeting minutes (Dr. Karen Davis-Bruno, Dated in DARRTS, February 25, 2021)

7. IND 120784: Review of Pharmacology and TK/ADME studies (Dr. Timothy W. Robison, Dated in DARRTS March 1, 2021)

Appendix 1

IND 120784: 30 Day Safety Review; Review of 13-week rat and 20-week monkey toxicology studies (Dr. Matthew Whittaker, Dated in DARRTS July 15, 2014)

DIVISION OF PULMONARY, ALLERGY and RHEUMATOLOGY PRODUCTS
NONCLINICAL 30 DAY SAFETY REVIEW

IND: 120,784
Drug: CCX168
Sponsor: Chemocentryx, Inc.
Drug Category: Complement component C5a receptor antagonist
Indication: Anti-neutrophil cytoplasmic autoantibody (ANCA)- associated vasculitis
Route: Oral
Review Completion Date: 7/15/14

INTRODUCTION

Chemocentryx, Inc. has developed CCX168 as an orally administered, small molecule (MW = 581 g/mol) antagonist of the human complement 5a receptor (C5aR) for the treatment of patients with anti-neutrophil cytoplasmic autoantibody (ANCA)- associated vasculitis. CCX168 was granted Orphan Drug designation for this indication by the FDA on June 2, 2014. A pre-IND meeting was held with the sponsor on April 21, 2014 and the initial IND was submitted on June 16, 2014.

ANCAs are circulating autoantibodies primarily directed against neutrophil-expressed proteins myeloperoxidase (MPO) and proteinase 3 (PR3). Under inflammatory conditions, neutrophils express MPO and PR3 on their cell surface. In patients with ANCA associated vasculitis, ANCAs bind to MPO and PR3 on the neutrophil cell surface, resulting in cell activation. Activated neutrophils subsequently release factors that directly damage blood vessel endothelium. They also release complement component C5a, an anaphylotoxin and neutrophil chemoattractant whose biological function is mediated by its activation of the C5a receptor (C5aR). The C5aR is a G-protein coupled receptor expressed on the surface of multiple cell types including macrophages, neutrophils, and endothelial cells. The release of C5a contributes to an amplification of neutrophil influx to sites of inflammation and leads to severe necrotizing inflammation of the blood vessel wall. CCX168 is designed to block C5aR activation and thus disrupt the development of ANCA associated vasculitis. By targeting the C5a receptor, CCX168 does not interfere with the formation of the complement C5b fragment-containing membrane attack complex (MAC). The MAC complex is important in immune defense against bacterial infections including *Neisseria*.

CCX168-M1, the major metabolite of CCX168, is also active at the C5aR at a similar potency to the parent compound. The sponsor predicts that M1 will be present at approximately 50% relative to the parent compound in ANCA associated vasculitis patients.

DRUG PRODUCT

The chemical structure of CCX168 is shown in Figure 1. The impurities detected in clinical drug product batches are present at levels below the 0.5% qualification threshold (ICH Q3B (R2)) for the maximum proposed clinical dose of 60 mg (30 mg b.i.d.) per day.

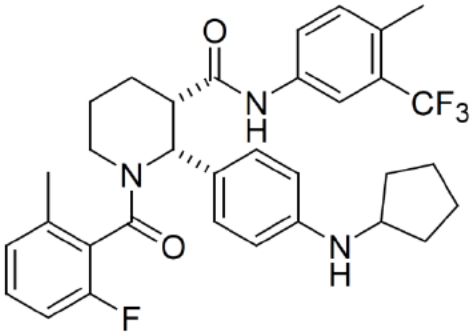


Figure 1. Chemical structure of CCX168

The 30 mg b.i.d. dose will require ingestion of a total of 6 capsules per day, given that CCX168 is presented in 10 mg capsules (Table 1). The total daily intake values for each component of the CCX168 drug product formulation at the 30 mg b.i.d. dose are seen in the far right column of Table 1.

Table 1. Composition of a single 10 mg (b) (4) of CCX168 and calculation of total daily intake values for each component at the proposed clinical dose of 30 mg b.i.d.

	% Composition	mg per unit Composition	Function	Grade	Amt per 30 mg bid dose (mg)
CCX168	(b) (4)	10	API	--	60
Polyoxyl 40 Hydrogenated Castor Oil (Cremophor RH40)					(b) (4)
Polyethylene glycol 4000 (PEG-4000)					
Gelatin Capsule, white, Size 0					
Gelatin band[a]					
Total					

[a] The product capsule is sealed with (b) (4) gelatin band

The clinical drug product formulation differs from the formulation used in nonclinical toxicity studies. However, the daily intake values of the excipients Cremophor RH40 and PEG-4000 at all proposed clinical doses are (b) (4) (b) (4)

Cremophor RH40:
Cremophor RH40 is described by the manufacturer [redacted]

Cremophor RH40 is present as an excipient at [redacted] mg/capsule in the approved oral product Neoral (cyclosporine) from Novartis (NDA 050715). Neoral is indicated for patients that have received organ transplants. The initial dose of Neoral in patients receiving renal transplants is 9 ± 3 mg/kg/day according to the current prescribing information. Neoral is presented at 100 mg/capsule. The calculation of the daily dose of Cremophor RH40 in patients receiving 9 mg/kg/day Neoral is seen below:

> 9 mg/kg/day Neoral * 60 kg (human weight) = 540 mg/day Neoral
> (540 mg/day) / (100 mg/capsule) = ~5 capsules/day
> 5 capsules/day * [redacted] mg Cremophor RH40/capsule = [redacted] **mg Cremophor RH40/day**

The [redacted] mg Cremophor/day exposure in patients receiving 9 mg/kg/day Neoral exceeds the projected [redacted] mg Cremophor RH40/day exposure in patients receiving the 30 mg b.i.d. dose of CCX168 in study CL003_168.

PEG 4000:
PEG 4000 is present as an excipient at [redacted] mg/tablet in the approved oral product Metformin hydrochloride (ANDA 076650; Mylan Pharmaceuticals). Metformin is present at 500 mg/tablet with a maximum recommended dose of 2,000 mg/day for the treatment of Type 2 diabetes. The calculation of the daily dose of PEG 4000 in patients receiving 2,000 mg/day Metformin is seen below:

> (2,000 mg/day Metformin) / (500 mg/tablet) = 4 tablets/day
> ([redacted] mg PEG 4000 / tablet) * (4 tablets/day) = [redacted] **mg PEG4000/day**

The [redacted] mg PEG4000/day exposure in patients receiving 2,000 mg/day Metformin HCl exceeds the projected [redacted] mg PEG4000/day exposure in patients receiving the 30 mg b.i.d. dose of CCX168 in study CL003_168.

PREVIOUS CLINICAL EXPERIENCE
Chemocentryx has completed its initial clinical study (CL001_168) in healthy volunteers, and a second clinical study in ANCA-associated glomerulonephritis patients (CL002_168) is currently ongoing. To date, all clinical studies have been conducted in Europe. The CCX168 drug product formulation to be used in proposed clinical study CL003_168 (Table 1) is consistent with what was used in CL002_168.

Study **CL001_168** (*n*= 48) tested single CCX168 doses at up to 100 mg and multiple daily doses (7 days) at up to 50 mg b.i.d with no serious adverse events reported.

Evidence for CCX168 inhibition of C5aR function in humans was shown in an *ex vivo* study using whole blood samples (Figure 2).

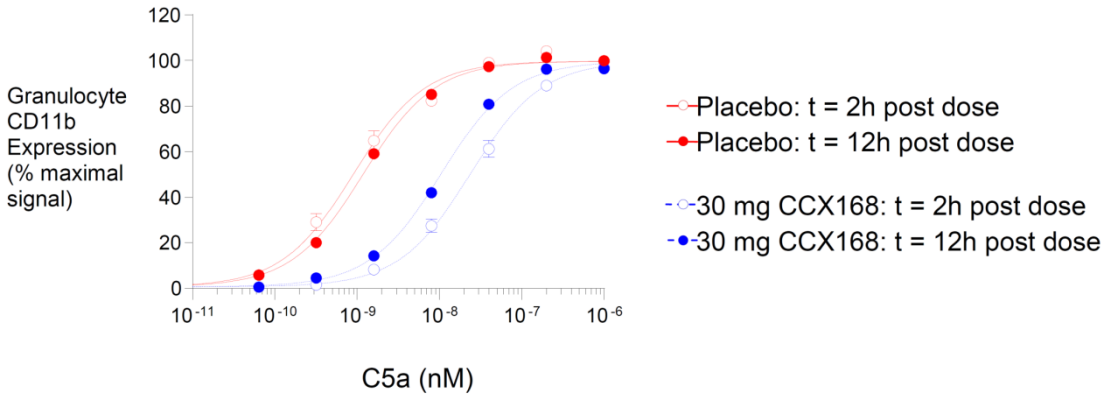


Figure 2. Evidence for inhibition of human C5aR function in whole blood samples of patients receiving 30 mg bid CCX168 for 7 days.

Briefly, this experiment measured C5a evoked CD11b expression in granulocytes in whole blood samples (day 7) from placebo and 30 mg b.i.d. treated subjects. The dose response curve was shifted to the right in samples (2 h and 12 h post dose) from patients that received 30 mg bid CCX168.

The sponsor also identified two CCX168 metabolites, M1 and M6 (Figure 3) in this study. The M1 metabolite (95% relative to CCX168) was found to be far more prevalent than M6 (~2%) in healthy subjects.

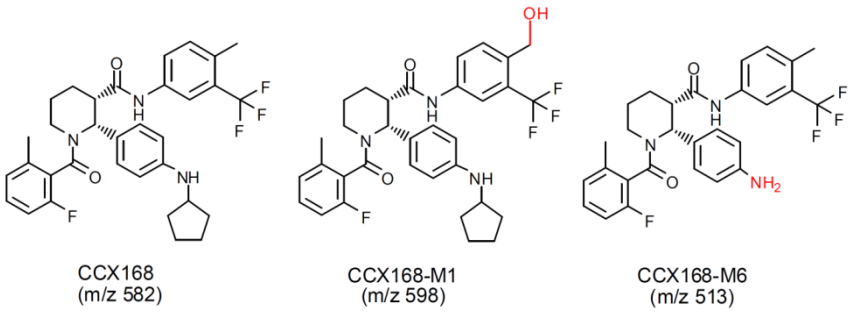


Figure 3. Structures of metabolites identified in human plasma samples in clinical study CL001_168.

Study **CL002_168** was designed to test the safety and efficacy of CCX168 in ANCA-associated glomerulonephritis patients (n = 26) that are receiving concomitant corticosteroid and cyclophosphamide treatment. Briefly, the objective of this study was to evaluate whether CCX168 could be used to reduce, or eliminate, the need for

glucocorticoid treatment in ANCA patients. The study was organized into 2 'steps'. In both steps, 30 mg b.i.d. CCX168 was compared vs. placebo. In step 1 of the study, patients in both the placebo and CCX168 groups received concomitant corticosteroid treatment. In step 2 of the study, only the placebo group received concomitant glucocorticoid treatment.

An interim study report for CL002 has been submitted in which the PK values following the first 30 mg dose of CCX168 to ANCA patients on day 1 are presented. Comparing the AUC_{0-6} values between step 1 (+ prednisone) and step 2 (- prednisone) suggests that the presence of prednisone does not affect the systemic exposure of CCX168 or its M1 and M6 metabolites (Table 2).

Table 2. Summary of pharmacokinetic parameters after the first 30 mg dose on day 1 of clinical study CL002_168. Note that Step 1: + glucocorticoids, Step 2 : no glucocorticoids.

Step 1

CCX168				CCX168-M1				CCX168-M6			
Gender	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-6hr} (hr•ng/mL)	Gender	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-6hr} (hr•ng/mL)	Gender	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-6hr} (hr•ng/mL)
Male	2.5 ± 1.0	209 ± 78.6	668 ± 273	Male	3.0 ± 1.2	33.8 ± 5.42	128 ± 26.9	Male	2.9 ± 1.7	2.66 ± 0.464	10.6 ± 2.06
Female	1.8 ± 1.0	253 ± 66.7	678 ± 177	Female	2.3 ± 1.3	47.8 ± 14.8	181 ± 59.0	Female	2.0 ± 1.4	2.58 ± 0.649	10.4 ± 2.49

Step 2

CCX168				CCX168-M1				CCX168-M6			
Gender	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-6hr} (hr•ng/mL)	Gender	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-6hr} (hr•ng/mL)	Gender	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-6hr} (hr•ng/mL)
Male	4.0 ± 1.6	132 ± 56.7	454 ± 185	Male	4.3 ± 1.3	26.6 ± 9.15	94.8 ± 48	Male	4.3 ± 1.3	1.93 ± 0.569	8.05 ± 2.96
Female	3.0 ± 0.8	227 ± 68.6	691 ± 164	Female	3.3 ± 1.0	51.4 ± 9.77	186 ± 34.3	Female	3.0 ± 0.8	2.87 ± 0.911	11.5 ± 3.53

Mean AUC_{0-6h} values from day 1 (step 1 and step 2) of this study were converted to AUC_{0-24h} values for comparison with the data from day 7 in clinical study CL001 as well as with the sponsor's predicted steady state values for CCX168 and M1 (Table 3) in ANCA associated glomerulonephritis patients. The current data suggests CCX168 exposure is comparable between healthy volunteers and ANCA associated glomerulonephritis patients. It appears that less of the M1 metabolite is formed in ANCA patients than in healthy subjects, but this data should be interpreted with caution as the data from CL002 represents exposure values after only a single dose.

Table 3. Comparison of CCX168 and M1 exposure in healthy volunteers and ANCA glomerulonephritis patients

Study	Subjects	CCX168 dose	Time point	AUC_{0-24} (ng*hr/ml)		M1 % relative to CCX168
				CCX168	**M1**	
CL001	Healthy	30 mg bid	**Day 7**, AUC_{0-12} (sum of AM & PM values)	1,846	1,750[1]	95%
CL002[2]	ANCA glomerulonephritis	30 mg bid	**Day 1** AUC_{0-6} x 4	2,492	592	24%
Sponsor's projected steady state AUC_{0-24}[3]	ANCA glomerulonephritis	30 mg bid	Steady state	6,135	3,089	50%

[1] Value taken from CL001_168 MetID (p. 9; data from PEG4000/CremophorRH40 formulation)
[2] AUC values are calculated from AUC_{0-6} values after first 30 mg dose on study day 1. Mean of data from Step 1 and Step 2 patients. Data from Interim PK report for clinical study CL002.
[3]Predicted values listed on page 28 of pre-IND meeting package (3/14/14)

The reported $T_{1/2}$ of CCX168 in healthy volunteers generally ranged from 3 – 5 hours in patients dosed at 30 mg b.i.d. The sponsor also reports that steady state plasma concentrations of CCX168 and M1 are reached by day 15 in ANCA associated vasculitis patients given that mean plasma trough concentrations are similar at days 15, 22, and 29.

PROPOSED CLINICAL TRIAL

Clinical trial CL003_168 is entitled "A randomized, double-blind, placebo-controlled, Phase 2 study designed to evaluate the safety and efficacy of CCX168 in subjects with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis".

This is the first clinical trial conducted with CCX168 in the U.S. The study will evaluate safety and tolerability of CCX 168 at doses of **10 mg b.i.d.** and **30 mg b.i.d.** for 12 weeks in adult patients (n = ~45) with ANCA- associated vasculitis. CCX168 will be administered in addition to standard of care treatment (IV cyclophosphamide or rituximab plus oral prednisone and rescue corticosteroid treatment (if necessary)). Efficacy of CCX168 will be based on the Birmingham Vasculitis Activity Score (BVAS). The current study design reflects recommendations made by the FDA clinical review team at the 4/21/14 pre-IND meeting (See pre-IND meeting minutes, 5/19/14). The 10 mg bid dose is projected by the sponsor to inhibit 80 – 90% of C5aR activity while the 30 mg b.id. dose is projected to inhibit 99% of C5aR activity.

The study protocol contains appropriate requirements for male and female study participants to use adequate contraception during the study and for at least three months after study completion.

SUPPORTING NON-CLINICAL STUDIES

Primary Pharmacology

In vitro pharmacology

Chemocentryx has carried out a series of in vitro studies to characterize the activity of CCX168 at the C5aR in multiple species. The current review will only examine the potency of CCX168 and the M1 metabolite with respect to inhibition of C5a mediated chemotaxis in leukocytes derived from humans and several nonclinical species (Table 4). The data presented in this table are derived from experiments carried out in multiple different studies.

Cells were collected from blood samples by centrifugation at 400xg at RT, then suspended at 10 million/ml in chemotaxis buffer. CCX168 or vehicle (DMSO) was then added to the cells. Recombinant human C5a was diluted in chemotaxis buffer and placed in the lower wells of a ChemoTX plate. Next, a 3 or 5 µm pore size polycarbonate membrane was placed onto the plate. Then 20 uL of the cells/CCX168 mixture was transferred onto each well of the membrane. The plates were then incubated at 37C for 90 – 180 minutes. Membranes were then removed and CyQUANT (DNA intercalating agent) was added to the lower wells. The amount of fluorescence corresponded to the number of migrated cells.

CCX168 and CCX168-M1 inhibited C5aR function in **human**, **cynomolgus monkey,** and **hamster** whole blood samples with A_2 values less than 18 nM (A_2 = concentration required for 2-fold rightward shift of C5a dose response curve). Both CCX 168 and M1 were found to be inactive or minimally active (A_2 > 1,000 nM) at **rat**, **mouse, and rabbit** C5aRs (Table 4).

Table 4. In vitro potency of CCX168 and its M1 metabolite for inhibition of **C5a mediated chemotaxis** in leukocytes of multiple species. Note that the numbers in **brackets** refer to the specific study number that the data were derived from. A_2 values are reported. This value generally corresponds to the IC_{50} when the agonist is present at its Kd value.

		A_2 value (nM)	
Species	Sample	CCX168	M1
Human	whole blood	1.7 [PC0346]	3 [PC0463]
Cynomolgus	whole blood	18 [PC0347]	1 [PC0484]
Hamster	whole blood	10 [PC0627]	6 [PC0627]
Rabbit	whole blood	1,400 [PC0627]	1,400 [PC0627]
Mouse	peritoneal cells in Mouse plasma	> 10,000 [PC0347]	> 10,000 [PC0484]
Rat	peritoneal cells in Rat plasma	> 10,000 [PC0347]	>1,000 [PC0484]

C5aR amino acid sequence alignment performed by the sponsor identified a potential key residue located within the 5th transmembrane region (TM-5) of C5aR with regard to species specific binding of CCX168 or M1. The amino acid sequences for human, cynomolgus, and hamster C5aR all contain a tryptophan residue at this location, while other species have variable amino acid residues here (Figure 4).

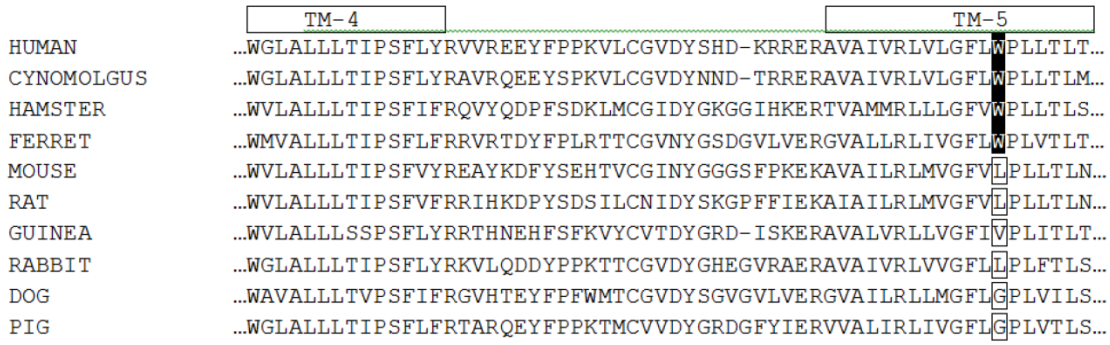


Figure 4. Amino acid sequence alignment of the C5a receptor for 10 species shows a potential key residue in the TM-5 region that may influence CCX168 and M1 binding.

In vivo pharmacology

Chemocentryx developed a mouse model of ANCA associated glomerulonephritis to evaluate the efficacy of oral CCX168 (Study PC0480_168). This model is comprised of human C5aR knock-in mice (murine C5aR gene replaced by human C5aR) that are injected IV with anti-myeloperoxidase antibody. These mice develop glomerular necrosis and display kidney crescent (fibrocellular deposit) formation.

Myeloperoxidase-injected mice were treated for 7 days with oral CCX168 at 0, 0.1, or 30 mg/kg (q.d.), or 4 mg/kg (b.i.d.). Animals were euthanized at day 7 and kidneys examined microscopically. Oral CCX168 dose-dependently inhibited kidney crescent formation and kidney necrosis in these mice (Figure 5). Urine parameters were also examined for evidence of kidney dysfunction. CCX168 treatment resulted in dose-dependent decreases in urinary total protein, leukocytes, and erythrocytes.

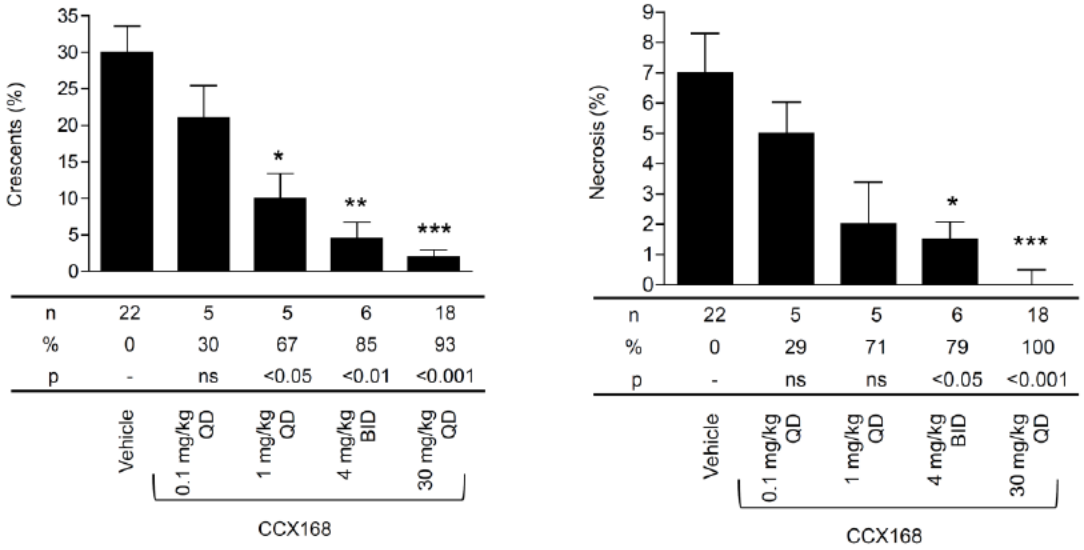


Figure 5. Oral CCX168 dose-dependently inhibits kidney crescent formation (left) and kidney necrosis (right) in a mouse model of ANCA associated glomerulonephritis (Study PC0480_1680.

Secondary Pharmacology

CCX168 was tested at concentrations up to 10 µM for activity at human chemokine/chemotactic receptors. These included human CCR1 – CCR12; CXCR1-CXCR7, C5L2, C3aR, ChemR23, GPR1 and FPR1. Specific assays included: inhibition of C5a mediated cell migration, inhibition of C5a mediated increases in intracellular Ca^{2+}, and inhibition of radioligand binding. CCX168 showed no significant reactivity at any of these receptors (Study **PC0348_168**).

An additional secondary pharmacology study evaluated the binding of CCX168 to a panel of 55 receptors (Study **PC0349_168**). Specifically, the study examined the extent to which 10 µM CCX168 could inhibit binding of radiolabeled reference compound to each receptor. Very limited CCX168 activity was seen. 10 µM CCX168 inhibited

agonist binding to adenosine A2A receptors by 42% and to A3 receptors by 33%. Agonist binding to the Na^+ channel (site 2) was inhibited by 59%. The 10 µM CCX168 concentration represents an ~1,000-fold greater concentration than the in vitro potency at C5aR.

The selectivity of **CCX168-M1** was tested at 10 µM against the same panel of 17 human chemokine/chemotactic receptors and 55 other receptors in study **PC0486_168**. Weak potency was observed at the human CB1 receptor (53% inhibition), Na^+ channel site 2 (65% inhibition) and the $GABA_A$ receptor (51% inhibition).

Neither CCX168 nor CCX168-M1 inhibited the glucocorticoid receptor or enzymes involved in metabolism of corticosteroids. This is a relevant finding given that the current standard of care for ANCA associated vasculitis involves oral prednisone as well as administration of rescue corticosteroid treatment if necessary.

Safety Pharmacology

hERG assay

CCX168 (Study PC0380_168):

CCX168 was tested for its ability to inhibit hERG tail currents in HEK293 cells stably transfected with the hERG potassium channel. CCX168 concentrations were 0.6, 1.2, 2.3, and 6.9 µM. No effects were observed at any doses tested.

CCX168-M1 (Study PC0490_168):

CCX168-M1 was tested in a separate hERG channel assay, designed similarly to the assay used to test CCX168. M1 concentrations tested were 1, 3, 10, and 15.8 µM (supernatant of 30 µM solution). M1 inhibited hERG channel currents by 38% at 3 µM. The 10 and 15.8 µM concentrations resulted in a similar degree of inhibition, likely due to limits of solubility of M1 (10 and 15.8 µM formulations were not fully in solution).

Overview of in vivo safety pharmacology studies

All *in vivo* safety pharmacology studies were conducted under GLP conditions using oral CCX168 in a vehicle comprised of PEG (b) (4) The T cell dependent antibody response (TDAR) assay, respiratory, renal, and CNS safety pharmacology studies were conducted in rats, a pharmacologically non-relevant species for CCX168.

The FDA nonclinical review team recommended that the sponsor repeat these studies in the monkey (pharmacologically relevant species) in their planned chronic monkey toxicology study (See Pre-IND meeting minutes, nonclinical question 6; 5/20/14). The sponsor argued against conducting these evaluations in the chronic monkey study citing limited clinical utility of the data generated in these studies given the availability of human data. The Division agreed that these studies are not required and that standard clinical observations in the chronic monkey study would be sufficient to fulfill the safety pharmacology study requirements.

Cardiovascular

Study PC0377_168:

The cardiovascular safety pharmacology study was conducted in telemetered male cynomolgus monkeys (n = 4). Each animal received a single oral dose of each dose level (0, 5, 15, 50 mg/kg) separated by a wash-out interval of at least 3 days. Blood pressure, heart rate, and ECG parameters were monitored continuously from 20 minutes prior to dosing to 24 hours after dosing. Toxicokinetic data was measured to confirm CCX168 exposure. The 50 mg/kg CCX168 dose has been shown to be saturating for CCX168 and M1 systemic exposure.

Group mean systolic, diastolic, and arterial **blood pressure** values were decreased by approximately 7 - 10% at the 50 mg/kg dose level relative to controls during the time period from 15 mins – 225 mins after dosing. No treatment related effects were observed on QTc interval.

Respiratory

Study PC0376_168:

The respiratory safety pharmacology involved the administration of single oral CCX168 doses (0, 3.5, 19, 73 mg/kg; CCX168 Lot 22) to male Sprague-Dawley rats. Animals were placed in whole body plethysmograph boxes and respiratory parameters (tidal volume, rate of respiration, minute volume) were measured at 15 minutes, 1, 2, 4, 8, and 24 hrs after dosing. No treatment related effects were observed at any dose tested.

CNS

Study PC0375_168:

Three groups of 6 male SD rats received a single oral dose of 5, 25, or 100 mg/kg (actual doses: 0, 3.5, 19, 73 mg/kg) and were observed for apparent pharmacological or toxicological signs over the course of 24 hours after dosing. Specific parameters measured included behavior, neuropharmacological signs, and locomotion.

Renal

Study PC0485_168:

6 groups of 8 male SD rats were included in this study. Treatment groups included water, vehicle (PEG (b) (4)), 30 mg/kg furosemide (positive control), and CCX168 at 5, 25, and 100 mg/kg. Animals received a single oral dose and urine volume was measured at 1, 2, 3, 4, 5, 6, and 24 hours post dose. Electrolyte content, total protein, specific gravity, osmolality, pH, creatinine, and urea nitrogen were measured in the 6 h and 24 h time points.

Increases in Cl^- and K^+ vs. control were observed at all doses over the time course of 6 – 24 h post dosing. However, there was no dose-response relationship, suggesting that the observed changes were not treatment-related. No differences between control and treated animals were observed in any other parameter.

ADME

Absorption

Oral bioavailability of CCX168 was found to range from 55-104% in SD rats when formulated in a vehicle comprised of PEG-(b) (4) (Study PC0365_168). Bioavailability studies were not conducted in cynomolgus monkeys.

Distribution

Study PC0632_168:

Protein binding of CCX168 and CCX168-M1 in plasma from CD-1 mice, SD rats, rabbits, hamsters, dogs, and humans was determined using commercially available plasma samples. CCX168 and the M1 metabolite were tested at 2.5, 10, and 50 µM plasma concentrations and subjected to equilibrium dialysis for 4 hours at 37°C. The mean % bound values for CCX168 and M1 were >99.9% in plasma from all species tested.

Metabolism

Study PC0623_168:

In vitro metabolism studies were conducted with liver microsomes from humans and several nonclinical species. Briefly, 1 µM [^{3}H]CCX168 was incubated with 1 mg/ml liver microsomes from various species at 37°C for 4 hours. M1, the major human metabolite formed in vivo (Figure 3, Table 2), is also formed to a comparable extent by monkey, rabbit, hamster, and rat liver microsomes (Table 5).

Table 5. In vitro metabolism of CCX168 in liver microsomes (Study PC0623_168).

ID	Percentage of total radioactivity				
	Human	**Monkey**	**Rabbit**	**Hamster**	**Rat**
CCX168	39.9	10.5	20.1	37.3	16.9
CCX168-M1	17.6	10.6	17.1	6.8	20.4
CCX168-M3	2.2	6.3	14.2	3.9	8.5
CCX168-M6	0.4	-	-	1	1.3
CCX168-M8	2.7	-	7.6	24.5	0.7
CCX168-M9	1.2	-	-	1.8	-
CCX168-M10	2.3	8.6*	21.6*	9.3	-
CCX168-M11	2.8			-	-
CCX168-M12	0.5	-	1.9	-	-
CCX168-M13	3	5.1	-	-	-
CCX168-M14	1.5	9.2	-	-	-
CCX168-M15	/	-	-	-	30.7

CYP3A4 was determined to be the major enzyme responsible for CCX168 metabolism (Study PC0373_168). CCX168 and CCX168-M1 are time dependent inhibitors of CYP3A4 function in human liver microsomes, with K_i values of 4.47 µM and 11.7 µM respectively (Studies PC0622_168 & PC0634_168).

Toxicology

13 week Rat Study (Oral) + 4 week recovery

Study PC0356_168:

Introduction

The GLP study was conducted (b) (4) Sprague-Dawley rats were dosed once per day by oral gavage at 0 (PEG (b) (4)), 3, 15, and 100 mg/kg/day CCX168. The main study consisted of 12 rats/sex/group while the recovery study (+4 weeks) included 5 rats/sex in the control and HD groups.

The toxicokinetic portion of the study consisted of 8-10 animals/sex/group. An additional subset of animals (n = 10/sex/group) was included in a T cell dependent antibody response (TDAR) assay, and received KLH antigen on days 8 and 22. The TDAR portion of the study was considered invalid as the positive control (dexamethasone) did not produce a clear inhibition of the immune response.

Results

Potential treatment related effects of CCX168 in rats were observed in HD animals upon histological examination of the pancreas (Table 6). The sponsor did not examine tissues from LD or MD animals. An information request was submitted to the sponsor on July 3, 2014 to seek justification for these pancreas findings (with particular concern for acinar cell atrophy in HD females) being considered unrelated to study drug.

Table 6. Potential treatment related histopathology findings in the 13 week rat study with CCX168 (Study PC0356_168)

	Main study								**Recovery**			
	Males				**Females**				**Males**		**Females**	
CCX168 dose (mg/kg/day)	**0**	**3**	**15**	**100**	**0**	**3**	**15**	**100**	**0**	**100**	**0**	**100**
# of animals on study	12	12	12	12	12	12	12	12	5	5	5	5
PANCREAS (# examined)	11	0	0	11	12	0	0	12	5	5	5	5
Lymphocytic infiltration												
minimal	1	NE	NE	3	1	NE	NE	2	1	2	0	1
Single cell necrosis												
minimal	0	NE	NE	1	0	NE	NE	0	0	0	0	0
Acinar atrophy												
minimal	0	NE	NE	0	0	NE	NE	3	0	0	0	0

Chemocentryx provided a response on July 7, 2014. Historical control data from the conducting laboratory (b) (4) was provided and is presented in Table 7. The incidences of lymphocytic infiltration and single cell necrosis are within the range of historical controls. The acinar atrophy finding in 3/12 HD females is outside of the historical control range for females at the testing facility. However, the sponsor provides reference to a recently published paper by Chadwick et al.[1] in which 26/36 (72%) control Sprague-Dawley rats had evidence of acinar cell atrophy/inflammation.

The sponsor has provided adequate historical control and literature-based evidence that the pancreatic lesions observed in this study were not related to CCX168 treatment. Therefore, the no observed adverse effect level (NOAEL) in the rat is **100 mg/kg/day.**

Table 7. Comparison of rat pancreas histopathology findings in study PC0356_168 vs incidence range in historical control rats at the conducting laboratory ((b) (4) July 1, 2007 – July 1, 2012).

Pancreas Observation[a]	Lymphocytic Infiltration	Inflammation Subacute/Chronic	Single Cell Necrosis	Acinar Atrophy
Range (b) (4) Historical Control Males (%)	0 to 40%	0 to 50%	0 to 50%	0 to 40%
Range (b) (4) Historical Control Females (%)	0 to 27%	0 to 10%	0 to 30%	0 to 13%
Control Males (Terminal Sacrifice)	1/11 (9%)	1/11 (9%)	0/11	0/11
CCX168 Males (Terminal Sacrifice)	3/11 (27%)	0/11	1/11 (9%)	0/11
Control Females (Terminal Sacrifice	1/12 (8%)	0/12	0/12	0/12
CCX168 Females (Terminal Sacrifice)	2/12 (17%)	0/12	0/12	3/12 (25%)

[1] Chadwick et al. (2014) Occurrence of spontaneous pancreatic lesions in normal and diabetic rats: A potential confounding factor in the nonclinical assessment of GLP-1- based therapies. *Diabetes*. 63, 1303 – 1314.

Toxicokinetics

Blood samples were taken from 3 TK animals/sex/group/timepoint on days 1 and 91 at the following time points: prior to dosing, 0.25, 0.5, 1, 2, 4, 8, and 24 hours post dose. Plasma CCX168 concentrations were measured at each time point via LC/MS methods. Chemocentryx quantified systemic exposure values for the M1 metabolite in a separate non-GLP assessment (PC0487_168_a) of plasma samples from the current study. Calculated systemic exposure values are seen in Table 8. The M1 metabolite was found to be present at 14 – 17% of the parent molecule at the 100 mg/kg/day dose in rats.

Table 8. Systemic exposure values for CCX168 and CCX168-M1 at week 13 in rat toxicology study (PC0356_168).

	CCX168 AUC_{0-24} (ng*hr/ml) [1]		**CCX168-M1 AUC_{0-24} (ng*hr/ml)** [2]	
CCX168 Dose (mg/kg/d)	Male	Female	Male	Female
3	3,703	3,795	ND	ND
15	18,608	21,555	ND	ND
100	56,637	113,993	9,537	16,705

[1] Data from GLP study PC0356_168

[2] Data from non-GLP toxicokinetic assessment PC0487_168_a

It is important to note that the current data do not support the conclusion that 100 mg/kg/day is a saturating dose. In the absence of dose-limiting toxicities, the sponsor should demonstrate that the highest possible CCX168 dose has been tested by providing evidence for saturation of absorption. A repeat dose study in rats at doses higher than 100 mg/kg will be necessary in order to establish a dose which saturation of absorption of both CCX168 and CCX168-M1 is achieved.

20 week Monkey Study (Oral) + 4 week recovery

Study PC0357_168:

Introduction

The GLP study was conducted (b) (4) Cynomolgus monkeys were dosed once per day by oral gavage at 0 (PEG (b) (4)), 5, 15, and 30 mg/kg/day CCX168 for the first 7 weeks of the study. The dosing route was changed to nasogastric lavage for weeks 13-20 to allow for increased systemic exposure of study drug. The main study consisted of 4 monkeys/sex/group while the recovery study (+4 weeks) included 2 monkeys/sex in the control and HD groups.

Results

Potential treatment related effects of CCX168 in monkeys were observed in the brain of 1 HD female (#119). An information request was submitted to the sponsor on July 3, 2014 to seek the sponsor's rationale for concluding that these findings were unrelated to study drug. In the July 7, 2014 response, the study pathologist concluded that the findings in this animal were consistent with a physical trauma such as banging its head off of the cage. This interpretation appears to be reasonable given that it is seen in only 1/8 HD animals. The absence of any comparable findings in MD animals, which had similar CCX168 and M1 exposures to the HD animals, provides further support for the conclusion that the brain findings are unrelated to CCX168 treatment. The NOAEL in the 20 week monkey study was judged to be the HD, **30 mg/kg/day.**

Table 9. Potential treatment related histopathology findings in the 20 week monkey study with CCX168 (Study PC0357_168)

	Main study								Recovery			
	Males				Females				Males		Females	
CCX168 dose (mg/kg/day)	0	5	15	30	0	5	15	30	0	30	0	30
number of animals on study	4	4	4	4	4	4	4	4	2	2	2	2
BRAIN (# examined)	4	4	4	4	4	4	4	4	2	2	2	2
Hydrocephalus												
minimal	0	0	0	0	0	0	0	1	0	0	0	0
Necrosis, focal												
minimal	0	0	0	0	0	0	0	1	0	0	0	0

Toxicokinetics

Blood samples were collected from all animals at day 1, week 7 (switch from oral gavage to nasogastric gavage), and day 135 at t = 0, 0.25, 0.5, 1, 2, 4, 8, and 24 hours post dose. Plasma CCX168 concentrations were measured at each time point via LC/MS methods Chemocentryx quantified systemic exposure values for the M1 metabolite in a separate non-GLP assessment (PC0487_168_a) of plasma samples from the current study. In the monkey, M1 was present at approximately 48 -54% of the parent compound (Table 10). The sponsor has demonstrated saturation of absorption of both CCX168 and the M1 metabolite in the monkey at 15 mg/kg/day.

Table 10. Systemic exposure values at week 20 for CCX168 and CCX168-M1 in 20 week monkey toxicology study (PC0357_168).

	CCX168 AUC_{0-24} (ng*hr/ml) [1]		**CCX168-M1 AUC_{0-24} (ng*hr/ml) [2]**	
CCX168 Dose (mg/kg/d)	Male	Female	Male	Female
5	2,828	1,926	ND	ND
15	13,440	18,432	7,260	7,500
30	15,456	15,198	7,960	7,420

[1]Data from GLP study PC0357_168

[2] Data from non-GLP toxicokinetic assessment PC0487_168_a

Genotoxicity

A complete battery of genotoxicity tests has been completed for CCX168 (Table 11). CCX168 was found to be negative in the Ames assay, *in vitro* mouse lymphoma forward mutation assay, and *in vivo* micronucleus assay. Chemocentryx also demonstrated that the M1 metabolite was formed in the *in vitro* assays under conditions of metabolic activation (e.g. +S9 rat liver fraction). A toxicokinetic analysis of plasma samples from SD rats in the *in vivo* micronucleus assay showed that the M1 metabolite was formed in these animals.

Table 11. Summary of genotoxicity testing for CCX168

Test	Study #	Doses	Result
Ames (GLP)	PC0378	up to 5,000 µg/plate	Negative either ± S9 at up to 5,000 µg/plate
	PC0488		LC-MS/MS study to demonstrate **M1**& **M6** metabolite formation upon incubation of CCX168 with Aroclor induced rat liver S9 results.
***In vitro* mouse lymphoma forward mutation assay** (GLP)	PC0379	up to 500 µg/ml	4 & 24 hr treatment periods ± S9 *Solubility issues at ≥ 100 µg/ml Negative
***In vivo* micronucleus assay** (SD rats) (GLP)	PC0320	500, 1000, 2000 mg/kg/day (oral, 2 consecutive days)	Negative
	PC0637	500, 1000, 2000 mg/kg/day (oral, 2 consecutive days)	TK study to establish the levels of **metabolite M1** formed when given to rats at the CCX168 doses in study PC0320

CONCLUSIONS

In their pre-IND meeting package, Chemocentryx provided projected human AUC_{0-24} values of 6,135 ng*hr/ml and 3,089 ng*hr/ml for CCX168 and M1 respectively at the 30 mg b.i.d. CCX168 dose, based on their existing clinical pharmacology data. The systemic exposures at the HD NOAELs in both rats monkeys provides adequate support for the 30 mg b.i.d. dose, the highest dose to be tested in study CL003_168 (Table 12).

Chemocentryx still must establish a saturating dose for CCX168 in the rat in order to adequately determine their high dose in upcoming chronic rat general toxicology and carcinogenicity studies.

Table 12. Safety margins based on systemic exposure data of CCX168 and M1 in 13 week rat and 20 week monkey studies.

Rat (PC0356_168)					**Monkey** (PC0357_168)				
	CCX168 safety margin[1]		CCX168-M1 safety margin[2]			CCX168 safety margin[1]		CCX168-M1 safety margin[2]	
CCX168 Dose (mg/kg/d)	Male	Female	Male	Female	CCX168 Dose (mg/kg/d)	Male	Female	Male	Female
3	0.60	0.62	ND	ND	5	0.46	0.31	ND	ND
15	3.03	3.51	ND	ND	15	2.19	3.00	2.35	2.43
100	9.23	18.58	3.1	5.4	30	2.52	2.48	2.58	2.40

[1]Safety factor relative to projected clinical steady state CCX168 $AUC_{0\text{-}24}$ at 30 mg b.i.d. dose : 6,135 ng*hr/ml
[2]Safety factor relative to projected steady state CCX168- M1 $AUC_{0\text{-}24}$ at 30 mg b.i.d. dose: 3,089 ng*hr/ml

COMMUNICATION WITH SPONSOR

4/21/14: pre-IND meeting:
A brief summary of the nonclinical points of discussion is provided. The meeting minutes were finalized on 5/19/14.

- FDA informed the sponsor that they have not demonstrated saturation of absorption of CCX168 or the M1 metabolite in the rat with the 100 mg/kg/day dose. Demonstration of saturation should be derived from data obtained in repeat dose studies in which steady state has been achieved for both the parent and the metabolite.
- Alternatively, the sponsor could demonstrate that they have achieved adequate exposure multiples with their 100 mg/kg/day dose vs. the human exposure at their highest proposed clinical doses.
- Given the lack of pharmacologic relevance of the rat for CCX168 or CCX168-M1, Chemocentryx intends to use the hamster (pharmacologically relevant) in reproduction toxicity and carcinogenicity studies.
- Chemocentryx intends to use the rat and hamster in carcinogenicity studies.
- Chemocentryx intends to use the rabbit and hamster in reproduction toxicity studies.
- FDA informed the sponsor that reproduction toxicity might be able to be conducted in parallel with late stage clinical trials due to the serious nature & unmet medical need of the proposed indication. Chemocentryx would need to show a lack of adverse effects in reproductive organs in general toxicity studies in 2 species plus require appropriate contraception requirements in clinical trials.

7/3/14: Nonclinical Information Request
The Division inquired about histopathology findings in high dose animals in the rat pancreas and in the monkey brain. The sponsor provided adequate justification that the findings in question were not related to drug treatment in their response dated 7/7/14.

NON-HOLD COMMMENTS TO BE RELAYED TO THE SPONSOR

Given the lack of identified dose-limiting toxicities in your 13 week rat study, high dose selection in your chronic rat toxicology and 2 year carcinogenicity studies will require adequate justification. The currently available rat toxicokinetic data has not provided evidence of saturation of absorption of either CCX168 or CCX168-M1 at the 100 mg/kg/day dose. As noted in the minutes from the April 21, 2014 Type B pre-IND meeting, the pharmacokinetic data used to justify saturation should be from repeated-dose studies in which steady-state exposure is achieved for both parent and metabolite.

Doses providing a 50-fold margin to the clinical systemic exposure are generally considered acceptable as the maximum dose for repeated-dose toxicity studies. To support phase 3 clinical trials in the United States, dose-limiting toxicity generally should be identified in at least one species when using the 50-fold margin of exposure as the limit dose. If this is not the case, a study of 1 month or longer duration in one species that is conducted at a 1,000 mg/kg limit dose, maximum feasible dose (MFD) or maximum tolerated dose (MTD), whichever is lowest, is recommended. However, on a case-by-case basis this study might not be warranted if a study of a shorter duration identifies dose-limiting toxicity at doses higher than those resulting in a 50-fold exposure margin (Guidance for Industry: M3(R2) Nonclinical Safety Stuides for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals).

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/s/

MATTHEW T WHITTAKER
07/15/2014

TIMOTHY W ROBISON
07/15/2014
I concur

Appendix 2

IND 120784: Review of 6-month toxicology study with rats and genetic toxicology studies (Dr. Matthew Whittaker, Dated in DARRTS November 9, 2017)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY RAT CARCINOGENICITY SPECIAL PROTOCOL ASSESSMENT REVIEW AND EVALUATION

Application number:	120784
Review number:	1
Supporting document/s:	SD 63 (6 month rat toxicity study), SD 85 (rat carcinogenicity study SPA)
PDUFA review deadline date:	November 24, 2017
CDER stamp date:	SD 63: October 27, 2016 SD 85: October 20, 2017
Product:	CCX168
Indication:	Anti-neutrophil cytoplasmic antibody (ANCA)-associated (b) (4) vasculitis
Therapeutic area:	Allergy and Immunology
Sponsor:	Chemocentryx
Review Division:	Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Reviewer:	Matthew Whittaker, Ph.D.
Supervisor/Team Leader:	Timothy Robison, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Angela Ramsey (Brandi Wheeler)

Template Version: August 29, 2016August 29, 2016

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1 Executive Summary

1.1 Introduction

Chemocentryx, Inc. is developing CCX168 as an orally administered, small molecule (MW = 581 g/mol) antagonist of the human complement 5a receptor (C5aR) for the treatment of patients with anti-neutrophil cytoplasmic autoantibody (ANCA) - associated (b) (4) vasculitis (AAV). Chemocentryx contends that CCX168 will be a glucocorticoid-sparing therapy for AAV. That is, CCX168 could replace oral prednisone in the treatment of patients with AAV and thus avoid the side effects (i.e. general immune suppression) associated with glucocorticoid therapy.

A request for Special Protocol Assessment (SPA) for proposed 2-year carcinogenicity studies to be conducted in Sprague Dawley rats and Syrian hamsters was submitted on October 10, 2017. The sponsor's proposed study design for the **rat** carcinogenicity study is based on the results of Study PC0655_168, a 26-week study in SD rats in which animals were administered doses of 0, 5, 15, 100 or 200 mg/kg/day CCX168. The adequacy of the sponsor's proposed dose selection for the 2-year study is the subject of this review.

The sponsor's proposed study design for the **hamster** carcinogenicity study is based on the results of Study PC0677_168, a 13-week study in Syrian hamsters. This study is evaluated in a separate review (see nonclinical review by Dong Zhao, Ph.D.).

1.2 Brief Discussion of Nonclinical Findings

CCX168 is pharmacologically active in humans, cynomolgus monkeys and hamsters, but has no activity in rats or mice. The Division agreed with the sponsor at the End-of-Phase 2 meeting (July 14, 2016) that rats and hamsters would be appropriate species for use in 2-year carcinogenicity studies.

Orally administered CCX168 has comparable pharmacokinetic characteristics between rats and humans (oral bioavailability, T_{max}, $T_{1/2}$, V_d). CCX168 metabolism is generally similar between rats and humans as the major metabolite is a hydroxyl conjugate (CCX168-M1) in both species.

An MTD was not determined from a 26-week oral toxicology study in which male and female Sprague-Dawley rats were dosed with 0, 5, 15, 100 and 200 mg/kg/day CCX168 by oral gavage. The sponsor's proposed doses (10, 30, 100 mg/kg/day) for their 2-year oral carcinogenicity study are derived from the observation that CCX168 exposure is saturated at 100 mg/kg/day in rats.

1.3 Internal Comments

None

1.4 Recommendations

The Executive Carcinogenicity Assessment Committee (ECAC) met on November 7, 2017 and reached the following conclusions that apply to both the hamster and rat 2-year carcinogenicity studies:

- The Committee concurred with doses of 10, 30 and 100 mg/kg/day for males and females, with the high dose based on saturation of systemic exposure.
- The mid- and low-doses for both sexes were selected based on adequate spacing of AUC.
- The Committee concurred with vehicle-control (PEG (b) (4)) and water-only control groups.
- The Committee noted that the 2-year carcinogenicity study will be performed in a different facility with a different source of animals than used in the 13-week oral toxicity study. The carcinogenicity study may not be acceptable if toxicity is significantly different due to these changes such that dose selection would have been altered.
- The Committee noted that the use of toxicokinetic dose groups is not needed for FDA.
- The Committee noted that clinical pathology at the end of the study is not needed for FDA.
- The Committee noted that ophthalmoscopic examination is not needed for FDA.

1.4.1 Clinical Study (ies) Safe to Proceed: Choose an item.

1.4.2 If Not Safe to Proceed

Nonclinical deficiencies

None

Nonclinical information needed to resolve deficiencies

None

1.4.3 Additional Recommendation(s) (Non-hold comments/advice to sponsor) if any.

The conclusions reached by the Executive CAC were captured in the Meeting Minutes and faxed to the sponsor on November 9, 2017.

2 Drug Information

2.1 Drug

Code Name(s): CCX168

CAS Registry Number(s): 1346623-17-3

Generic Name: Avacopan

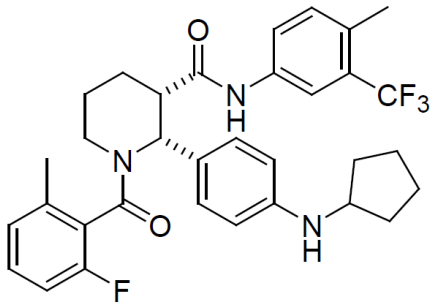
Chemical Name:

(2R,3S)-2-[4-(Cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide

Molecular Formula/Molecular Weight:

$C_{33}H_{35}F_4N_3O_2$
581 g/mol

Structure or Biochemical Description:



Pharmacologic Class: Complement C5a receptor antagonist

2.3 Drug Formulation

CCX168 is presented in 10 mg gelatin capsules. The maximum clinical dose is 30 mg BID, which will require ingestion of a total of 6 capsules per day. The total daily doses of each component of the drug product formulation are shown in Table 1. The amounts of each excipient are (b) (4) See the nonclinical review dated 7/15/14 for calculations and comparisons.

Table 1. Total daily intake values for each component of the proposed clinical formulation of CCX168 at 30 mg BID dose.

	% Composition	mg per unit Composition	Function	Grade	Amt per 30 mg bid dose (mg)
CCX168	(b) (4)	10	API	--	60
Polyoxyl 40 Hydrogenated Castor Oil (Cremophor RH40)					(b) (4)
Polyethylene glycol 4000 (PEG-4000)					
Gelatin Capsule, white, Size 0					
Gelatin band[a]					
Total					

[a] The product capsule is sealed with (b) (4) gelatin band

2.4 Comments on Novel Excipients

There are no novel excipients in the drug product formulation.

2.5 Comments on Impurities/Degradants of Concern

The proposed specifications and controls for CCX168 drug substance and drug product are adequate from the Pharm/Tox perspective to support Phase 3 clinical development. See the nonclinical review dated 10/27/16 for evaluation of the CCX168 drug substance and drug product specifications.

2.7 Previous Clinical Experience

Previous clinical experience: Y
If yes, Phase: Phase III Trial

2.8 Regulatory Background

Date	Event	Comment
June 16, 2014	Initial IND submission	Adequate nonclinical support for proposed clinical doses in studies up to 13 weeks duration
July 14, 2016	End-of-Phase 2 Meeting	The Division agreed that it would be acceptable to conduct carcinogenicity studies in rats and hamsters
October 27, 2016		Finalized study reports for chronic rat and monkey toxicology studies were submitted to IND
November 1, 2016	CMC-only End-of-Phase 2 meeting	The current CCX168 drug substance specification limits for multiple impurities (b) (4) (b) (4) The current specifications are considered acceptable based on adequate nonclinical support
October 10, 2017	SPA submissions for rat & hamster 2-year carcinogenicity protocols	Both the rat and hamster protocols were submitted under the same SPA. The Division requested that the rat protocol be separated and submitted as a separate SPA per *FDA Guidance for Industry: Special Protocol Assessment (May 2002)*
October 20, 2017	SPA submission for rat 2-year carcinogenicity protocol re-submitted to IND	

3 Studies Submitted

3.1 Studies Reviewed

Study #	Date submitted	Species	Description
Study PC0655-168 (b) (4) # 8306673	10/27/16	SD Rat	26-Week Oral toxicity study in Rats with a 6-Week Recovery phase

3.3 Previous Reviews Referenced

Date	Review	Author
7/15/14	30 day IND safety review	Whittaker
12/3/15	Safety evaluation of Cremophor RH40 and PEG-4000 levels at the 100 mg BID dose of CCX168	Whittaker
10/27/16	CMC consultation memo	Whittaker

4 Pharmacology

4.1 Primary Pharmacology

Primary pharmacology studies have been reviewed previously (see nonclinical review dated 7/15/14). Both CCX168 and its major metabolite, CCX168-M1 (see *section 5.1 PK/ADME*), have inhibitory activity at the human C5aR. Table 2 summarizes the potency of CCX168 and CCX168-M1 with respect to inhibition of C5a mediated chemotaxis in leukocytes derived from humans and several nonclinical species. Both CCX168 and CCX168-M1 inhibited C5aR function in human, cynomolgus monkey, and hamster whole blood samples with A_2 values less than 18 nM (A_2 = concentration required for 2-fold rightward shift of C5a dose response curve). Both CCX 168 and M1 were found to be inactive or minimally active (A_2 > 1,000 nM) at rat, mouse, and rabbit C5aRs.

Table 2. In vitro potency of CCX168 and its M1 metabolite for inhibition of C5a mediated chemotaxis in leukocytes of multiple species. Note that the numbers in brackets refer to the specific study number that the data were derived from. A_2 values are reported. This value generally corresponds to the IC_{50} when the agonist is present at its Kd value.

		A_2 value (nM)	
Species	Sample	**CCX168**	**CCX168-M1**
Human	whole blood	1.7 [PC0346]	3 [PC0463]
Cynomolgus	whole blood	18 [PC0347]	1 [PC0484]
Hamster	whole blood	10 [PC0627]	6 [PC0627]
Rabbit	whole blood	1,400 [PC0627]	1,400 [PC0627]
Mouse	peritoneal cells in Mouse plasma	> 10,000 [PC0347]	> 10,000 [PC0484]
Rat	peritoneal cells in Rat plasma	> 10,000 [PC0347]	>1,000 [PC0484]

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

PK parameters of CCX168 in humans, rats, and hamsters

The major pharmacokinetic parameters of orally administered CCX168 are generally comparable between humans, rats and hamsters. These values are summarized in Table 3.

- T_{max} is comparable between humans, rats, and hamsters (approximately 2 hours).
- CCX168 volume of distribution is very high in both rats and humans, providing evidence for extensive distribution of CCX168 into tissues.
- CCX168 elimination in humans is described as having a rapid early phase followed by a long terminal phase. After a single dose of CCX168 in humans, $T_{1/2}$ is approximately 6 hours. $T_{1/2}$ after the final dose in a 7-day study was calculated to be 162 hrs. CCX168 is eliminated rapidly ($T_{1/2}$ approximately 6 hours) in both rats and hamsters.

Table 3. Summary of relevant CCX168 pharmacokinetic values in humans, SD rats, and hamsters. All values are derived from the latest day of pharmacokinetic evaluation in each respective study (except where noted). ND = not determined.

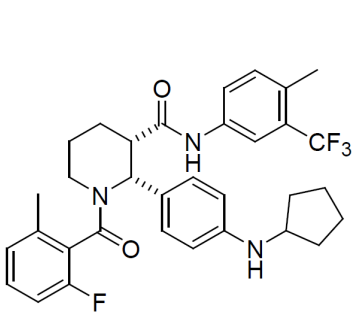
	Human[a]	**Sprague Dawley Rat**		**Syrian Hamster[d]**
Route	**Oral**	**IV[b]**	**Oral[c]**	**Oral**
Dose (mg/kg)	0.17	0.5	15	30
Vehicle	PEG (b) (4) (b) (4) (b) (4)	(b) (4)	PEG (b) (4) (b) (4)	PEG (b) (4) (b) (4)
C_{max} (ng/ml)	31.4	ND	3830	3880
T_{max} (hr)	1.9 ± 0.6	-	2.0	2.0
$T_{1/2}$ (h)	Day 1: 6.1 Day 7: 162	1.9	Day 1: 4.26 Week 26: 6.58	Day 1: 6.45 Week 13: 6.46
Vd_{ss} (L/kg)	58.7	1.8	ND	ND

[a] Study CL001_168. 7-day PK study (once daily dosing). 10 mg dose (0.17 mg/kg based on 60 kg body weight) was selected as a representative dose.
[b] Study PC0365_168. Single dose rat PK dose study.
[c] Study PC0655_168. 26-week rat toxicity study. 15 mg/kg/day selected as representative dose
[d] Study PC0677_168. 13-week hamster toxicity study. 30 mg/kg/day dose selected as a representative dose

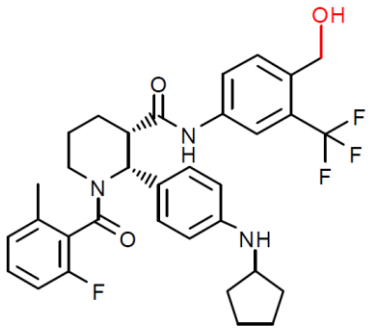
ADME parameters of oral CCX168 in humans, rats and hamsters

The ADME characteristics of orally administered CCX168 are generally comparable between humans, rats, and hamsters. The results of relevant human and nonclinical ADME studies that have been completed to date are summarized in Table 4.

- Orally administered CCX168 is highly bioavailable in humans and rats.
- CCX168 is highly protein bound in all species
- CCX168 showed extensive distribution to tissue in rats in a whole body autoradiography study.
- CCX168-M1 is the major metabolite of CCX168 in peripheral blood in humans (11.9% of total plasma radioactivity in a single dose [^{14}C]CCX168 metabolite characterization study, Study CL004_168). There were no other metabolites detected at more than 10% of total radioactivity in this study
- CCX168-M1 is a hydroxylated metabolite of the parent compound (Figure 1)



CCX168



CCX168-M1
(m/z 598)

Figure 1. Molecular structures of CCX168 and CCX168-M1. The location of the added hydroxyl group is shown in red.

- CCX168-M1 is a pharmacologically active metabolite of CCX168 (See Section 4.1)
- **CCX168-M1 is produced in vitro (liver microsomes) and in vivo in both rats and hamsters.**
- CCX168 is eliminated primarily in the feces in both humans and rats.

Table 4. Summary of available relevant ADME data in humans, rats, and hamsters. ND = not determined.

	Human		Sprague Dawley Rat		Syrian Hamster	
	Study #	Result	Study #	Result	Study #	Result
ABSORPTION						
Oral bioavailability	CL004_168 (single dose, 100 mg [^{14}C]CCX168)	93.7%[a]	PC0365_168	30 mg/kg: 104% 100 mg/kg: 55%	ND	ND
DISTRIBUTION						
Plasma protein binding	PC0632_168	>99.9% protein bound	PC0632_168	>99.9% protein bound	PC0632_168	>99.9% protein bound
Whole body autoradiography	ND	ND	PC0641_168 (single dose, 15 mg/kg [^{14}C]CCX168)	Extensive distribution to tissues	ND	ND
METABOLISM						
In vitro metabolite characterization	PC0623_168 ([^{3}H]CCX168 in liver microsomes)	% total radioactivity **CCX168**: 39.9% **CCX168-M1**: 17.6%	PC0623_168 ([^{3}H]CCX168 in liver microsomes)	% total radioactivity **CCX168**: 16.9% **CCX168-M1**: 20.4%	PC0623_168 ([^{3}H]CCX168 in liver microsomes)	% total radioactivity **CCX168**: 37.3% **CCX168-M1**: 6.8%
In vivo metabolite characterization	CL004_168 (single dose, 100 mg [^{14}C]CCX168)	Plasma metabolites (% total radioactivity) **CCX168**: 18% **CCX168-M1**: 11.9%	ND	ND	ND	ND
In vivo CCX168 & CCX168-M1 quantitation	CL002_168 (12 weeks, 30 mg BID)	Systemic Exposure **CCX168-M1**: 21.9% of CCX168 (based on AUC_{0-6} on day 1)	PC0655_168 (26 wk tox study)	Systemic Exposure **CCX168-M1**: 2.9 – 15.2% of CCX168 (based on AUC_{0-24} at wk 26)	PC0677_168 (13 wk tox study)	Systemic Exposure **CCX168-M1**: 5.5%-8.3% of CCX168 (based on AUC_{0-24} at wk 13)
ELIMINATION						
Mass balance study	CL004_168 (single dose, 100 mg [^{14}C]CCX168)	Feces: 77.2% Urine: 9.5%	PC0641_168 (single dose, 15 mg/kg [^{14}C]CCX168)	Feces: 94.4% Urine: 1.9%	ND	ND

[a] Sponsor's estimated value. No IV group included for calculation of oral bioavailability

Evidence for CCX168 and CCX168-M1 exposure saturation in rats and hamsters

- The 100 mg/kg once daily oral dose of CCX168 results in saturation of systemic exposure of both CCX168 and CCX168-M1 in both rats and hamsters.
  - Increasing the total CCX168 dose and/or dosing frequency beyond 100 mg/kg/day does not result in appreciable increases in systemic exposure of CCX168 or CCX168-M1

Rats

7-day study (PC0639_168)

Male and female SD rats were administered oral CCX168 in a vehicle of (b) (4) PEG (b) (4) either once or twice per day for 7 days.

$AUC_{0\text{-}24}$ data at day 7 (Table 5) provides evidence for systemic exposure saturation of both CCX168 and CCX168-M1 at the 100 mg/kg once daily CCX168 dose. There was no appreciable increase in systemic exposure of CCX168 or CCX168-M1 when CCX168 was administered at 100 mg/kg twice daily. Systemic exposure at the 300 mg/kg dose was decreased markedly relative to the 100 mg/kg dose. This appears to suggest decreased solubility of CCX168 in solution or in the GI tract at this dose.

Table 5. Sponsor's table summarizing mean CCX168 and CCX168-M1 systemic exposures in **SD rats** after 7 days of once daily or twice daily oral administration. QD = once daily, BID = twice daily. Source: Chemocentryx background information for CCX168 SPA (10/10/17).

Dose (mg/kg)	**CCX168 $AUC_{0\text{-}24hr}$ (ng•hr/mL)**		**CCX168-M1 $AUC_{0\text{-}24hr}$ (ng•hr/mL)**	
	M	**F**	**M**	**F**
100 q.d.	98,400	111,600	12,300	13,900
300 q.d.	53,900	54,600	8,300	10,500
50 b.i.d	88,200	117,900	9,300	17,800
100 b.i.d.	114,500	122,400	17,500	16,100
300 b.i.d.	27,800	37,100	3,500	8,700

Hamsters

13-week study (PC0677_168)

Male and female Syrian hamsters were administered oral CCX168 in a vehicle of (b) (4) PEG (b) (4) either once or twice per day for 13 weeks.

$AUC_{0\text{-}24}$ data at week 13 (Table 6) provides evidence for systemic exposure saturation of both CCX168 and CCX168-M1 at the 100 mg/kg once daily CCX168 dose. There was no evidence for an appreciable increase in systemic exposure of CCX168 or CCX168-M1 in animals that received 500 mg BID CCX168.

Table 6. Cmax and AUC_{0-24} data for CCX168 and CCX168-M1 at the conclusion of 13 weeks of dosing in **hamsters**.

	CCX168 Toxicokinetic parameters - HAMSTERS							
CCX168 dose (mg/kg/day)	10		30		100		1000 (500 BID)	
Sex	M	F	M	F	M	F	M	F
CCX168 (Week 13)								
C_{max} (ng/ml)	1000	1420	3060	4700	4650	4790	1800	1890
AUC_{0-24} (ng*hr/ml)	6280	6610	18000	21400	40600	39200	31700	33400
CCX168-M1 (Week 13)								
C_{max} (ng/ml)	39.9	35.1	101	112	186	159	133	110
AUC_{0-24} (ng*hr/ml)	427	352	1300	1170	2600	2350	2630	2240

6 General Toxicology

6.2.1 Repeat-Dose Toxicity: RAT

Study Title: 26-week oral gavage toxicity and toxicokinetic study with CCX168 In rats with a 6-week recovery phase

Study no.:	PC0655_168
Study report location:	EDR Module 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 10, 2014
Duration:	26
Duration Units:	weeks
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CCX168, Lot SD-112-9-0904, 99.9% CCX168, Lot SD-112-9-0923, 99.9% CCX168, Lot SD-112-9-0911, 99.9% CCX168, Lot D-14-030, 100%
Approximate Days of Use:	Lot SD-112-9-0904: Days 1 – 22 Lot SD-112-9-0923: Days 23 – 63 Lot SD119-9-0911: Days 64 – 85 Lot D-14-030: Days 86 – 184
Target Organs:	Choose an item.

Key Study Findings

- There were no apparent treatment-related toxicities at any of the doses tested.
  - Note that the rat is not a pharmacologically relevant species for CCX168 (see Table 2)
- CCX168 exposure was **saturated** at the 100 mg/kg/day dose. CCX168 C_{max} and AUC_{0-24} were not markedly increased in animals that received 100 mg/kg BID (total daily dose of 200 mg/kg) relative to those that received 100 mg/kg once per day.
  - The study is considered valid even in the absence of notable toxicities given that saturation of exposure was demonstrated
- Based upon the observed saturation, the NOAEL was 100 mg/kg/day, the lowest dose where the saturation was first observed.

Methods

Doses:	See Table 7 below
Frequency of dosing:	Groups 1 & 6: 2x per day Groups 2 – 5: 1x per day
Route of administration:	ORAL GAVAGE
Dose volume:	Groups 1 & 6: 2.5 ml/kg/dose (**5 ml/kg/day)** Groups 2 – 5: **5 ml/kg/dose**
Formulation/Vehicle:	(b) (4) mixture: *****Polyethylene glycol (b) (4) * (b) (4) Note: Clinical formulation includes (b) (4) mixture *Polyethylene glycol 4000 ***** (b) (4)
Species:	RAT
Strain:	SPRAGUE-DAWLEY (b) (4)
Dedicated Juvenile Animal Study:	N
Number/Sex/Group:	20
Age:	6 – 7 weeks
Weight:	166 – 266 g (males) 138 – 217 g (females)
Satellite groups:	Toxicokinetic animals: Groups 1, 5, 6
Unique study design:	Groups 1 and 6 received twice daily dosing (8 hours apart). All other dose groups received once daily dosing
Deviation from study protocol:	The noted study protocol deviations were considered minor in nature

Table 7. Overview of study design for 26-week toxicology study in SD rats (Study PC0655-168). Note that groups 1 and 6 received 2x/day dosing.

				Number of animals					
				Main study		Recovery		TK	
Group	Dose (mg/kg)	Frequency	Total dose (mg/kg/day)	Males	Females	Males	Females	Males	Females
1	*0*	***2x/d***	*0*	*20*	*20*	*5*	*5*	*4*	*4*
2	0	1x/d	0	20	20	0	0	4	4
3	5	1x/d	5	20	20	0	0	10	10
4	15	1x/d	15	20	20	0	0	10	10
5	100	1x/d	100	20	20	5	5	10	10
6	*100*	***2x/d***	*200*	*20*	*20*	*5*	*5*	*10*	*10*

OBSERVATIONS AND RESULTS

Mortality

There were 6 premature deaths in the study. There was no evidence for a relationship of these deaths to CCX168 treatment.

Table 8. Summary of premature deaths in 26-week rat toxicity study with CCX168.

Animal #	Dose group (mg/kg)	Sex	Day of death	Reason
B17620	15	F	87	Blood collection
B17495	100 BID	M	87	Blood collection
B17568	0	F	160	Reflux/aspiration of gavage material
B17538	0 BID	F	166	
B17591	5	F	9	
B17640	100	F	147	Undetermined

Clinical Signs

Methods:

- Cageside observations were conducted for each toxicity animal once daily during the dosing and recovery phases, except on days when detailed observations were conducted
- Detailed observations were conducted for each animal once during the predose phase and for each toxicity animal prior to dosing on Day 1 and weekly throughout the dosing and recovery phases.

Results

- The finding of Non-formed feces was observed in controls and all treatment groups starting after study day 134 (Table 9)
  - There was no evidence for a CCX168-related increase in incidence of this finding
  - All animals received the same volume of vehicle per day (5 ml/kg/day)
  - Polyethylene glycol (a component of the vehicle formulation) is a known laxative
  - The observed findings appear to be attributable to the effects of PEG (b) (4) and/or (b) (4) in the vehicle formulation

Table 9. Summary of relevant clinical observations in 26-week toxicity study of CCX168 in SD rats.

	Main study												Recovery					
	Males						Females						Males			Females		
Group	1	2	3	4	5	6	1	2	3	4	5	6	1	5	6	1	5	6
CCX168 dose (mg/kg)	0 BID	0	5	15	100	100 BID	0 BID	0	5	15	100	100 BID	0 BID	100	100 BID	0 BID	100	100 BID
number of animals	25	20	20	20	25	25	25	20	20	20	25	25	5	5	5	5	5	5
NON-FORMED FECES # of observations (# of animals)	27 (12)	5 (5)	5 (5)	8 (7)	13 (11)	13 (12)	6 (6)	7 (7)	8 (6)	7 (7)	4 (4)	8 (8)	0	0	2 (2)	1 (1)	1 (1)	2 (2)
Study days (range)	134-184	184	141-184	183-184	134-184	134-184	184	184	176-184	184	184	184	0	0	R1	R1	R1	R1

Body Weights

Methods:

- Body weights were measured once weekly throughout the dosing and recovery phases.

Results:

- There was no effect of CCX168 treatment on mean body weight or mean body weight gain in males or females at any time point during the dosing period. Mean initial and terminal body weight values are shown in Table 10.

Table 10. Mean body weight data in control rats during weeks 1 – 26 of treatment with CCX168. **NOTE**: Group 1 is the vehicle control reference for Group 6. Group 2 is the vehicle control reference for Groups 3 - 5

	Main study											
	Males						Females					
Group	1	2	3	4	5	6	1	2	3	4	5	6
CCX168 dose (mg/kg)	0 BID	0	5	15	100	100 BID	0 BID	0	5	15	100	100 BID
Week 1												
n	25	20	20	20	25	25	25	20	20	20	25	25
Body weight (g)	204	213	212	214	209	202	166	168	172	172	163	165
Week 26												
n	25	20	20	20	25	24	24	19	19	19	24	25
Body weight (g)	708	727	696	716	709	683	356	365	368	377	351	352
Absolute BW (% control)	**100%**	**100%**	**96%**	**98%**	**98%**	**96%**	**100%**	**100%**	**101%**	**103%**	**96%**	**99%**
Δ week 1 (g)	504	514	484	502	500	481	190	197	196	205	188	187
BW Gain (% Initial)	247.1%	241.3%	228 3%	234.6%	239.2%	238.1%	114.5%	117.3%	114.0%	119.2%	115.3%	113 3%
BW Gain (% control)	**100.0%**	**100.0%**	**94.6%**	**97.2%**	**99.1%**	**96.4%**	**100.0 %**	**100.0%**	**99.5%**	**104.1%**	**95.4%**	**98.4%**

Clinical pathology

Methods:
Blood samples for hematology, coagulation, and clinical chemistry were collected from fasted main study animals via a jugular vein on main study days 84 and 183 as well as recovery day 43. The anticoagulants were sodium citrate for coagulation tests and potassium EDTA for hematology tests. Samples for clinical chemistry were collected without anticoagulant. Urine samples for urinalysis and urine chemistry were collected chilled during the overnight period before blood collection from animals fasted overnight.

The investigators evaluated complete sets of parameters for hematology, coagulation, clinical chemistry, and urinalysis. The specific parameters measured are excerpted from the sponsor's study report below:

3.5.1.2 Hematology Tests

red blood cell (erythrocyte) count	platelet count
hemoglobin	white blood cell (leukocyte) count
hematocrit	differential blood cell count
mean corpuscular volume	blood smear
mean corpuscular hemoglobin	reticulocyte count
mean corpuscular hemoglobin concentration	

3.5.1.3 Coagulation Tests (Scheduled Collections Only)

prothrombin time	activated partial thromboplastin time

3.5.1.4 Clinical Chemistry Tests

glucose	gamma glutamyltransferase
urea nitrogen	aspartate aminotransferase
creatinine	calcium
total protein	inorganic phosphorus
albumin	sodium
globulin	potassium
albumin:globulin ratio	chloride
cholesterol	triglycerides
total bilirubin	lipase
alanine aminotransferase	amylase
alkaline phosphatase	

3.5.1.5 Urinalysis Tests

appearance (clarity and color)	ketones
volume	bilirubin
specific gravity	urobilinogen
pH	blood
protein	microscopic examination of sediment
glucose	

Results:
There was no evidence for physiologically relevant CCX168-related changes to hematology, coagulation, clinical chemistry, or urinalysis parameters in male or female rats.

Histopathology

Adequate Battery:
A complete battery of tissues was examined microscopically for all animals in all dose groups.

Organ/Tissue			Organ/Tissue		
adrenal (2)	W	P,E	muscle (biceps femoris)		P,E
animal identification			optic nerve (2)[a]		P,E
aorta		P,E	ovary (2)	W	P,E
brain	W	P,E	pancreas		P,E
cecum		P,E	pituitary gland	W	P,E
cervix		P,E	prostate	W	P,E
colon		P,E	rectum		P,E
duodenum		P,E	salivary gland (mandibular [2])	W	P,E
epididymis (2)	W	P,E	sciatic nerve		P,E
esophagus		P,E	seminal vesicle	W	P,E
eye (2)[a]		P,E	skin/subcutis		P,E
femur with bone marrow (articular surface of the distal end)		P,E	spinal cord (cervical, thoracic, and lumbar)		P,E
gross lesions		P,E	spleen	W	P,E
Harderian gland[a]		P,E	sternum with bone marrow		P,E
heart	W	P,E	stomach		P,E
ileum		P,E	testis (2)[a]	W	P,E
jejunum		P,E	thymus	W	P,E
kidney (2)	W	P,E	thyroid (2 lobes) with parathyroid	W	P,E
liver	W	P,E	tongue		P,E
lung with large bronchi	W	P,E	trachea		P,E
mammary gland (females)		P,E	urinary bladder		P,E
mandibular lymph nodes		P,E	uterus	W	P,E
mesenteric lymph nodes		P,E	vagina		P,E

E = Examined microscopically; P = Processed; W = Weighed.
a Collected in modified Davidson's fixative and stored in 10% neutral-buffered formalin.

Peer Review:
Peer review of the microscopic findings was not described in the study report.

Histological Findings

- Microscopic findings in the **kidney** (chronic progressive nephropathy, inflammatory cell infiltrate), **liver** (mononuclear cell infiltrate, hepatocyte necrosis), **pancreas** (mononuclear cell infiltrate), and **prostate** (mixed cell infiltrate) were observed with comparable frequency and severity in males and females across controls and all treatment groups (Table 11).

- There was no evidence for CCX168-related microscopic findings.

- It is unlikely that the observed findings are related to the (b) (4): PEG (b) (4) vehicle formulation for the following reasons:

- The findings generally did not show evidence for reversal in the vehicle group after the 6-week treatment-free period.
- The frequencies of these observations were generally consistent with reports of spontaneous findings in control male and female SD rats[1].

- Collectively, there was no evidence for CCX168-related or vehicle-related lesions after 26 weeks of oral treatment in SD rats.

[1] Giknis, M. and Clifford, C. (2012) Histopathology findings in 4 – 26 week old Crl:CD (SD) rats. *Charles River Laboratories.*

Table 11. Microscopic lesions observed after 26-weeks of vehicle or CCX168 treatment in SD rats.

	Main study												Recovery					
	Males						Females						Males			Females		
Group	1	2	3	4	5	6	1	2	3	4	5	6	1	5	6	1	5	6
CCX168 dose (mg/kg)	0	0 BID	5	15	100	100 BID	0	0 BID	5	15	100	100 BID	0	100	100 BID	0	100	100 BID
number of animals	20	20	20	20	20	20	20	20	20	20	20	20	5	5	5	5	5	5
KIDNEY (# examined)	20	20	20	20	20	19	19	19	19	19	19	20	5	5	5	5	5	5
Chronic progressive nephropathy																		
minimal	11	9	7	9	11	10	4	8	8	7	4	6	3	2	3	0	0	1
slight	1	1	0	0	0	2	0	0	0	0	0	1	0	1	1	0	0	0
TOTAL	**12**	**10**	**7**	**9**	**11**	**12**	**4**	**8**	**8**	**7**	**4**	**7**	**3**	**3**	**4**	**0**	**0**	**1**
Mononuclear cell infiltration																		
minimal	1	0	0	0	1	2	2	2	3	3	1	3	1	0	0	0	0	0
slight	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
TOTAL	**1**	**0**	**0**	**0**	**1**	**2**	**2**	**2**	**3**	**4**	**1**	**3**	**1**	**0**	**0**	**0**	**0**	**0**
LIVER (# examined)	20	20	20	20	20	19	19	19	19	19	19	20	5	5	5	5	5	5
Mononuclear cell infiltrate																		
minimal	16	17	19	18	17	17	14	11	13	15	13	14	5	5	4	4	4	4
slight	1	2	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL	**17**	**19**	**19**	**18**	**17**	**18**	**14**	**11**	**13**	**15**	**13**	**14**	**5**	**5**	**4**	**4**	**4**	**4**
Hepatocyte necrosis, focal																		
minimal	1	1	0	0	0	0	1	0	0	3	1	4	1	0	0	0	1	0
slight	0	0	1	1	0	0	2	2	2	0	0	0	0	0	0	0	0	0
moderate	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0
TOTAL	**1**	**1**	**1**	**1**	**0**	**0**	**3**	**2**	**3**	**3**	**1**	**5**	**1**	**0**	**0**	**0**	**1**	**0**
PANCREAS (# examined)	20	20	20	20	20	19	19	19	19	19	19	20	5	5	5	5	5	5
Mononuclear cell infiltrate																		
minimal	6	5	9	3	6	7	4	8	7	4	4	4	3	1	3	1	1	1
slight	1	1	0	0	1	0	0	0	0	1	0	1	0	1	1	0	0	0
TOTAL	**7**	**6**	**9**	**3**	**7**	**7**	**4**	**8**	**7**	**5**	**4**	**5**	**3**	**2**	**4**	**1**	**1**	**1**
PROSTATE (# examined)	20	20	20	20	20	19	0	0	0	0	0	0	5	5	5	0	0	0
Inflammation, mixed cell																		
minimal	5	3	3	4	5	5	-	-	-	-	-	-	0	1	2	-	-	-
slight	1	2	5	2	1	1	-	-	-	-	-	-	3	0	1	-	-	-
moderate	0	0	0	0	0	1	-	-	-	-	-	-	0	0	0	-	-	-
TOTAL	**6**	**5**	**8**	**6**	**6**	**7**	**-**	**-**	**-**	**-**	**-**	**-**	**3**	**1**	**3**	**-**	**-**	**-**

Toxicokinetics

Methods

Blood samples were collected from non-fasted TK animals via a jugular vein on day 1, week 3 and week 26. Samples were collected from 3 animals/sex/group/time point at selected time points from pre-dose out to 24 hours post dose. The collection schedule is shown in Table 12.

Table 12. Sponsor's table summarizing the blood sample collection schedule from TK rats in 26 week toxicity study with CCX168.

Group	Subgroup	Set	Dosing Interval	Time Points[a]
1 and 2	2	1st three/sex/group	Day 1, Week 26	2 hours postdose
3, 4, 5	2	1st three/sex/group	Day 1, Week 26	Predose and 4 hours postdose
3, 4, 5	2	2nd three/sex/group	Day 1, Week 26	1 and 8 hours postdose
3, 4, 5	2	3rd three/sex/group	Day 1, Week 26	2 and 24 hours postdose
6	2	1st three/sex/group	Day 1, Week 3, Week 26	Predose and 4 and 10 postdose
6	2	2nd three/sex/group	Day 1, Week 3, Week 26	1, 8 and 12 postdose
6	2	3rd three/sex/group	Day 1, Week 3, Week 26	2, 9 and 24 postdose

Note: If an animal assigned to a specific time point died prior to its scheduled toxicokinetic collection, another animal in the same dose group was used for sample collection. One toxicokinetic animal/sex/group served as a replacement animal.

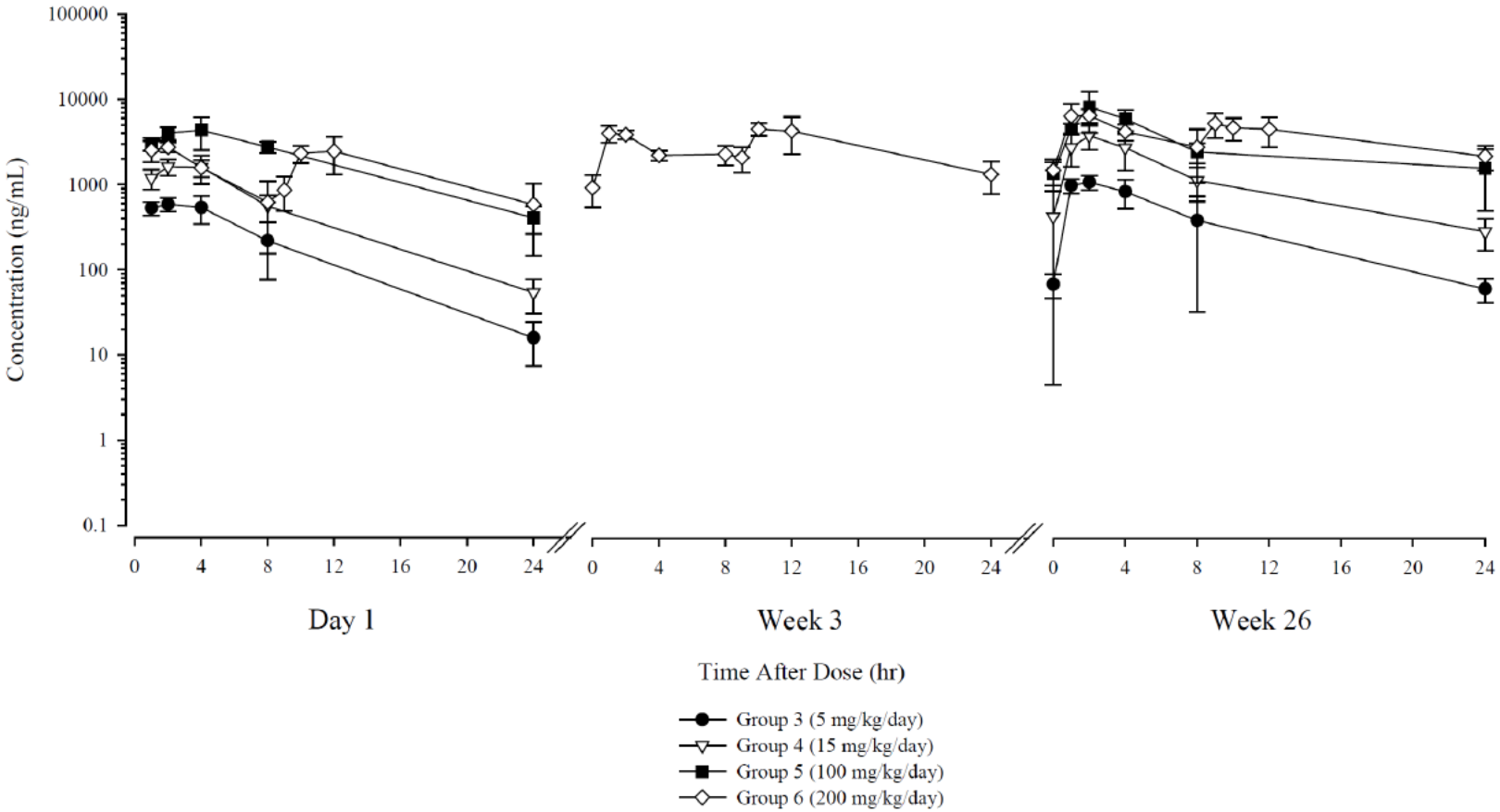
a Blood collection times were approximate and based on the first daily dose.

Samples were processed to plasma and analyzed for CCX168 and the metabolites CCX168-M1 and CCX168-M6 (the M6 metabolite is a very minor metabolite in humans and monkeys [<1%] and is therefore not discussed further in this review).

Results:

CCX168 Exposure

- CCX168 AUC_{0-24} increased proportionally with dose between 5 and 15 mg/kg/day (Figure 2;
- Table 13).
- The exposure increased between 15 – 100 mg/kg/day was less than dose-proportional.
- CCX168 exposure was **saturated** at the 100 mg/kg/day dose.
    - Mean (male & female) CCX168 AUC_{0-24} was decreased in animals in the 200 mg/kg/day (100 mg BID) group relative to the 100 mg/kg/day group at day 1
    - At week 26, mean CCX168 AUC_{0-24} increased by only 1.3-fold in the 200 mg/kg/day (100 mg BID) group relative to the 100 mg/kg/day group, despite the 2-fold increase in dose
    - This data is consistent with a 7-day study conducted in SD rats (Study PC0639_168, see Table 5)
    - It is important that the current study demonstrate saturation of CCX168 exposure given the absence of observable treatment-related toxicities at any of the doses tested.
- There was no evidence for sex differences in CCX168 exposure.
- CCX168 accumulated at all doses over the course of the 26 week study. Both C_{max} and AUC_{0-24} were increased at all doses at week 26 relative to week 1. The magnitude of accumulation was approximately 2-fold for C_{max} and AUC_{0-24} across all doses.



Notes: Animals in Groups 3, 4, and 5 were dosed once daily at the same time as the first daily dose for animals in Group 6.
Animals in Group 6 were dosed twice daily (100 mg/kg/dose) with approximately 8 hours between each dose, based on the last animal dosed for each sex.

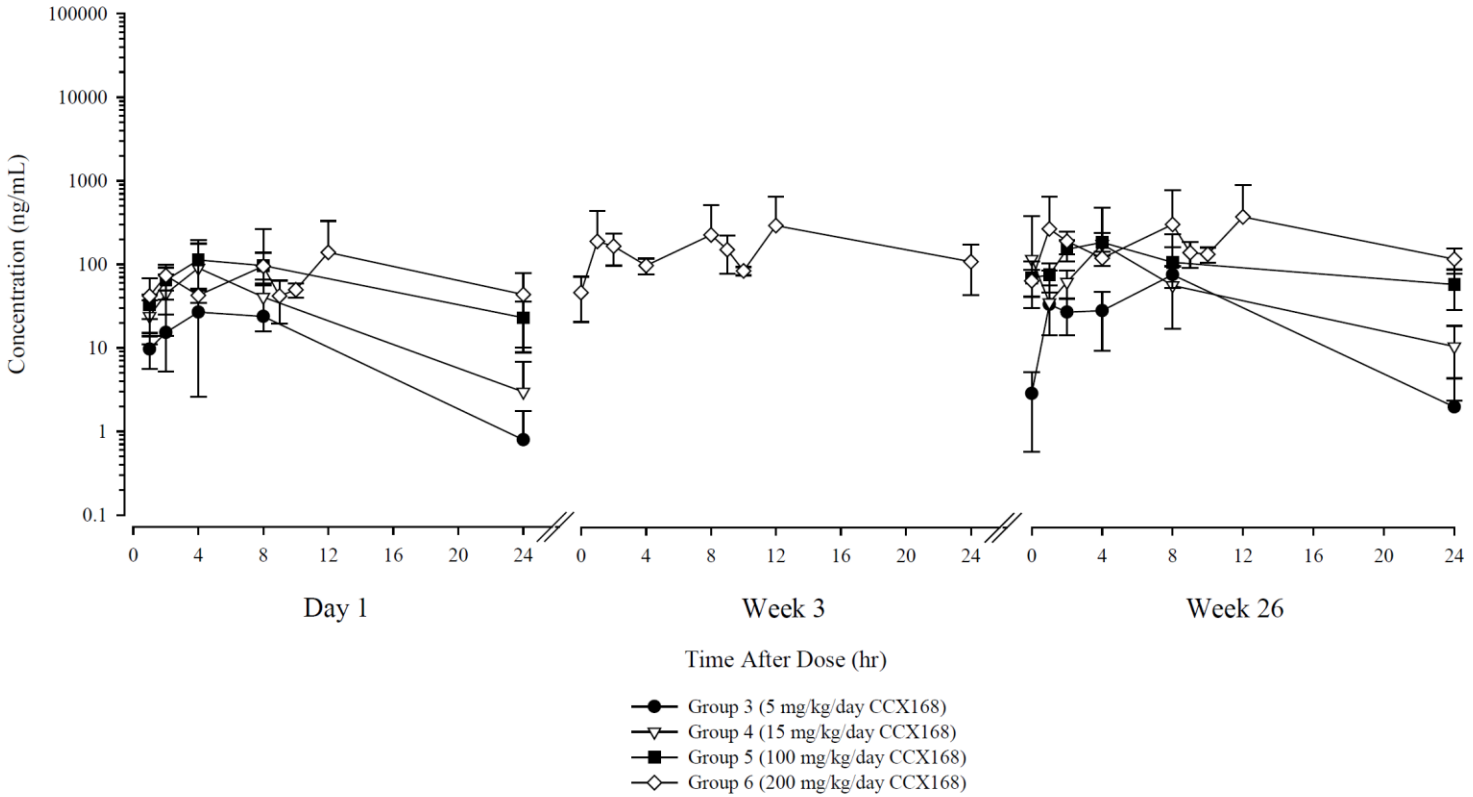
Figure 2. Sponsor's graph showing CCX168 plasma concentration over time (male and female data combined) in rats over the course of 26 weeks of treatment. Note that the 200 mg/kg/day group received 2 separate 100 mg/kg doses per day, separated by 8 hours.

Table 13. Summary of **CCX168** toxicokinetic parameters in rats treated with oral CCX168 at week 1 and after 26 weeks of treatment. Note that AUC is saturated at the 100 mg/kg/day dose

	CCX168 Toxicokinetic parameters							
Group	3		4		5		6	
CCX168 dose (mg/kg/day)	5		15		100		100 BID	
Sex	M	F	M	F	M	F	M	F
Day 1								
C_{max} (ng/ml)	515	672	1780	1630	4980	3870	3120	2620
T_{max} (h)	4	2	4	2	4	2	12	2
AUC_{0-24} (ng*hr/ml)	5270	5450	13400	15400	53200	52600	43600	32400
Week 26								
C_{max} (ng/ml)	1070	1190	4000	3650	5430	11500	6100	7370
T_{max} (h)	1	2	2	2	4	2	2	1
AUC_{0-24} (ng*hr/ml)	9780	9360	29800	32300	60400	85900	82700	106000

CCX168-M1 Exposure

- CCX168-M1 AUC_{0-24} increased proportionally with dose between 5 and 15 mg/kg/day (Figure 3; Table 14). CCX-168-M1 exposure in rats generally constituted less than 15% of total systemic exposure.
- M1 exposure was increased at 100 mg BID compared to 100 mg QD at week 26 (unlike the results observed in the 7-day rat PK study [Table 5]).
    - This is not considered to be a concern regarding the adequacy of dose selection for the 2 year carcinogenicity study given that saturation of exposure has been demonstrated for the parent compound, which comprises ≥85% of the total drug exposure.
- Evidence for CCX168-M1 accumulation was seen at all doses over the course of the 26-week study. Accumulation ratios generally ranged from 2 – 3x at week 26 relative to day 1.
- There was no clear evidence for sex differences in CCX168-M1 exposure.



Notes: Animals in Groups 3, 4, and 5 were dosed once daily at the same time as the first daily dose for animals in Group 6.
Animals in Group 6 were dosed twice daily (100 mg/kg/dose) with approximately 8 hours between each dose, based on the last animal dosed for each sex.
Only Group 6 animals had toxicokinetic samples collected during Week 3.

Figure 3. Sponsor's graph showing **CCX168-M1** plasma concentration over time (male and female data combined) in rats over the course of 26 weeks of treatment. Note that the 200 mg/kg/day CCX168 group received 2 separate 100 mg/kg doses per day, separated by 8 hours.

Table 14. Summary of **CCX168-M1** toxicokinetic parameters in rats treated with oral CCX168 at week 1 and after 26 weeks of treatment.

	CCX168-M1 Toxicokinetic parameters							
Group	3		4		5		6	
CCX168 dose (mg/kg/day)	5		15		100		100 BID	
Sex	M	F	M	F	M	F	M	F
Day 1								
C_{max} (ng/ml)	34.5	44.7	115	65.6	95.9	130	206	85.7
T_{max} (h)	8	4	4	4	8	4	12	2
AUC_{0-24} (ng*hr/ml)	409	323	649	934	1520	1720	2390	1350
Week 26								
C_{max} (ng/ml)	138	45.4	292	67.2	177	198	545	214
T_{max} (h)	8	4	4	8	4	4	12	12
AUC_{0-24} (ng*hr/ml)	1490	403	1690	1100	2420	2500	7090	3780

CCX168-M1 exposure relative to CCX168 exposure

- CCX168-M1 AUC_{0-24} values ranged from approximately 3 – 15% of parent compound CCX168 at week 26 (Table 15).

Table 15. CCX168-M1 AUC values as percentage of parent at week 26 in rats.

	AUC_{0-24} values at week 26							
Group	3		4		5		6	
CCX168 dose (mg/kg/day)	5		15		100		100 BID	
Sex	M	F	M	F	M	F	M	F
CCX168 AUC_{0-24} (ng*hr/ml)	9780	9360	29800	32300	60400	85900	82700	106000
CCX168-M1 AUC_{0-24} (ng*hr/ml	1490	403	1690	1100	2420	2500	7090	3780
M1 as % of parent	15.2%	4.3%	5.7%	3.4%	4.0%	2.9%	8.6%	3.6%

Dosing Solution Analysis

Stability
CCX168 formulations were tested for stability at concentrations of 0.1 and 120 mg/ml. Formulations were found to be stable under room temperature and refrigerated conditions for up to 15 days.

It is noted that test article formulations were prepared at least once per week during the study.

Homogeneity
Homogeneity testing was conducted on day 1 and during week 26 of the study. Quadruplicate samples (1.00 mL each) were taken from the top, middle, and bottom strata of the 1-, 3-, 20-, and 40-mg/mL formulations (in PEG (b) (4)). Solutions were considered to be homogeneous as all values were found to range from 98.2 – 104.2% of the nominal concentration.

Concentration verification
Drug formulation concentrations were measured for vehicle, 1, 3, 20, and 40 mg/ml solutions (in PEG (b) (4)) on day 1 and weeks 8, 17, and 26. The means of all formulations ranged from 95.5 – 105.1% of the nominal concentration.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study Title: Evaluation of CCX168 in a bacterial reverse mutation assay with a confirmatory assay

Study no.:	PC0378_168
Conducting laboratory and location:	(b) (4)
Date of study initiation:	6/16/09
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CCX168 Lot 05CCX03-01-95 99.7% purity

Key Study Findings

- CCX168 was found to be incompletely soluble at ≥333 µg/plate (-S9) and ≥1000 µg/plate (+S9)
- There was no evidence for a CCX168-induced increase in number of revertant colonies in any of the tester strains with or without S9.
- A separate study (Study PC0488_168) confirmed that the CCX168-M1 metabolite (pharmacologically active, major human metabolite) was formed upon incubation of CCX168 with S9
- CCX168 and its metabolite, CCX168-M1, were negative for mutagenicity.

Methods

Strains:	Salmonella TA98 Salmonella TA100 Salmonella TA1535 Salmonella TA1537 E. coli WP2*uvr*A
Concentrations in definitive study:	33.3, 100, 333, 1000, 3330, 5000 µg/plate ±S9
Basis of concentration selection:	There was no observed cytotoxicity at up to 5000 µg/plate in the dose-range finding assay
Negative control:	DMSO
Positive control:	See sponsor's table below
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Tester strains were exposed to test article using the plate incorporation methodology. Bacteria, test article, and S9 mix when applicable (10% S9 in S9 mix (S9 obtained from (b) (4)) were combined in molten top agar, then overlaid onto a bottom agar plate. Plates were incubated for 52 ± 4 hrs at 37 ± 2°C

Tester Strain(s)	S9	Positive Control	Dose (µg/plate)	CAS No.	Lot No.
TA98	–	2-nitrofluorene	1.0	607-57-8	01508BE
TA100, TA1535	–	sodium azide	2.0	26628-22-8	017K0136
TA1537	–	ICR-191	2.0	17070-45-0	115K1328 116K1026
WP2*uvr*A	–	4-nitroquinoline-N-oxide	1.0	56-57-5	117K1485
TA98	+	benzo[a]pyrene	2.5	50-32-8	017K1044
TA100, TA1535, TA1537	+	2-aminoanthracene	2.5	613-13-8	12317CE
WP2*uvr*A	+	2-aminoanthracene	25.0	613-13-8	12317CE

Study Validity

- Study design and execution were considered valid based upon the following criteria
  - The tester strains used in the study were adequate
  - Positive controls produced the expected responses
  - The CCX168 doses tested were adequate

- It is also noted that an additional study was conducted to confirm that incubation of CCX168 with rat liver S9 fraction resulted in formation of the CCX168-M1 metabolite (Study PC0488_168).
    - 0.2 µM and 2 µM CCX168 were incubated with rat liver S9 (0.5 mg/ml protein) at 37°C for up to 4 hrs
    - M1 metabolite was formed, with maximum levels achieved at t = 30 minutes
    - M6, another rat metabolite of CCX168, was also detectable at t = 30 minutes

7.2 *In Vitro* Assays in Mammalian Cells

Study Title: Evaluation of CCX168 in a L5178Y TK$^{+/-}$ mouse lymphoma forward mutation assay with a confirmatory assay

Study no.:	PC0379 168
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 20, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CCX168 05CCX03-01-95 99.7% purity

Key Study Findings

- Upon addition to the aqueous treatment medium, the test article precipitated from solution at concentrations ≥100 µg/mL with or without S9.
- There was no evidence for CCX168-induced mutation at the thymidine kinase locus in the mouse lymphoma L5178Y cell line at the doses tested with or without S9 activation.

Methods

Cell line:	L5178Y *tk*$^{+/-}$ cells
Concentrations in definitive study:	0.781, 1.56, 3.13, 6.25, 12.5, 25.0, 50.0, 100, 200, 300, 400, 500 µg/ml. Incomplete solubility was observed at Concentrations ≥100 µg/ml ± S9.
Basis of concentration selection:	The concentrations selected were established based on solubility limitations in the preliminary dose-range finding assay. Incomplete solubility was observed at Concentrations ≥250 µg/ml. Concentrations ≥500 µg/ml were discarded due to excessive precipitation.
Negative control:	DMSO
Positive control:	Methyl methanesulfonate (MMS) Methylcholanthrene (MCA)
Formulation/Vehicle:	DMSO

Incubation & sampling time:	+S9 (obtained from (b) (4) 10 – 20 µl/ml final concentration in cultures) and -S9: 4-hour treatment at 37°C; 2-3-days phenotypic expression, then 13 – 14-day incubation before cell counting -S9: 24-hour treatment at 37°C, 2-3 days phenotypic expression, then 13 days before cell counting
Criteria for a positive response:	The test article is considered to produce a positive response if it induces a dose-dependent increase in mutant frequency (Total mutant colonies / Total viable colonies) to $\geq 90 \times 10^{-6}$ above the average mutant frequency of the concurrent vehicle control cultures (consistent with the established Global Evaluation Factor for the Mouse Lymphoma assay[2])

Study Validity

- The study is considered valid for the following reasons:
  - The CCX168 doses tested were adequate
  - All positive and negative controls produced expected results

[2] Moore et al. (2006) Mouse lymphoma thymidine kinase gene mutation assay: follow-up meeting of the international workshop on genotoxicity testing- Aberdeen, Scotland, 2003 – assay acceptance criteria, positive controls, and data evaluation. *Environmental and Molecular Mutagenesis.* 47, 1 – 5.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study Title: Evaluation of the effects of CCX168 on bone marrow micronucleus formation in Sprague Dawley rats following oral administration

Study no:	PC0320_168
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 13, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CCX168 Lot 05CCX03-02-97-1 99.7% Purity

Key Study Findings

- Oral CCX168 did not induce statistically significant increases in micronucleated PCEs in rat bone marrow at doses up to 2,000 mg/kg/day. It is noted that saturation occurs with doses ≥100 mg/kg/day rats.
- Chemocentryx conducted an additional study (PC0637_168) in SD rats to quantify the extent of CCX168-M1 formation under the conditions used in the in vivo micronucleus experiment
    - CCX168-M1 AUC was approximately 15% of the CCX168 AUC
- CCX168 and its metabolite, CCX168-M1, were negative for clastogenicity.

Methods

Doses in definitive study:	0, 500, 1000, 2000 mg/kg
Frequency of dosing:	Once per day (2 total doses)
Route of administration:	Oral
Dose volume:	20 ml/kg
Formulation/Vehicle:	PEG (b) (4)
Species/Strain:	Sprague-Dawley rat
Number/Sex/Group:	5
Satellite groups:	None
Basis of dose selection:	2,000 mg/kg is maximum dose listed for in vivo genotoxicity studies in ICH S2(R1). It is noted that CCX168 systemic exposure is saturated in rats at a dose of 100 mg/kg/day.
Negative control:	Vehicle
Positive control:	Cyclophosphamide

Study Validity

- The study is considered valid for the following reasons:
  - Appropriate doses of CCX168 were tested
  - The positive control agent (cyclophosphamide) induced a statistically significant increase in micronucleated PCEs relative to control

8 Carcinogenicity

Study Title: Planned CCX168 Oral Carcinogenicity Study in Rats

Study no.:	PC0675-168
Conducting laboratory and location:	(b) (4) (Note that this is a different laboratory from the one that conducted the 26-week rat toxicology study)
Date of study initiation:	December, 2017 (Planned)
GLP compliance:	Yes
Drug, lot #, and % purity:	CCX168 Lot number & purity to be determined
CAC concurrence:	Yes

Summary of Sponsor's Draft Protocol: Chemocentryx is proposing a 104-week carcinogenicity study in Sprague Dawley rats (*n* = 57/sex/group). CCX168 will be prepared in a vehicle comprised of PEG (b) (4) These parameters are consistent with the 26-week dose-range finding study in rats (Study PC0655_168). The proposed dose groups are shown in Table 16. Toxicokinetic evaluation is proposed to take place at a single time point, during Week 4. Note that Group 1 represents the Vehicle control group while Group 2 represents the Water Only control group.

Table 16. Sponsor's summary table outlining the design of the proposed 2-year rat carcinogenicity study with CCX168.

Group number	Group description	Dose level (mg/kg/day)	Animal numbers			
			Carcinogenicity (Subgroup 1)		Toxicokinetics (Subgroup 2)	
			Male n=25 or 57	Female n=25 or 57	Male n=0, 3 or 9	Female n=0, 3 or 9
1	Control I	0	R0001-R0057	R0601-R0657	R0058-R0060	R0658-R0660
2	Control II	0	R0101-R0157	R0701-R0757	-	-
3	Low	10	R0201-R0257	R0801-R0857	R0258-R0266	R0858-R0866
4	Intermediate	30	R0301-R0357	R0901-R0957	R0358-R0366	R0958-R0966
5	High	100	R0401-R0457	R1001-R1057	R0458-R0466	R1058-R1066
6	Health Screen*	Not dosed	R0501-R0525	R1101-R1125	-	-
Spare animals, (15 males and 15 females ordered).						
The addition of a spare animal to a study group will documented by Protocol Amendment.						
*Health Screen animals will not be dosed and will be retained on study for viral analysis only (see section 6.1.1). all analysis will be for information only and not reported as part of this study.						
Control I = polyethylene glycol (b) (4) [(b) (4) v:v]						
Control II = Purified water						

Methods

Doses:	0 (vehicle), 0 (water), 10, 30, 100 mg/kg
Frequency of dosing:	Once per day
Dose volume:	5 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	PEG (b) (4)
Basis of dose selection:	The high dose of 100 mg/kg/day results in maximal exposure to the test article and its major metabolite M1.
Species/Strain:	Rat / Sprague Dawley (b) (4)
Number/Sex/Group:	Main Study: 57 /sex/group
Age:	Not more than 8 weeks at start of dosing
Animal housing:	Groups of up to 3 per cage
Paradigm for dietary restriction:	Not applicable
Dual control employed:	No. There are 2 control groups that are to receive different treatments Control I: PEG (b) (4) Control II: Water
Interim sacrifice:	No
Satellite groups:	Yes Toxicokinetic study: 9/sex/group

Health Screen

Prior to initiation and after 6, 12, 18, and 24 months on study, a health screen (blood sampling) will be conducted on the first 5 surviving Group 6 (untreated)males and females (Pneumonia Virus of Mice, Reovirus Type 3, Encephalomyelitis Virus, Sendai Virus, Lymphocytic Choriomeningitis Virus, Kilham Rat Virus, Rat Coronavirus/Sialodacryoadenitis Virus, Mycoplasma Pulmonis, Toolan's H-1 Virus). Group 6 decedents will undergo macroscopic examination and tissues are to be retained in fixative (no microscopic evaluation).

In addition, the kidneys, liver, lungs and gross abnormalities of 10 animals/sex will be examined microscopically soon after arrival (these animals are to be ordered in addition to those of Group 6).

Mortality

All animals will be checked twice daily for mortality or moribundity.

Clinical Signs

Physical exams, including palpation for tissue masses will be conducted once weekly and on the day of terminal necropsy.

Body Weights

Time period	Body weight measurement frequency
Day 1 – Week 16	Once weekly
Week 17 – Week 69	Once every 4 weeks
Week 70 – Week 105	Once weekly

Feed Consumption

Time period	Body weight measurement frequency
Day 1 – Week 16	Once weekly
Week 17 – Week 69	Once every 4 weeks

- Animals will be group housed. Food consumption will be calculated as g/animal/day.

Ophthalmoscopy

The sponsor is planning to include ophthalmic examinations at weeks 26, 52, 78, and 104. The sponsor was advised that these examinations are not required for FDA (see ECAC Meeting Minutes dated 11/9/17).

Clinical pathology

Blood samples will be collected at the time of necropsy from all main study animals for analysis of clinical chemistry, hematology, and coagulation parameters. Blood samples will also be taken from animals that die prematurely when possible. The sponsor was advised that clinical pathology assessment is not required for FDA (see ECAC Meeting Minutes dated 11/9/17).

Necropsy

All main study animals are to be sacrificed and all tissues examined microscopically at the conclusion of the treatment period. Animals that are found dead or euthanized prior to the end of the study will also be examined microscopically. The tissues to be collected and examined are listed in Table 17**Error! Reference source not found.**. Tissues are to be fixed, embedded, sectioned and stained using standard procedures. TK animals will not be subject to necropsy and no tissues will be collected from these animals.

Table 17. Sponsor's list of tissues to be collected from main study animals and observed microscopically

7.5 Tissue list							
Tissue / organ				**Tissue / organ**			
Bone Marrow Smear (femur)	P[1,2]			Skin/Subcutis (x1)	P		E
Brain (x6)	P		E	Mammary Gland (x1)	P		E
Spinal Cord, Cervical (x1)	P		E	Heart (x1)	P		E
Spinal Cord, Thoracic (x1)	P		E	Aorta (x1)	P		E
Spinal Cord, Lumbar (x1)	P		E	Muscle, Biceps Femoris (x2)	P		E
Adrenal (x2)	P		E	Kidney (x2)	P		E
Pituitary (x1)	P		E	Urinary Bladder (x1)	P		E
Nerve, Sciatic (x1)	P		E	Testis (x2)	P[6]		E
Eye (x2)	P[3]		E	Epididymis (x2)	P[6]		E
Nerve, Optic (x2)	P		E	Ovary (x2)	P		E
Harderian Gland (x2)	P[4]			Oviduct (x2)	P		
Thyroid (x2) and Parathyroid	P		E	Seminal Vesicle (x2)	P[7]		E
Trachea (x1)	P		E	Prostate (x1)	P		E
Oesophagus (x1)	P		E	Uterus (x3)	P[8]		E
Lung (x2)	P[5]		E	Vagina (x1)	P		E
Spleen (x1)	P		E	Femur + Marrow (x1)	P[9]		E
Thymus (x1)	P		E	Sternum + Marrow (x1)	P		E
Lymph Node, Mesenteric (x1)	P		E	Larynx (x1)			
Liver (x 2)	P		E	Lacrimal Gland (x2)			
Pancreas (x1)	P		E	Zymbal's Gland (x2)	P		
Stomach (x1)	P		E	Lymph Node, Bronchial (x1)			
Duodenum (x2)	P		E	Head (not processed)	P		
Jejunum (x1)	P		E	Nasal Cavity (x4)	P		
Colon (x1)	P		E	Nasopharynx (x2)	P		
Ileum (x1)	P		E	Nose/Nares (x1)	P		
GALT/Peyers patch (x1)	P		E	Lymph Node, Popliteal (x2)			
Caecum (x1)	P		E	Ureter (x2)			
Rectum (x1)	P		E	Dosing sites (variable)			
Mandibular Salivary Gland (x2)	P		E	Untreated skin site (x3)			
Sublingual Salivary Gland (x2)	P		E	Animal identification	P		
Parotid Salivary Gland (x1)				Gross lesions (variable)	P		E[10]
Lymph Node, Mandibular (x1)	P		E	Tissue masses (variable)	P		E
Tongue (x1)	P		E	Lymph Node, Axillary			
				Preputial/clitoral gland (x1)	P		E

Legend:

P = Tissues preserved; W = Organs weighed; E = Tissues processed and examined microscopically.

(xN) = number of sections for histopathology.

Footnotes:

1: See section 6.2 for evaluation required.

2: Smear prepared; air dried, then fixed in methanol. Samples will not be taken from animals dead prior to necropsy.

3: Tissue taken into Davidson's fixative.

4: Preserved with the head (*in situ*) unless histopathological processing is required.

5: Tissue includes mainstem bronchi and bronchioles.

6: Tissue taken into Modified Davidsons fixative and processed to at least the block stage.

7: Tissue includes coagulating glands.

8: Tissue includes cervix.

9: Tissue includes femorotibial joint.

10:Gross lesions processed in accordance with current Histology Standard Operating Procedure

Additional information:

Fixative will be neutral buffered 10% formalin unless specified otherwise.

Left and right organs will be weighed together.

Bone tissue designated for histopathological examination will be decalcified using Kristenson's fluid.

Toxicokinetics

- Blood samples will be taken from TK animals during week 4 at the following time points: pre-dose, 0.5, 1, 2, 4, and 7 hours post dose.

- Plasma CCX168, CCX168-M1, and CCX168-M6 concentrations will be quantified and pharmacokinetic parameters will be determined using Phoenix WinNonlin Version 6.4.

- The TK analysis in the current study could provide empirical evidence that the rats are being exposed to expected levels of CCX168 and CCX168-M1. However, the sponsor was advised that toxicokinetic assessment is not required for FDA (see ECAC Meeting Minutes dated 11/9/17).

11 Integrated Summary and Safety Evaluation

The sponsor has proposed to evaluate the carcinogenic potential of CCX168 administered by oral gavage in rats for a minimum of 104 weeks. The rat is not a pharmacologically relevant species for CCX168 as CCX168 has no activity toward its target (complement C5a receptor) in rats. However, based upon in vitro studies in liver microsomes as well as in vivo studies, the metabolism and pharmacokinetic properties of CCX168 appear to be comparable between rats and humans. Orally administered CCX168 is highly bioavailable in rats and humans. T_{max}, V_d, and $T_{1/2}$ values are all similar between both species. CCX168 is highly protein bound in both rat and human plasma (>99.9%). CCX168-M1, a hydroxylated metabolite of the parent compound, is the major human metabolite. CCX168-M1 is also a major metabolite in rats. The proportion of CCX168-M1 formed in humans is greater than in rats (Humans: CCX168-M1: 21.9% of CCX168; Rats: CCX168-M1: 3 - 15% of CCX168). Rats dosed at 100 mg/kg/day CCX168 are expected to achieve a systemic CCX168-M1 exposure level approximately equal to that in humans at the maximum recommended human dose (Table 18).

CCX168 was negative in a standard genetic toxicology battery including the in vitro bacterial reverse mutation assay, in vitro mouse lymphoma assay, and in vivo rat micronucleus assay. CCX168-M1 was demonstrated to be present under the conditions of the in vitro bacterial reverse mutation assay and in vivo rat micronucleus assay and could be concluded to be negative for genotoxicity.

Chemocentryx has proposed oral CCX168 doses of **10, 30, and 100 mg/kg/day** for the 2-year carcinogenicity study in rats based upon systemic exposure levels of CCX168 and CCX168-M1 achieved in a 26-week rat toxicity study.

Design and dose selection for the 2-year carcinogenicity study with rats:
General aspects of the study design and dose selection appear acceptable. The sponsor is proposing to include both a vehicle control and a water-only control group. This is considered to be appropriate given the nature of the vehicle (PEG (b) (4)).

A maximum tolerated dose could not be determined from a 26-week toxicity study in which rats were administered CCX168 by oral gavage at doses of 0, 5, 15, 100, and 200 mg/kg/day. There were no treatment related mortalities and no significant treatment related effects on body weight gain. There were no target organs of toxicity identified in this study. Systemic exposure of CCX168 is saturated at the 100 mg/kg/day dose.

Systemic Exposure Comparisons between Rats and Humans:
In the SPA background information document, the sponsor references clinical PK data from studies CL001_168 and CL002_168 to establish projected mean steady state AUC_{0-24} values for CCX168 and CCX168-M1 at the recommended clinical CCX168 dose of 30 mg b.i.d. The values are as follows:

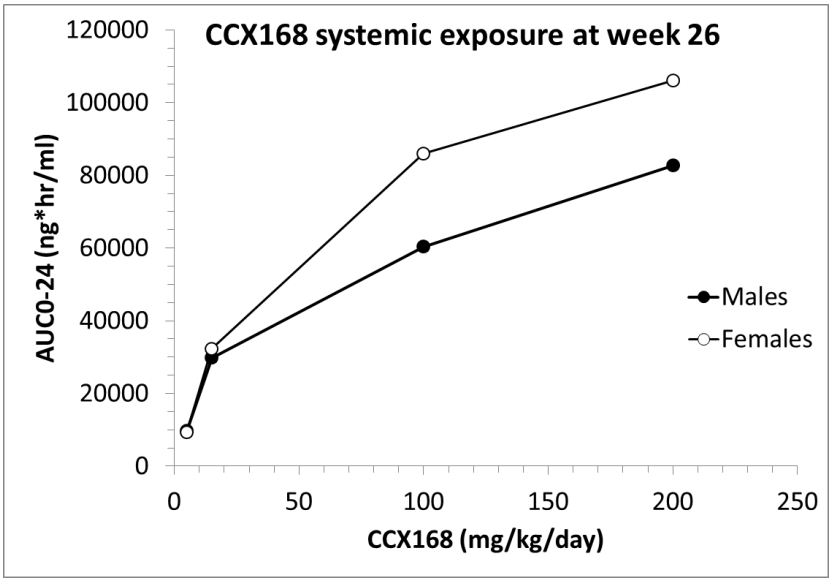
- CCX168: 5638 ng*hr/ml
- CCX168-M1: 2780 ng*hr/ml

Rat CCX168 and CCX168-M1 systemic exposure values at the sponsor's proposed doses were predicted based upon data from the 26-week toxicity study (see Figure 4). These values were then compared against the sponsor's predicted clinical steady state AUC_{0-24} values for CCX168 and CCX168-M1 to compute exposure margins (Table 18).

The sponsor-proposed high dose of 100 mg/kg/day provides for an expected exposure margin of 11 for males and 15 for females. While these exposure margins do not achieve the desired 25-to-1 exposure ratio outlined in ICH-S1C(R2), CCX168 exposure is saturated in rats at this dose. Significantly higher exposures are not achievable.

The 100 mg/kg/day dose also provides for an exposure margin of approximately 1 for the CCX168-M1 metabolite in males and females. The FDA M3(R2) Questions and Answers Document (2013) states that "…characterization of a metabolite toxicity would generally be considered adequate when animal exposure is at least 50% the exposure seen in humans". Therefore, the toxicity of CCX168-M1 can be expected to be adequately characterized in this study.

The sponsor has proposed middle and low doses of 30 and 10 mg/kg respectively in both males and females. Based on the available exposure data from the 26-week rat toxicology study, these doses are expected to provide adequate AUC separation (see Table 18). The executive CAC agreed with these conclusions.



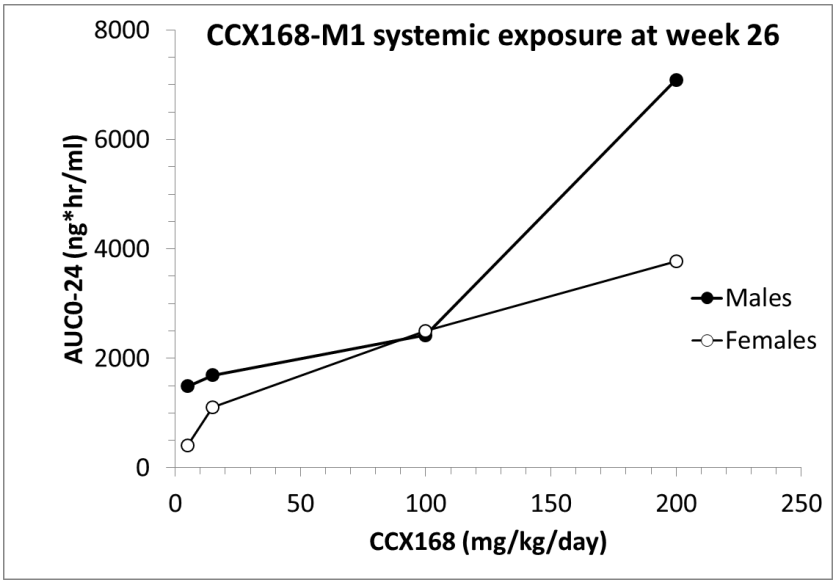


Figure 4. CCX168 (top) and CCX168-M1 (bottom) systemic exposure values at week 26 of a 26-week toxicity study in SD rats.

Table 18. Predicted CCX168 and CCX168-M1 exposures in 2-year rat carcinogenicity study and calculated exposure margins relative to the maximum clinical dose. Note that the sponsor proposes to use doses of 10, 30, and 100 mg/kg/day in males and females.

		CCX168		CCX168-M1	
Sex	Sponsor's proposed CCX168 dose	Predicted AUC_{0-24} (ng*hr/ml)[a]	Exposure margin[b]	Predicted AUC_{0-24} (ng*hr/ml)[a]	Exposure margin[c]
Males	10	20000	3.5	1600	0.5
	30	35000	6	1900	0.7
	100	60000	11	2500	0.9
Females	10	20000	3.5	750	0.3
	30	42000	7	1300	0.5
	100	85000	15	2500	0.9

[a] Values estimated from reported AUC_{0-24} values at week 26 in chronic toxicity study
[b] Sponsor's projected steady state human CCX168 AUC_{0-24}: 5638 ng*hr/ml
[c] Sponsor's projected steady state human CCX168-M1 AUC_{0-24}: 2780 ng*hr/ml

Executive Carcinogenicity Assessment Committee (ECAC) Meeting Summary
The Executive CAC met to discuss the proposed rat carcinogenicity study for CCX168 on November 7, 2017. The conclusions of the meeting were conveyed to the sponsor by fax on November 9, 2017.

The Committee concurred with the sponsor's proposed oral doses of 10, 30, and 100 mg/kg/day in males and females. The high dose was based on saturation of exposure of CCX168 at doses ≥ 100 mg/kg/day. The Committee also concurred with the sponsor's proposed low and middle doses of 10 and 30 mg/kg/day respectively based on adequate exposure separation. The Committee concurred with the sponsor's proposed inclusion of vehicle-control (PEG (b) (4)) and water-only control groups. The Committee noted that the conduct of the following aspects of the proposed study design are not required by FDA: toxicokinetic evaluation, ophthalmoscopic examinations, and clinical pathology evaluation. Finally, the Committee noted that the conducting laboratory and source of animals in the proposed 2-year carcinogenicity study are different from those in the 26-week toxicity study. The sponsor was informed that the carcinogenicity study may not be acceptable if toxicity is significantly different due to these changes such that dose selection would have been altered.

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/s/

MATTHEW T WHITTAKER
11/09/2017

TIMOTHY W ROBISON
11/09/2017
I concur

Appendix 3

IND 120784: Review of 13-week toxicology study with hamster (Dr. Dong Zhao, Dated in DARRTS November 14, 2017)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	IND 120784
Review number:	4
Supporting document/s:	SD 64, SD 82, SD 83
PDUFA review deadline date:	November 24, 2017
CDER stamp date:	SD 64: 11/14/2016
	SD 82: 10/05/2017
	SD 83: 10/10/2017
Product:	CCX168
Indication:	Anti-neutrophil cytoplasmic antibody (ANCA) – associated vasculitis
Therapeutic area:	Allergy and Immunology
Sponsor:	Chemocentryx
Review Division:	Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Reviewer:	Dong Zhao, Ph.D., D.A.B.T.
Supervisor/Team Leader:	Andrew Goodwin, Ph.D.
Division Director:	Badrul Chowdhury, MD, Ph.D.
Project Manager:	Brandi E. Wheeler, PharmD

Template Version: July 13, 2017

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1 Executive Summary

1.1 Introduction

Chemocentryx is developing CCX168, an antagonist of the human complement 5a receptor (C5aR), as an oral treatment for Anti-neutrophil cytoplasmic antibody (ANCA) – associated vasculitis (AAV) under IND 120784. In the present submissions, the sponsor submitted a Special Protocol Assessment requests (SD 83 and 85 received 10/10/2017 and 10/20/2017, respectively) for carcinogenicity studies evaluating CCX168 and its major human metabolite CCX168-M1 in rats and hamsters. Hamster is a pharmacologically relevant species as CCX168 inhibits hamster C5aR with potencies similar to that observed with human whole blood. Dose selection for the proposed carcinogenicity study with hamster is based on the 13-week hamster toxicity study.

1.2 Brief Discussion of Nonclinical Findings

Genotoxicity studies evaluating CCX168 have been reviewed previously and the test item was found negative in all assays including in vitro bacterial mutagenicity (Ames test) and mammalian cell mutagenicity (mouse lymphoma forward-mutation assay) studies, as well as the in vivo rat bone marrow micronucleus study.

The effects of CCX168 on the immune system (T-cell dependent antibody response [TDAR]) were evaluated in both the 13-week rat general toxicity study, as well as a stand-alone 28-day rat study. The chronic non-human primate study also incorporated immunophenotypic and TDAR evaluations. There was no evidence of immune system toxicity or suppression that might impact the carcinogenicity studies.

The major metabolite CCX168-M1, identified in human plasma in clinical studies, constituted approximately 12% of total plasma exposure in humans and was also detected in nonclinical species including Golden Syrian hamster. The extent of plasma protein binding for CCX168 or its metabolite CCX168-M1 were measured in humans as well as other six species including Syrian hamsters. Both CCX168 and its metabolite CCX168-M1 were protein bound reversibly at >99.9% in plasma of all species tested.

In the 3-month toxicity study in hamster, animals received vehicle, 10, 30, 100 and 1000 (500 BID) mg/kg/day CCX168. No test item related adverse findings were identified throughout the 3-month dosing and 4-week recovery period. Test item-related findings were limited in a few parameters in clinical chemistry: Higher mean triglyceride concentration were observed in the male hamsters at 100 and 1,000 mg/kg/day and minimally higher mean alanine aminotransferase, aspartate aminotransferase and phosphorus were observed in the males at 1,000 mg/kg/day. No similar changes were noted in animals at the recovery period. These findings were not considered adverse due to low incidence/magnitude and lack of histopathological correlation. In conclusion, the administration of up to 1000 mg/kg/day of CCX168 for 3 months was well tolerated. No findings were observed that were judged likely to affect survival in a two-year carcinogenicity study. However, the highest exposures were detected in animals at the 100 mg/kg/day. This results, together with the findings noted in the 7-day hamster DRF study, indicated that 100 mg/kg/day generated the maximal exposure for both CCX168 and CCX168-M1 metabolite. The no-observed-adverse- effect level (NOAEL) for

general toxicity of CCX168 is determined as 100 mg/kg/day. Exposure values for CCX168 at the 100 mg/kg/day were C_{max} = 4,410 ng/mL, and AUC_{0-24} = 39,900 ng·hr/mL for combined sexes on day 91 of dose administration.

For the purposes of CCX168 dose selection for the two-year hamster carcinogenicity study, the sponsor selected the proposed doses for the two-year hamster carcinogenicity study based on data obtained from the 13-week hamster general toxicology studies. Due to lack of toxicity and the safety margin at the MTD (1000 mg/kg/day) was < 25-fold, the sponsor selected 100 mg/kg/day as the high dose based on the saturation of absorption. This dose represents exposure margins of approximately 7- and 1-fold, respectively, of the human plasma AUC at the 30 mg b.i.d. MHRD for CCX168 parent and CCX168-M1 metabolite in patients with AAV. The sponsor selected 10 and 30 mg/kg/day as low and mid-dose, respectively, because they were well spaced out to study dose relationship (2-3x AUC separation) and were unlikely to generate exposure overlap based on the results from the 3-month hamster study.

1.3 Internal Comments

None

1.4 Recommendations

The Executive Carcinogenicity Assessment Committee (ECAC) met on November 7, 2017 and reached the following conclusions that apply to both the hamster and rat 2-year carcinogenicity studies:

- The Committee concurred with doses of 10, 30 and 100 mg/kg/day for males and females, with the high dose based on saturation of systemic exposure.
- The mid- and low-doses for both sexes were selected based on adequate spacing of AUC.
- The Committee concurred with vehicle-control (PEG (b) (4)) and water-only control groups.
- The Committee noted that the 2-year carcinogenicity study will be performed in a different facility with a different source of animals than used in the 13-week oral toxicity study. The carcinogenicity study may not be acceptable if toxicity is significantly different due to these changes such that dose selection would have been altered.
- The Committee noted that the use of toxicokinetic dose groups is not needed for FDA.
- The Committee noted that clinical pathology at the end of the study is not needed for FDA.
- The Committee noted that ophthalmoscopic examination is not needed for FDA.

The Special Protocol Assessment – Agreement letter was issued November 9, 2017.

1.4.1 Clinical Study (ies) Safe to Proceed:

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2 Drug Information

2.1 Drug

Code Name(s): CCX168

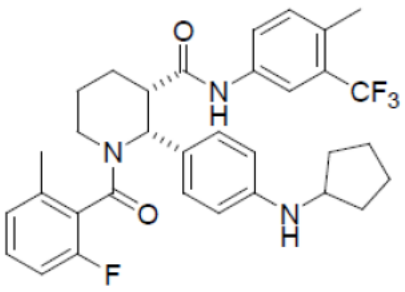
CAS Registry Number: 1346623-17-3

Generic Name: Avacopan

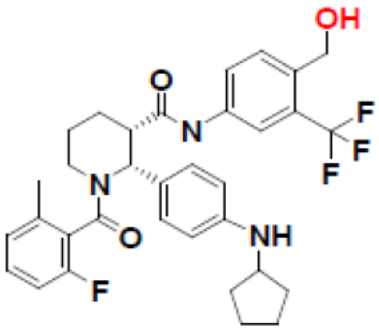
Chemical Name: (2R,3S)-2-[4-(Cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide

Molecular Formula/Molecular Weight: $C_{33}H_{35}F_4N_3O_2$ / 581.6 g/mol

Structure or Biochemical Description:



CCX168



CCX168-M1 metabolite

Pharmacologic Class: Complement C5a receptor antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

Table 1 Summary of the related INDs for Avacopan (CCX168)

IND Number	Indication/Division	Dose/Duration	Application Status/Date
		(b) (4)	Active on Oct 29, 2014
			Active on Jul 30, 2017

2.3 Drug Formulation

Table 2 CCX168 Capsule, 10 mg, composition

	% Composition	mg per capsule Composition	Function	Grade
CCX168	(b) (4)	10	API	--
Polyoxyl 40 Hydrogenated Castor Oil (Cremophor RH40)				(b) (4)
Polyethylene glycol 4000 (PEG-4000)				
Gelatin capsule, light orange/yellow, Size 0				
Gelatin sealing band[a]				
Total				

[a] The product capsule is sealed with a clear gelatin band

2.4 Comments on Novel Excipients

No comment. The levels of Cremophor RH40 and PEG-4000 were discussed by Dr. M. Whittaker in a previous review on 2014 and 2015, respectively.

2.5 Comments on Impurities/Degradants of Concern

The proposed specifications and controls for CCX168 drug substance and drug product are adequate from the Pharm/Tox perspective to support Phase 3 clinical development. See the nonclinical review dated 10/27/16 by Dr. M Whittaker for evaluation of the CCX168 drug substance and drug product specifications.

2.6 Clinical Information

Current Clinical Phase: Phase III Trial

2.6.2 Previous Clinical Experience

Previous clinical experience: Y
If yes, Phase: Phase III Trial

2.8 Regulatory Background

Nov 1, 2016. Type C meeting: further discuss the proposed Phase III study design
July 14, 2016. End of Phase II meeting: Sponsor seeks feedback on their revised phase 3 clinical trial and on their approach to assessing adequate assay sensitivity for QT/QTc evaluations.

3 Studies Submitted

3.1 Studies Reviewed

PC0677_168: A 13-Week Toxicity and Toxicokinetic Study of CCX168 by Oral Gavage in Hamsters with a 4-Week Recovery Period

3.2 Studies Not Reviewed

NA

3.3 Previous Reviews Referenced

IND 120784 Pharmacology/Toxicology IND Review and Evaluation, 12/03/2015

IND 120784 Pharmacology/Toxicology IND Review and Evaluation, 7/15/2015

4 Pharmacology

CCX168 is a potent antagonist of the human C5a receptor (hC5aR). As measured in vitro with a myeloid human cell line, avacopan functionally inhibited C5a-mediated chemotaxis with a potency (IC_{50}) of 0.92 nM. Additionally, CCX168 displaced [^{125}I]-C5a from hC5aR with an IC_{50} of 0.65 nM. CCX168 also inhibits C5aR in cynomolgus monkeys and hamsters with potencies similar to that observed with human whole blood. Like CCX168, CCX168-M1 has high potency for cynomolgus monkey, hamster, and human C5aR.

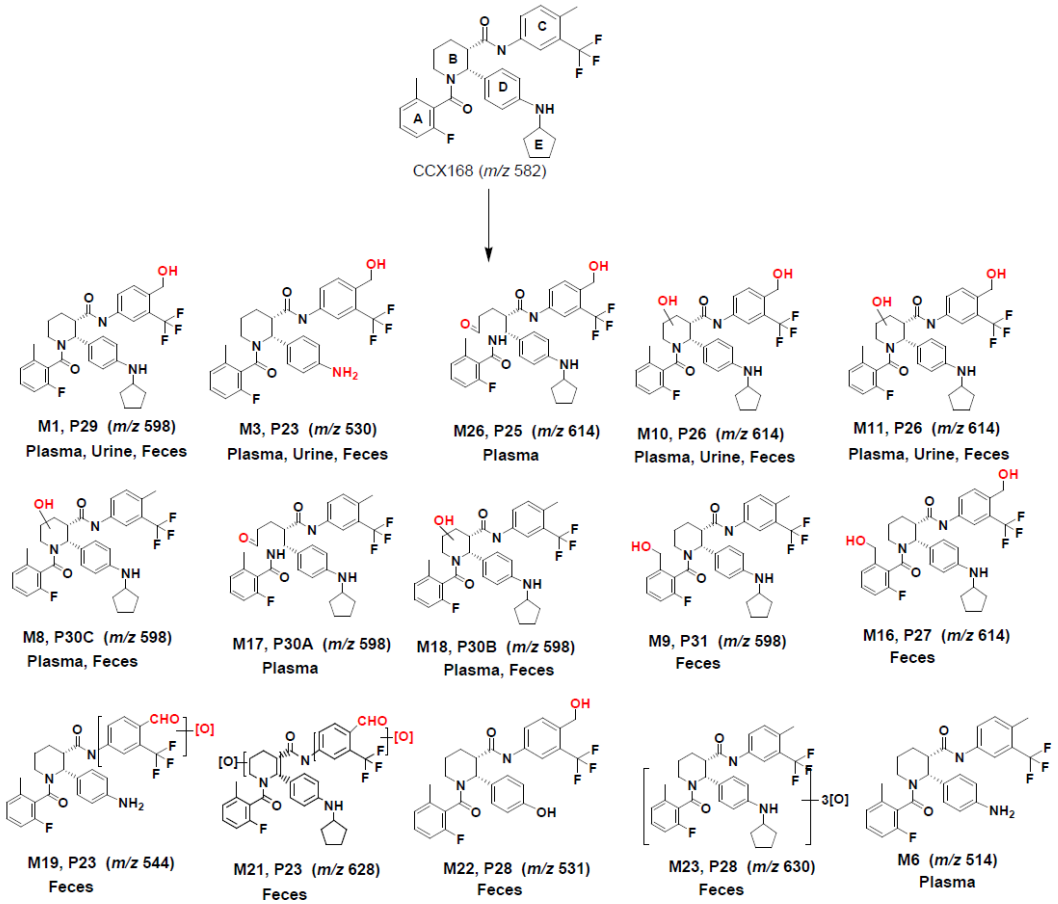
5 Pharmacokinetics/ADME/Toxicokinetics

Following IV dosing, CCX168 showed moderate total body clearance (30 – 50% of liver blood flow in mice, rats, and dogs. The terminal elimination half-life was approximately 2 hours in mice and Sprague Dawley (SD) rats.

Bioavailability varied from 17% to 100% with different formulations in rat. Several organic vehicles were explored in rat, rabbit (NZW) and hamster (Syrian) oral pharmacokinetics at several dose levels. The maximum exposure following single oral administration was reached at 100 mg/kg in PEG (b) (4) in rat. The same vehicle has been used in the 7-day range finder study and the following 13-week MTD study in hamster.

Definitive in vivo metabolite profiling studies with an oral dose of [^{14}C]-CCX168 in rats, monkeys, and humans showed that CCX168 was the most abundant radioactive component in plasma across these species, while CCX168-M1 was the major circulating metabolite. In human plasma, CCX168 and CCX168-M1 accounted for 18% and 11.9% of the total plasma radioactivity, respectively. Analysis of plasma samples from rats and hamsters studies indicated that levels of CCX168-M1 in these species were greater than or similar to the levels in human plasma. The potential and measured metabolite structures are presented in the following table.

Figure 1 Proposed Human Metabolites of CCX168



5.2 Toxicokinetics

In the 7-day dose range finding study in hamster, up to 600 mg/kg/day of CCX168 were administered to animals with exposure peaked at 100 mg/kg/day on Day 7 (shown in the following table). The data suggested that 100 mg/kg/day generated maximal exposure levels in hamster, and that twice daily dosing regimens did not achieve further increases in exposure. This result was comparable to the data in the later 3-month study. Both the 7-day and 13-week studies were conducted with the PEG [(b) (4)] ([(b) (4)] v:v] vehicle.

Table 3 Group mean TK parameters from the 7-day dose range finding study in hamster

Dose (mg/kg)	CCX168 $AUC_{0\text{-}24hr}$ (ng•hr/mL)		CCX168-M1 $AUC_{0\text{-}24hr}$ (ng•hr/mL)		CX168 C_{max} (ng/mL)		CCX168-M1 C_{max} (ng/mL)	
	M	F	M	F	M	F	M	F
10 q.d.	3,170	1,970	440	190	320	220	35	23
100 q.d.	14,300	19,100	2,100	2,180	1,600	1,500	130	140
200 q.d.	16,000	19,500	1,980	2,510	1,170	1,290	130	130
50 b.i.d.	18,100	24,000	2,200	2,880	1,880	1,870	170	170
100 b.i.d.	23,700	20,100	3,900	3,900	1,750	1,300	220	220
300 b.i.d.	16,600	20,700	3,000	4,050	1,200	1,000	180	220

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study Title: A 13-Week Toxicity and Toxicokinetic Study of CCX168 by Oral Gavage in Hamsters with a 4-Week Recovery Period

Study no.:	PC0677_168
Study report location:	EDR SD #82
Conducting laboratory and location:	(b) (4)
Date of study initiation:	10/13/2016
Duration:	13 weeks
Duration Units:	weeks
GLP compliance:	Y
QA statement:	Y
Drug, lot #, and % purity:	D-15-012, 99%

Key Study Findings

There were 6 groups (Groups 1-6) of 15 animals/sex/group in the main study. In the recovery study, there were 5 animals/sex/group in Groups 1, 4, 5 and 6. For Groups 1 through 4, male and female hamsters were given the test article (CCX168) and/or the control article formulations once daily via oral gavage for 13 weeks (91 days) at a dose level of 0, 10, 30 or 100 mg/kg/day, respectively. For Groups 5 and 6, male and female hamsters were given the test article and/or the control article formulations twice daily via oral gavage (approximately 8 hours apart) for 13 weeks (91 days) at a dose level of 0 or 500 mg/kg/dose.

- No test item related adverse findings were identified throughout the 3-month dosing and 4-week recovery period.
- Test item-related findings were limited in a few parameters in clinical chemistry: Higher mean triglyceride concentration were observed in the male hamsters at 100 and 1,000 mg/kg/day and minimally higher mean alanine aminotransferase, aspartate aminotransferase and phosphorus were observed in the males at 1,000 mg/kg/day. No similar changes were noted in animals at the recovery period. These findings were not considered adverse due to low incidence/magnitude and lack of histopathological correlation.
- In conclusion, the administration of up to 1000 mg/kg/day of CCX168 for 3 months was well tolerated. No findings were observed that were judged likely to affect survival in a two-year carcinogenicity study. However, the highest exposures were detected in animals at the 100 mg/kg/day. This results, together with the findings noted in the 7-day hamster DRF study, indicated that 100 mg/kg/day generated the maximal exposure for both CCX168 and CCX168-M1 metabolite. The no-observed-adverse- effect level (NOAEL) for general toxicity of CCX168 is determined as 100 mg/kg/day. Exposure values for CCX168 at the

100 mg/kg/day were C_{max} = 4,410 ng/mL, and AUC_{0-24} = 39,900 ng·hr/mL for combined sexes on day 91 of dose administration.

Methods

Doses:	QD: 0, 10, 30 or 100 mg/kg/day (Groups 1-4) BID: 0 or 1000 mg/kg/day (Groups 5-6)
Frequency of dosing:	QD or BID
Route of administration:	ORAL
Dose volume:	5 mL/kg/day
Formulation/Vehicle:	Polyethylene glycol (b) (4) (b) (4) (V:V (b) (4))
Species:	HAMSTER
Strain:	Golden Syrian
Dedicated Juvenile Animal Study:	N
Number/Sex/Group:	15 main, plus 5 recovery (Groups 1, 4, 5, and 6 only)
Age:	89 days of age upon arrival
Weight:	125-154 g at randomization
Satellite groups:	3/sex/group for controls (groups 1 and 5) 9/sex/group for groups 2-4 12/sex/group for group 6
Deviation from study protocol:	None of the protocol deviations listed in the study report affected the outcome and the integrity of the study.

Observations and Results

Mortality

A total of 16 animals were found dead or euthanized prior to the scheduled necropsy throughout the study. 10 of them were main/recovery animals. The causes of the death for the main study animals are summarized in the following table. These deaths are not considered to be test item-related because they did not occur in a dose-dependent fashion and the gross pathology or histopathology findings in a majority of the animals revealed that the deaths were related to dose intubation errors. Histopathological assessment was not performed to the 6 satellite animals. But those mortalities did not occur in a dose-related fashion (3 at 10 mg/kg/day, 1 at 30 mg/kg/day, and 2 at 100 mg/kg/day), suggesting they were not test-item related either.

Table 4 Summary of findings in main/recovery study animals that were found dead or euthanized early

Dose Group	1		2		3		
Dose Level (mg/kg/day)	0		10		30		
Animal No.	9211	9418	9223	9233	9242	9438	9441

Sex	Male	Female	Male	Male	Male	Female	Female
Doses Administered	32	13	25	11	50	65	7 7
Mode of Death	UE	UE	FD	UE	UE	FD	FD
Day of Death	DS 32	DS 13	DS 26	DS 11	DS 50	DS 65	DS 77
Bodyweights							
Body weight change	-6.7% DS 20 to 32	-8.1% DS 12 to 13	UR	-6.9% DS 1 to 10	-9.5% DS 40 to 50	-10.8% DS 42 to 64	UR
Necropsy Observations							
All tissues appeared normal	-	X	X	-	X	X	X
Clear fluid accumulation	-	-	-	X	-	-	-
Dilation of the brain	-	-	-	X	-	-	-
Opening through the muscle wall of the right side of the abdomen (hernia)	X	-	-	-	-	-	-
Notable Microscopic Observations							
	Microscopic findings in trachea consistent with gavage-related dosing error	Microscopic findings in trachea and nasal cavity consistent with gavage-related dosing error	UR	Brain: marked ventricular dilatation	Microscopic findings in larynx and trachea suggestive of gavage-related dosing error	Microscopic findings in trachea, larynx, and nasal cavity consistent with gavage-related dosing error	Microscopic findings in trachea consistent with gavage-related dosing error

Dose Group	**4**		**6**
Dose Level (mg/kg/day)	**100**		**1,000 (500 mg/kg BID)**
Animal No.	9263	9461	9504
Sex	Male	Female	Female
Doses Administered	25	78	169
Mode of Death	UE	UE	UE[a]
Day of Death	DS 26	DS 78	DS 85
Bodyweights			
Body weight change	-7.7% DS 24 to 26	UR	UR
Necropsy Observations			
All tissues appeared normal	X	X	X
Notable Microscopic			
	Microscopic findings in trachea and lung consistent with gavage-related dosing error	Microscopic findings in larynx consistent with gavage-related dosing error	UR

- = Finding not present; DS = Day of Study; FD = Found Dead; UE = Unscheduled Euthanasia; UR = Unremarkable

[a] Female 9504 was euthanized after being found outside the cage and sperm was detected in a vaginal smear.

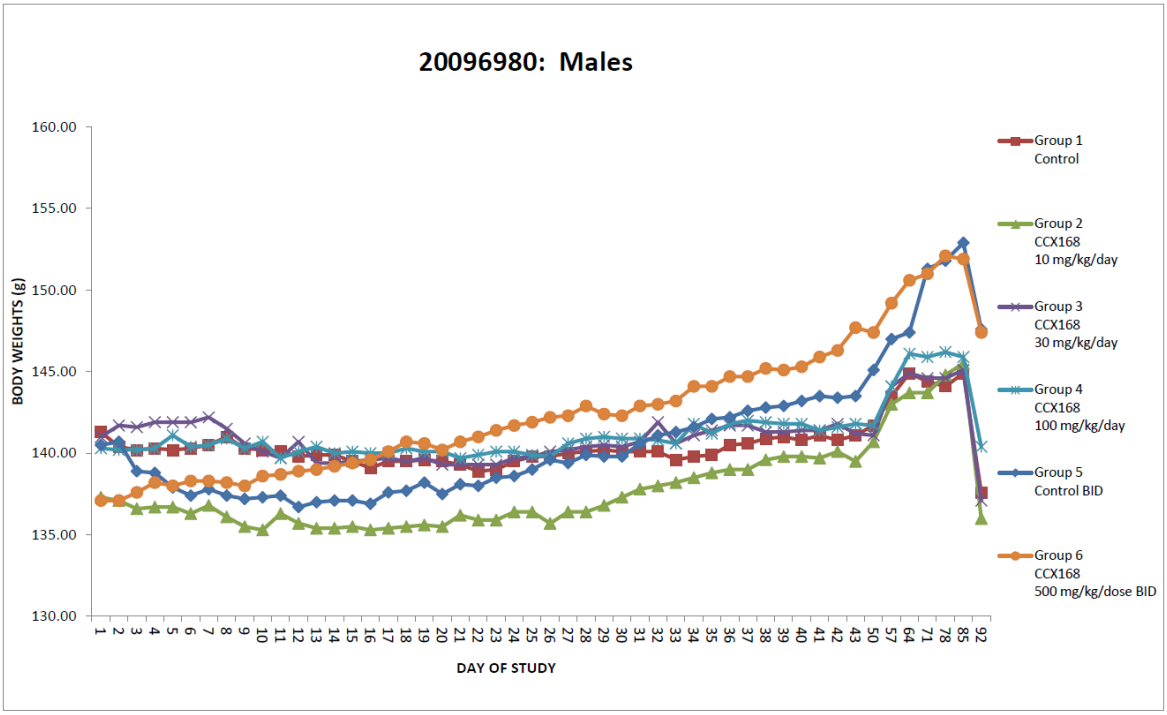
Clinical Signs

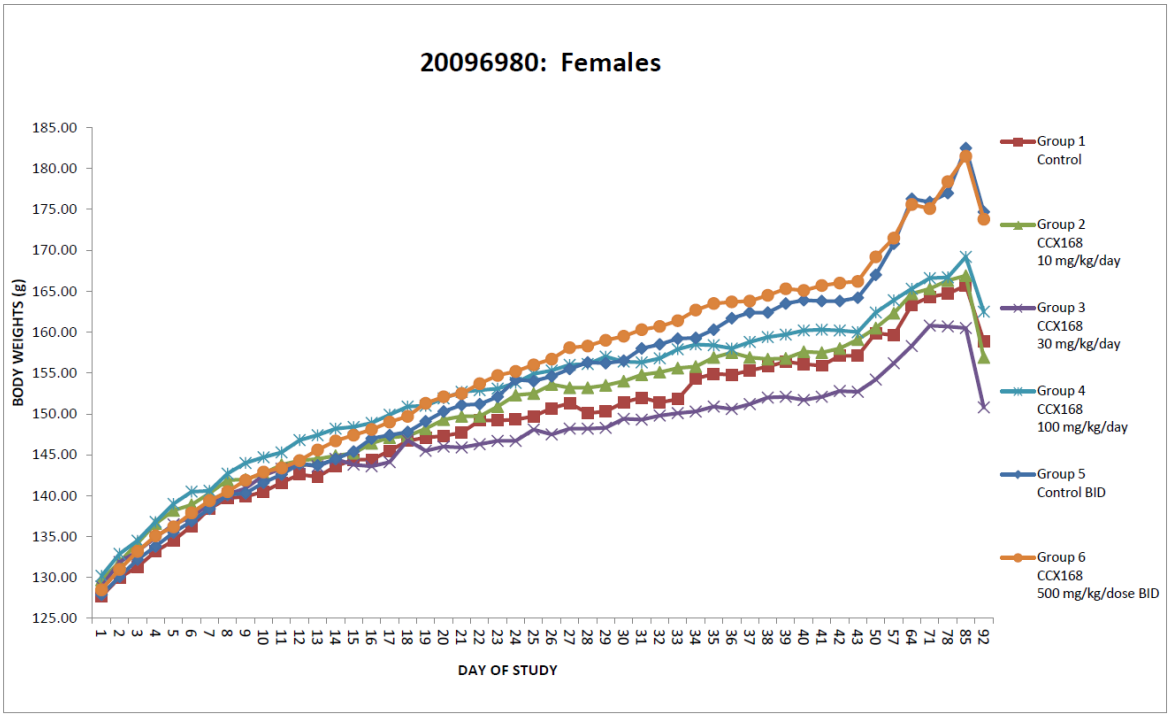
No test item related clinical finding was identified during the study.

Body Weights

There were no consistent body weight changes identified throughout the study. All changes in the dosing groups were < 10% relative to the respective controls at any time points.

Figure 2 Mean body weights in the dosing period





Feed Consumption

There were no consistent food consumption changes identified throughout the study.

Ophthalmoscopy

There were no test item-related ophthalmic changes in the male and female hamsters when examined during the last week of dose administration.

ECG

NA

Hematology and Coagulation

There were no definitive test item related changes in hematology or coagulation parameters identified throughout the study.

Clinical Chemistry

Test item related differences in clinical chemistry parameters were limited to males and included minimally increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglycerides (TRIG), and phosphorus (PHOS) at 1000 and/or 100 mg/kg/day. Following a 4-week recovery period, there were no CCX168-associated alterations in clinical chemistry parameters. None of the findings were adverse due to low incidence/magnitude and lack of histopathological correlation. The observed clinical chemistry changes were not judged to be likely to affect survival in a two-year carcinogenicity study.

Table 5 CCX168-related clinical chemistry changes (percent difference)

Group	1		2		3		4		5		6	
Dose (mg/kg/day)	0		10		30		100		0[a]		1,000[a]	
Sex Parameter	M	F	M	F	M	F	M	F	M	F	M	F
ALT (IU)												
DS 92	49.1	70.7	–	–	–	–	–	–	48.2	105.2	↑105%*	–
DS 120	71.4	145.5	NA	NA	NA	NA	–	–	47.6	93.4	–	–
AST (IU)												
DS 92	58.6	55.1	–	–	–	–	–	–	42.6	73.5	↑45.7%	–
DS 120	76.2	83.5	NA	NA	NA	NA	–	–	61.4	77.6	–	–
TRIG (mg/dL)												
DS 92	61.1	83.5	–	–	–	–	↑45.0%*	–	74.5	102.9	↑74.3%**	–
DS 120	93.6	158.5	NA	NA	NA	NA	–	–	101.6	112.6	–	–
PHOS (mg/dL)												
DS 92	4.99	5.49	–	–	–	–	↑12.3%	–	5.84	5.31	↑26.9%**	–
DS 120	6.20	6.60	NA	NA	NA	NA	–	–	5.84	6.18	–	–

M = Males; F = Females; NA = not applicable

A dash (–) indicates absence of test item-related change. Values for groups administered control article are actual values. Values for groups administered the test item indicate percent difference relative to control Group 1 mean value.

[a] Hamsters were dosed twice per day (approximately 8 hours apart).

* Statistically significant from control Group 1 at $p \leq 0.05$.

** Statistically significant from control Group 1 at $p \leq 0.01$.

Urinalysis

There were no test item-related changes identified in urinalysis parameters at the end of dosing or recovery phase.

Gross Pathology

No test item-related gross findings were noted.

Organ Weights

No test item-related organ weight changes were noted.

Histopathology

Adequate Battery: An adequate battery of tissues/organs were collected as listed in the following table from all surviving animals at the time of necropsy.

Tissue	Weigh	Collect	Microscopic Evaluation	Comment
Artery, aorta	-	X	X	-
Body cavity, nasal	-	X	X	Level 3
Bone marrow smear	-	X	-	Two bone marrow smears will be collected from the femur for possible examination from all main and recovery study animals. Smears will not be collected from animals that are found dead. Bone marrow smears will be allowed to air dry and will not be fixed in formalin.
Bone marrow	-	X	X	Collect bone marrow with femur and sternum.
Bone, femur	-	X	X	-
Bone, sternum	-	X	X	-
Brain	X	X	X	Seven brain levels to be examined to include olfactory bulb, which is to be collected with nasal cavity (level 4[a]).
Cervix	X	X	X	Collect and weigh with uterus and oviduct.
Epididymis	X	X	X	Paired weight and examination.
Esophagus	-	X	X	-
Eye	-	X	X	Paired examination; preserve in Davidson's fixative. Rinse per Testing Facility SOP.
Gall bladder		X	X	-
Gland, adrenal	X	X	X	Paired weight and examination.
Gland, harderian	-	X	X	Both collected; only 1 required for microscopic examination.
Gland, mammary	-	X	X	For males, examine only if present in routine section of skin.
Gland, parathyroid	X	X	X	Examine only if present in the routine section of thyroid. Fixed weight.
Gland, pituitary	-	X	X	-
Gland, prostate	X	X	X	-
Gland, salivary	-	X	X	Both collected; only 1 required for microscopic examination.
Gland, seminal vesicle	X	X	X	Paired examination.
Gland, thyroid	X	X	X	Paired weight and examination; weight includes parathyroid. Fixed weight.
Gross lesions/masses	-	X	X	All animals.
Heart	X	X	X	-
Kidney	X	X	X	Paired weight and examination.
Large intestine, cecum	-	X	X	-
Large intestine, colon	-	X	X	-
Large intestine, rectum	-	X	X	-
Larynx	-	X	X	-
Liver	X	X	X	-

Tissue	Weigh	Collect	Microscopic Evaluation	Comment
Lung	X	X	X	-
Muscle, skeletal	-	X	X	-
Nerve, optic	-	X	X	Examine only if present in the routine section of the eye. Preserve in Davidson's fixative with eye. Rinse per Testing Facility SOP.
Nerve, sciatic	-	X	X	Both collected; only 1 required for microscopic examination
Oviduct	X	X	X	Collect and weigh with uterus and cervix
Ovaries	X	X	X	Paired weight and examination.
Pancreas	-	X	X	-
Skin	-	X	X	Inguinal.
Small intestine, duodenum	-	X	X	-
Small intestine, ileum	-	X	X	-
Small intestine, jejunum	-	X	X	-
Spinal cord	-	X	X	Examine one transverse and one longitudinal section from each of the following areas cranial cervical, mid-thoracic, lumbar (intumescence)
Spleen	X	X	X	-
Stomach	-	X	X	-
Testis	X	X	X	Paired weight and examination. Preserve in Modified Davidson's fixative. Rinse per Testing Facility SOPs.
Thymus	X	X	X	-
Tongue	-	X	X	-
Trachea	-	X	X	-
Urinary bladder	-	X	X	-
Uterus	X	X	X	Collect and weigh with oviduct and cervix
Vagina	-	X	X	-

X = Procedure to be conducted; - = Not applicable; SOP = Standard Operating Procedures.

[a] Young, J. Histopathologic Examination of the Rat Nasal Cavity, Fundamental and Applied Toxicology, 1:309-312 (July/August 1981).

Peer Review: No peer review pathologist recorded and no peer review statement identified in the study report. Therefore, peer review appeared not conducted.

Histological Findings

No test item-related microscopic findings were noted during dosing and recovery periods.

Special Evaluation

NA

Toxicokinetics

Plasma concentrations of CCX168 and its major human metabolite CCX168-M1 were measured with samples collected prior to dosing on Day 1, 29 and 91, respectively. Group mean data are summarized in the following tables.

Table 6 Summary of the CCX168 TK Parameters in Hamster Plasma

Interval	Group	Dose level (mg/kg/dose)	Dose level (mg/kg/day)	Sex	$C_{max\ 0\text{-}24}$ (ng/mL)	$AUC_{0\text{-}24}$ (ng·hr/mL)
Day 1	2	10	10	M	893	5220
				F	632	4240
				MF	748	4730
	3	30	30	M	1940	13400
				F	1520	12100
				MF	1730	12800
	4	100	1 0	M	4340	25400
				F	3500	29800
				MF	3490	27600
	6	500	1000	M	1230	16900
				F	1530	24400
				MF	1220	20600
Day 91	2	10	10	M	1000	6280
				F	1420	6610
				MF	995	6490
	3	30	30	M	3060	18000
				F	4700	21400
				MF	3880	19900
	4	100	1 0	M	4650	40600
				F	4790	39200
				MF	4410	39900
	6	500	1000	M	1800	31700
				F	1890	33400
				MF	1780	32500

Table 7 Summary of the CCX168-M1 TK Parameters in Hamster Plasma

Interval	Group	Dose level (mg/kg/dose)	Dose level (mg/kg/day)	Sex	$C_{max\ 0\text{-}24}$ (ng/mL)	$AUC_{0\text{-}24}$ (ng·hr/mL)
Day 1	2	10	10	M	34.5	319
				F	22.9	230
				MF	28.7	274
	3	30	30	M	80.7	936
				F	50.6	849
				MF	65.7	893
	4	100	100	M	90.4	1450
				F	122	1730
				MF	97.0	1590
	6	500	1000	M	49.0	944
				F	102	1400
				MF	71.3	1170
Day 91	2	10	10	M	39.9	427
				F	35.1	352
				MF	36.4	389
	3	30	30	M	101	1300
				F	112	1170
				MF	102	1240
	4	100	100	M	186	2600
				F	159	2350
				MF	169	2480
	6	500	1000	M	133	2630
				F	110	2240
				MF	117	2430

For CCX168, there were no consistent sex difference in exposure. There were no significant increases in exposure between Day 1 and Day 91. The increases in CCX168 $C_{max0-24}$ and AUC_{0-24} values were generally dose proportional from 10 to 30 mg/kg/day and generally less than dose proportional from 10 to 100 mg/kg/day. The $C_{max0-24}$ and AUC_{0-24} levels at 100 mg/kg/day were slightly higher than those at 1000 mg/kg/day in all intervals including Day 1, Day 29 (not shown) and Day 91, suggesting the 100 mg/kg/day was the maximal exposure dose.

For CCX168-M1, there were no consistent sex difference in exposure. There were no significant increases in exposure between Day 1 and Day 91. The increases in CCX168-M1 $C_{max0-24}$ and AUC_{0-24} values were generally dose proportional from 10 to 30 mg/kg/day and generally less than dose proportional from 10 to 100 mg/kg/day. Similar to the parent, the $C_{max0-24}$ and AUC_{0-24} levels of CCX168-M1at 100 mg/kg/day were not lower than those at 1000 mg/kg/day in all intervals including Day 1, Day 29 (not shown) and Day 91, suggesting the 100 mg/kg/day was the maximal exposure dose. The CCX168-M1 metabolite to parent ratios based on C_{max} and AUC were comparable after both QD and BID dosing.

Dosing Solution Analysis

All homogeneity and concentration verification results met acceptance criteria. The homogeneity and concentration results were within or equal to ± 10% of theoretical concentration and each individual sample concentration result was within or equal to ± 15%, meeting specifications for concentration verification. The relative standard deviation (RSD) of each concentration was ≤ 5% for each group, meeting specifications for homogeneity. There were no significant peaks detected in the control samples.

8 Carcinogenicity

The following is a summary of the draft protocol of the two-year Golden Syrian hamster carcinogenicity submitted by the sponsor as part of SD #83.

Study Title: CCX168: 104 Week Oral (Gavage) Administration Carcinogenicity Study in the Hamster

Study no.:	PC0674_168 1001560 ((b) (4) Study No.)
Study report location:	NA
Conducting laboratory and location:	(b) (4)
Date of study initiation:	To be determined
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Information -17-043

Appropriateness of Test Models

The Golden Syrian hamster is an acceptable test system for the CCX168 carcinogenicity assessment as it is the only pharmacologically relevant rodent species.

Methods

Doses:	Group 1: 0 (PEG (b) (4)), Group 2: 0 (Control 2: purified water), Groups 3-5: 10, 30 and 100 mg/kg/day CCX168
Frequency of dosing:	QD
Dose volume:	5 mL/kg
Route of administration:	PO
Formulation/Vehicle:	Polyethylene glycol (b) (4) (b) (4) v:v]
Basis of dose selection:	Based on 3-month MTD study in hamster, reviewed elsewhere in this document. High dose selection based on saturation of exposure.
Species/Strain:	HsdHan:AURA Hamster (Syrian Golden), Harlan
Number/Sex/Group:	65/sex/group
Age:	<7-8 weeks old
Animal housing:	≤3 animals/cage
Paradigm for dietary restriction:	*Ad libitum* access to 5LF2 EU Rodent Diet
Dual control employed:	One water control and one vehicle control
Interim sacrifice:	TK satellite animals will be euthanized after the last sample collection on Week 26
Satellite groups:	3/sex/group control Group 1 satellite 9/sex/group satellite for Groups 3-5

Observations and Results

Mortality

Observe animal in cage twice daily to monitor health status throughout the dosing period.

Clinical Signs

Post dosing observations will be performed to characterize the nature and timing of reactions to treatment for all main study animals daily during the 1st week of dosing. Additional observations may be carried out as deemed necessary by the study director. All animals will be removed from cage for physical examination including palpation for tissue masses once weekly and on the day of terminal necropsy.

Body Weights

Individual body weight will be measured based on the following procedure.

Animal cohort	Frequency of observation
All animals	Day –7 (randomization body weight check). Once weekly from Day 1 (before dose) to Week 16 Once every 4 weeks from the start of Week 17 Once weekly from the start of Week 69 Week 105: Terminal body weight (only taken for animals necropsied)

Feed Consumption

At least once weekly from Week 1 to 16, and then at least one week in every 4 thereafter for all main study animals.

Ophthalmoscopy

The sponsor is planning to include ophthalmic examinations at weeks 26, 52, 78, and 104. The sponsor was advised that these examinations are not required for FDA (see ECAC Meeting Minutes dated 11/9/17).

Clinical Pathology

~0.6 mL of blood will be collected from abdominal aorta immediately prior to exsanguination from each main study animal at the terminal necropsy. Blood sample will be aliquoted into tubes with different anticoagulants: lithium heparin/serum for clinical chemistry; EDTA for hematology. Parameters to be measured are listed in the following table.

6.1.2.1 Hematology	
Hemoglobin concentration	Mean cell hemoglobin
Red blood cell count	Mean cell hemoglobin concentration
Packed cell volume	Red cell distribution width
Reticulocyte count	Platelet count
Mean cell volume	Total and differential white cell count
Blood smear (prepared only)[1]	
6.1.2.2 Clinical chemistry	
Aspartate aminotransferase	Total protein
Alanine aminotransferase	Albumin
Alkaline phosphatase	Globulin
Gamma glutamyl transferase	Albumin / globulin ratio

Sodium	Total cholesterol
Potassium	Glucose
Calcium	Urea
Inorganic phosphate	Total bilirubin
Chloride	Creatinine
Triglycerides	Creatinine kinase
Red blood cell count	Total and differential white cell count
Footnotes:	
1 Blood smears will be prepared from each hematology specimen then labelled, stained, stored and archived. Smears may be examined to confirm the hematology results. Any further requirements will be discussed with the sponsor.	

Toxicokinetics

Week 4: Blood samples for toxicokinetics will be collected from satellite animals during Week 4 at the following time points:
2 hours after dosing.

Week 26: Blood samples for toxicokinetics will be collected from Toxicokinetic animals during Week 26 at the following time points:
0 (pre-dose) and 1, 2, 4 and 7 hours after dosing.
Three animals/sex/group will be sampled at each time point. Individual animals to be sampled at each time point on each occasion will be documented in the study records.
Control animals will be sampled at the 2-hour time point only.

Gross Pathology

Early termination	Where survival approaches 25 animals in any one treatment group, early termination will be considered in consultation with the Sponsor. Males and females will be considered separately.
Method of termination (kill and discard for satellite animals)	Intraperitoneal injection of sodium pentobarbitone (overdose). Death will be confirmed by cervical dislocation and/or exsanguination.

Method of termination (main study animals for necropsy)	Isoflurane anesthesia. Once a suitable deep plane of anesthesia has been established, major blood vessels will be severed to exsanguinate the animal. If urgent euthanasia of an animal in extremis is necessary, the animal may be killed by intraperitoneal injection of sodium pentobarbitone (overdose) and death will be confirmed by cervical dislocation and/or exsanguination.
Macroscopic examination	Performed under the general supervision of a pathologist. All lesions will be recorded.
Organ weights	Dissected free from fat and other contiguous tissue prior to weighing.
Tissue preservation	Dissected free from fat and other contiguous tissue prior to fixation.
Processing and embedding	Tissues embedded in paraffin wax unless stated otherwise.
Microtomy and staining	Wax blocks sectioned at a nominal 5 µm and stained with hematoxylin and eosin unless stated otherwise.
Microscopic evaluation	Will be performed by the study pathologist

Histopathology

Peer Review: not included in the study plan

Organs and tissues from control and all main study groups will be collected, preserved, prepared and examined microscopically according to the table below. Where histopathology is performed, additional sections and stains may be requested by the Study Pathologist, to further characterize any observed findings.

Table 8 List of tissues to be collected, preserved, processed and examined microscopically

Tissue / organ				Tissue / organ			
Bone Marrow Smear (femur)				Skin/Subcutis (x1)	P		E
Brain (x6)	P		E	Mammary Gland (x1)	P		E
Spinal Cord, Cervical (x1)	P		E	Heart (x1)	P		E
Spinal Cord, Thoracic (x1)	P		E	Aorta (x1)	P		E
Spinal Cord, Lumbar (x1)	P		E	Muscle, Biceps Femoris (x2)	P		E
Adrenal (x2)	P		E	Kidney (x2)	P		E
Pituitary (x1)	P		E	Urinary Bladder (x1)	P		E
Nerve, Sciatic (x1)	P		E	Testis (x2)	P[4]		E
Eye (x2)	P[1]		E	Epididymis (x2)	P[4]		E
Nerve, Optic (x2)	P		E	Ovary (x2)	P		E
Harderian Gland (x2)	P[2]			Oviduct (x2)	P		
Thyroid (x2) and Parathyroid	P		E	Seminal Vesicle (x2)	P[5]		E
Trachea (x1)	P		E	Prostate (x1)	P		E

Oesophagus (x1)	P		E	Uterus (x3)	P[6]		E
Lung (x2)	P[3]		E	Vagina (x1)	P		E
Spleen (x1)	P		E	Femur + Marrow (x1)	P[7]		E
Thymus (x1)	P		E	Sternum + Marrow (x1)	P		E
Lymph Node, Mesenteric (x1)	P		E	Larynx (x1)			
Liver (x 2)	P		E	Lacrimal Gland (x2)			
Pancreas (x1)	P		E	Zymbal's Gland (x2)	P		
Stomach (x1)	P		E	Lymph Node, Bronchial (x1)			
Duodenum (x2)	P		E	Head (not processed)	P		
Jejunum (x1)	P		E	Nasal Cavity (x4)	P		
Colon (x1)	P		E	Nasopharynx (x2)	P		
Ileum (x1)	P		E	Nose/Nares (x1)	P		
GALT/Peyers patch (x1)	P		E	Lymph Node, Popliteal (x2)			
Caecum (x1)	P		E	Ureter (x2)			
Rectum (x1)	P		E	Dosing sites (variable)			
Mandibular Salivary Gland (x2)	P		E	Untreated skin site (x3)			
Sublingual Salivary Gland (x2)	P		E	Animal identification	P		
Parotid Salivary Gland (x1)				Gross lesions (variable)	P		E[8]
Lymph Node, Mandibular (x1)	P		E	Tissue masses (variable)	P		E
Tongue (x1)	P		E	Lymph Node, Axillary			
				Preputial/clitoral gland (x1)	P		E

Legend:
P = Tissues preserved; W = Organs weighed; E = Tissues processed and examined microscopically.
(xN) = number of sections for histopathology.
Footnotes:
1: Tissue taken into Davidson's fixative.
2: Preserved with the head (*in situ*) unless histopathological processing is required.
3: Tissue includes mainstem bronchi and bronchioles.
4: Tissue taken into Modified Davidsons fixative and processed to at least the block stage.
5: Tissue includes coagulating glands.
6: Tissue includes cervix.
7: Tissue includes femorotibial joint.
8: Gross lesions processed in accordance with current Histology Standard Operating Procedure
Additional information:
Fixative will be neutral buffered 10% formalin unless specified otherwise.
Left and right organs will be weighed together.
Bone tissue designated for histopathological examination will be decalcified using Kristenson's fluid.

Dosing Solution Analysis

Samples for dosing solution analysis will be collected on Day 1 (homogeneity analysis), Week 1, 4, 13, 26, 39, 52, 65, 78, 91 and 104 (concentration analysis). The achieved concentrations should meet the following criteria:
Concentration analysis: The mean % nominal concentration should be between 90 to 110% and with a relative standard deviation (RSD) ≤5.0%.

Homogeneity analysis: The mean % nominal concentration should be between 90 to 110% and with a relative standard deviation (RSD) ≤5.0%.

Evaluation

The reviewer's recommendations in terms of dose levels for the test articles are presented elsewhere in this review. The following comments will be conveyed to the sponsor:

- The proposed clinical pathology assessment in main study animals the terminal necropsy is not needed for the FDA.
- TK assessments is not required because all the proposed dose levels are the same as in the 3-month hamster study.
- The 7-day study, 13-week study, and 2-year carcinogenicity study in hamsters have been / will be conducted in three different test facilities. The carcinogenicity study may not be acceptable if the toxicity observed is significantly different.
- Based on the 3-month hamster study, non-test item-related mortality happened in about 5% of the total animal population. This is higher than most of the other rodent species. We recommend the sponsor to look at the historical data in the contract lab and adjust the group size if warranted.
- The Sponsor will be requested to contact the division prior to taking action if there are any issues with survival in the study.

11 Integrated Summary and Safety Evaluation

Chemocentryx has submitted an SPA request for a hamster study protocol to assess the carcinogenicity of the human C5aR antagonist, CCX168. Supporting studies included 7-day and 13-week hamster toxicology studies.

Genotoxicity studies evaluating CCX168 have been reviewed previously and the test item was found negative in all assays including in vitro bacterial mutagenicity (Ames test) and mammalian cell mutagenicity (mouse lymphoma forward-mutation assay) studies, as well as the in vivo rat bone marrow micronucleus study.

The effects of CCX168 on the immune system (T-cell dependent antibody response [TDAR]) were evaluated in both the 13-week rat general toxicity study, as well as a stand-alone 28-day rat study. The chronic non-human primate study also incorporated immunophenotypic and TDAR evaluations. There was no evidence of immune system toxicity or suppression that might impact the carcinogenicity studies.

The major metabolite CCX168-M1, identified in human plasma in clinical studies, constituted approximately 12% of total plasma exposure in humans and was also detected in nonclinical species including Golden Syrian hamster. The extent of plasma protein binding for CCX168 or its metabolite CCX168-M1 were measured in humans as well as other six species including Syrian hamsters. Both CCX168 and its metabolite CCX168-M1 were protein bound reversibly at >99.9% in plasma of all species tested.

In the 3-month toxicity study in hamster, animals received vehicle, 10, 30, 100 and 1000 (500 BID) mg/kg/day CCX168. No test item related adverse findings were identified throughout the 3-month dosing and 4-week recovery period. Test item-related findings were limited in a few parameters in clinical chemistry: Higher mean triglyceride concentration were observed in the male hamsters at 100 and 1,000 mg/kg/day and minimally higher mean alanine aminotransferase, aspartate aminotransferase and phosphorus were observed in the males at 1,000 mg/kg/day. No similar changes were noted in animals at the recovery period. These findings were not considered adverse due to low incidence/magnitude and lack of histopathological correlation. In conclusion, the administration of up to 1000 mg/kg/day of CCX168 for 3 months was well tolerated. No findings were observed that were judged likely to affect survival in a two-year

carcinogenicity study. However, the highest exposures were detected in animals at the 100 mg/kg/day. This results, together with the findings noted in the 7-day hamster DRF study, indicated that 100 mg/kg/day generated the maximal exposure for both CCX168 and CCX168-M1 metabolite. The no-observed-adverse- effect level (NOAEL) for general toxicity of CCX168 is determined as 100 mg/kg/day. Exposure values for CCX168 at the 100 mg/kg/day were C_{max} = 4,410 ng/mL, and AUC_{0-24} = 39,900 ng·hr/mL for combined sexes on day 91 of dose administration.

For the purposes of CCX168 dose selection for the two-year hamster carcinogenicity study, the sponsor selected the proposed doses for the two-year hamster carcinogenicity study based on data obtained from the 13-week hamster general toxicology studies. Due to lack of toxicity and the safety margin at the MTD (1000 mg/kg/day) was < 25-fold as projected in the following table, the sponsor selected 100 mg/kg/day as the high dose based on the saturation of absorption. This conclusion is justified based on the TK data from general toxicology studies with CCX168 as well as the sponsor's exploratory studies with varying formulations and dosing regimens. The proposed high dose of 100 mg/kg/day represents exposure margins of approximately 7- and 1-fold, respectively, compared to the human plasma AUC at the MHRD (30 mg b.i.d.) for CCX168 parent and CCX168-M1 metabolite in patients with AAV. The sponsor selected 10 and 30 mg/kg/day as low and mid-dose, respectively, because they were well spaced out to study dose relationship (2-3x AUC separation) and were unlikely to generate exposure overlap based on the results from the 3-month hamster study. The reviewer concurs with the sponsor's proposed dose levels for the two-year hamster carcinogenicity study.

Table 9 Mean CCX168 AUC_{0-24} Parameters in Rat and Hamster Studies and Margins Relative to Human Exposure with 30 mg CCX168 b.i.d.

Proposed Doses (mg/kg/day)	Hamster AUC (ng•hr/mL)		Phase I CL001_168 study (healthy volunteer), Day 7		Phase II CL002_168 study (patients), Day 85	
	CCX168	CCX168-M1	Margin Relative to CCX168	Margin Relative to CCX168-M1	Margin Relative to CCX168	Margin Relative to CCX168-M1
10	6490	389	3.5	0.2	1.2	0.1
30	19900	1240	10.8	0.8	3.5	0.4
100	39900	2480	21.6	1.6	7.1	0.9

*AUC in human: CL001 study (measured): 1846 ng.hr/ml for CCX168, 1598 ng.hr/ml for CCX168-M1; CL002 study (projected): 5638 ng.hr/ml for CCX168, 2780 ng.hr/ml for CCX168-M1

AUC in hamster: average of males and females at Day 91 in 13-week study.

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/s/

DONG ZHAO
11/14/2017

ANDREW C GOODWIN
11/14/2017
I concur

Appendix 4

IND 120784: ECAC meeting minutes (Dr. Karen Davis-Bruno, Dated in DARRTS November 9, 2017)

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Executive CAC Protocol Minutes
Date of Meeting: November 7, 2017

Committee: Karen Davis Bruno, PhD, OND IO, Chair
Paul Brown, PhD, OND IO, Member
Dan Mellon, PhD, DAAAP, Alternate Member
Timothy Robison, PhD, DPARP, Pharm Tox Team Leader
Andrew Goodwin, PhD, DPARP, Pharm Tox Supervisor (Acting)
Matthew Whittaker, PhD, DPARP, Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Standardized Study Data (December 2014) and the latest Study Data Technical Conformance Guide.

IND# 120784
Drug Name: CCX168
Sponsor: Chemocentryx

Background
Chemocentryx, Inc. is developing CCX168 as an orally administered, small molecule antagonist of the human complement 5a receptor (C5aR) for the treatment of patients with anti-neutrophil cytoplasmic autoantibody (ANCA) - associated renal vasculitis (AAV). CCX168 is pharmacologically active in humans, monkeys and hamsters, but not in rats or mice. CCX168-M1 is a pharmacologically active, hydroxyl-metabolite of the parent compound. M1 comprises >10% of total human exposure and is formed in both hamsters and rats. CCX168 was negative in the *in vitro* bacterial reverse mutation assay, *in vitro* mouse lymphoma forward-mutation assay, and *in vivo* rat bone marrow micronucleus study. Requests for Special Protocol Assessment (SPA) for proposed 2-year oral carcinogenicity studies to be conducted in Syrian hamsters and Sprague Dawley rats were submitted on October 10, 2017 and October 20, 2017, respectively.

Hamster Carcinogenicity Study Dose Selection
CCX168 dose selection is supported by the results of a 13-week toxicity study in Syrian hamsters (Study PC0677 168) that evaluated oral gavage doses of 0 (vehicle of PEG (b) (4)), 10, 30, 100, or 1000 (500 b.i.d.) mg/kg/day. There were no adverse effects observed at any dose tested. Toxicokinetic data indicated that there was a saturation of systemic exposure for CCX168 and its metabolite, CCX168-M1, at doses ≥ 100 mg/kg/day.

Chemocentryx is proposing to include both a vehicle control group (PEG (b) (4) (b) (4)) and a water-only control group in the 2-year carcinogenicity study. The vehicle composition is the same as that used in the 13-week toxicity study. The proposed high dose for

males and females in the 2-year hamster carcinogenicity study is 100 mg/kg/day. This dose will achieve maximal exposure (AUC) in male and female hamsters. Anticipated CCX168 exposure at the proposed high dose level for males and females is approximately 7-fold higher than projected steady state human exposures at the maximum clinical dose of 30 mg b.i.d. Anticipated CCX168-M1 exposure at the 100 mg/kg/day dose is approximately equivalent to the projected human CCX168-M1 exposure at the 30 mg b.i.d. dose. Doses of 10 and 30 mg/kg/day are proposed for the low and middle doses, respectively.

Rat Carcinogenicity Study Dose Selection

CCX168 dose selection is supported by the results of a 26-week toxicity study (Study PC0655 168) in Sprague Dawley rats that evaluated oral gavage doses of 0 (vehicle of PEG (b) (4)), 5, 15, 100, or 200 (100 b.i.d.) mg/kg/day. There were no adverse effects observed at any dose tested. Toxicokinetic data indicated that there was a saturation of systemic exposure for CCX168 at doses ≥ 100 mg/kg/day.

Chemocentryx is proposing to include both a vehicle control group (PEG (b) (4) (b) (4)) and a water-only control group in the 2-year carcinogenicity study. The vehicle composition is the same as that used in the 26-week toxicity study. The proposed high dose for males and females in the 2-year rat carcinogenicity study is 100 mg/kg/day. This dose will achieve maximal exposure in male and female rats. Anticipated CCX168 exposure at the proposed high dose level for males and females is approximately 11- and 15-fold higher, respectively, than projected steady state human exposures at the maximum clinical dose of 30 mg b.i.d. Anticipated CCX168-M1 exposure at the 100 mg/kg/day dose is approximately equivalent to the projected human CCX168-M1 exposure at the 30 mg b.i.d. dose. Doses of 10 and 30 mg/kg/day are proposed for the low and middle doses, respectively.

Executive CAC Recommendations and Conclusions

Hamster

- The Committee concurred with doses of 10, 30 and 100 mg/kg/day for males and females, with the high dose based on saturation of systemic exposure.
- The mid- and low-doses for both sexes were selected based on adequate spacing of AUC.
- The Committee concurred with vehicle-control (PEG (b) (4)) and water-only control groups.
- The Committee noted that the 2-year carcinogenicity study will be performed in a different facility with a different source of animals than used in the 13-week oral toxicity study. The carcinogenicity study may not be acceptable if toxicity is significantly different due to these changes such that dose selection would have been altered.
- The Committee noted that the use of toxicokinetic dose groups is not needed for FDA.
- The Committee noted that clinical pathology at the end of the study is not needed for FDA.
- The Committee noted that ophthalmoscopic examination is not needed for FDA.

Rat

- The Committee concurred with doses of 10, 30 and 100 mg/kg/day for males and females, with the high dose based on saturation of systemic exposure.
- The mid- and low-doses for both sexes were selected based on adequate spacing of AUC.

- The Committee concurred with vehicle-control (PEG [redacted] (b) (4)) and water-only control groups.
- The Committee noted that the 2-year carcinogenicity study will be performed in a different facility with a different source of animals than used in the 26-week oral toxicity study. The carcinogenicity study may not be acceptable if toxicity is significantly different due to these changes such that dose selection would have been altered.
- The Committee noted that the use of toxicokinetic dose groups is not needed for FDA.
- The Committee noted that clinical pathology at the end of the study is not needed for FDA.
- The Committee noted that ophthalmoscopic examination is not needed for FDA.

As a point of information, the S1A-S1C carcinogenicity study guidelines are a current topic of an expert working group (EWG) of the International Conference on Harmonization. For further information on the current status of the EWG's activities, and particularly the S1 concept paper, business plan, and regulatory notice document, please visit:
http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html

Karen Davis Bruno, PhD
Chair, Executive CAC

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/s/

KAREN L DAVIS BRUNO
11/09/2017

Appendix 5

IND 120784: Early termination criteria for 104-week carcinogenicity study with rats (Dr. Matthew Whittaker, Comments were conveyed on 08-13-2019, Dated in DARRTS August 22, 2019)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

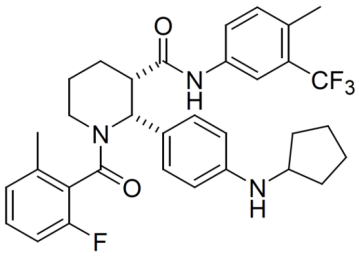
PHARMACOLOGY/TOXICOLOGY IND ASSESSMENT AND EVALUATION

Application Number*:	120784
Supporting Document Number/s:	210
CDER Receipt Date:	8/7/19
Sponsor:	Chemocentryx
Product:	CCX168
Pharmacologic Class:	Complement C5a receptor antagonist
Indication:	ANCA-associated vasculitis
Therapeutic area:	Allergy and Immunology
Review Division:	Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Reviewer:	Matthew Whittaker, Ph.D.
Supervisor/Team Leader:	Timothy Robison, Ph.D.
Division Director:	Sally Seymour, M.D.
Project Manager:	Brandi Wheeler
Purpose of Review:	Other Response to sponsor inquiry regarding termination of dose groups in rat carcinogenicity study
Reviewer Completion Date:	August 21, 2019

Template Version: May 23, 2019

Nonclinical Summary

Drug Information[+]

Type of Product:	Small molecule
Code/ Generic Name:	CCX168
Structure or Biochemical Description:	
Molecular Formula/ Molecular Weight:	581 g/mol

1 Background

1.1 Regulatory History

8/7/19 Chemocentryx submitted an inquiry to DPARP regarding the conduct of their ongoing 104-week carcinogenicity study in SD rats. The sponsor sought ECAC agreement on their proposed approach for early termination of selected treatment groups based on survival number.

11 Nonclinical Discussion

Chemocentryx provided a table of animal numbers at week 85 of their ongoing rat carcinogenicity study with CCX168 (Table 1).

Table 1. Sponsor-submitted table of animal numbers in ongoing rat carcinogenicity study with CCX168 – Week 85 Inlife Update (formatting of table adjusted by reviewer).

Group number	Male					Female				
	1[a]	2[b]	3	4	5	1[a]	2[b]	3	4	5
Dose (mg/kg/day)	0	0	10	30	100	0	0	10	30	100
No. of Animals at Study Initiation Carcinogenicity	57	57	57	57	57	57	57	57	57	57
TK (all terminated following final collection)	3	0	9	9	9	3	0	9	9	9
Current Main Study Survival (Number)	38	33	34	42	44	**26**	39	32	34	30

[a] Control group (Group 1) administered vehicle (polyethylene glycol-(b) (4) (formerly (b) (4))

[b] Control group (Group 2) administered water

Sponsor proposal

- At this time, ChemoCentryx proposes (b) (4)
- (b) (4) **Does the eCAC agree with this proposal?**

Division response

Based on the established early termination procedures defined by the CDER Executive Carcinogenicity Assessment Committee (ECAC), the following response was prepared by the Division in collaboration with all current members of the ECAC:

We have reviewed your submission on 8/5/19 pertaining to your ongoing carcinogenicity study with CCX168 in Sprague-Dawley rats. The ECAC does not agree with your proposal. We have the following comments to address the specific circumstances in your ongoing study.

(1) Once the survival number in Group 1 females declines to 20, all females (including drug-treated) on the study should be terminated.
(2) For animals in drug-treated groups:
    a. If the survival number in a particular group & sex declines to 15 prior to week 100, only animals of that group & sex should be terminated.

b. If the survival number in a particular group & sex declines to 15 at week 100 or later, all groups of a sex (including controls) should be terminated.

The response was submitted to Chemocentryx on 8/14/19. Chemocentryx informed the Division that they accepted the Agency's recommendations on 8/19/19.

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/s/

MATTHEW T WHITTAKER
08/22/2019 09:20:54 AM

TIMOTHY W ROBISON
08/22/2019 09:48:25 AM
I concur

Appendix 6

NDA 214487: ECAC meeting minutes (Dr. Karen Davis-Bruno, Dated in DARRTS, February 25, 2021)

Executive CAC Final Study Minutes
Date of Meeting: February 23, 2021

Committee: Karen Davis Bruno, PhD, OND IO, Chair
Paul Brown, PhD, OND IO, Member
Tim McGovern, PhD, OND IO, Member
Ron Wange, PhD, OND IO, Member
Eleni Salicru, PhD, DPT-II, Alternate Member
Timothy Robison, PhD, DABT, DPT-II, Pharm/Tox Team Leader
Ijeoma Uzoma, PhD, DPT-II, Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

Application Type and Number(s): NDA 214487
Drug Name: Avacopan (CCX168) capsule
Sponsor: ChemoCentryx

Background
CCX168 is a small molecule antagonist of complement component 5a receptor (C5aR), that is being developed as an oral treatment for adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis.

CCX168 was negative in all genotoxicity assays including in vitro bacterial mutagenicity study (Ames test), in vitro mammalian cell mutagenicity study (mouse lymphoma forward-mutation assay), and in vivo rat bone marrow micronucleus study.

The Applicant conducted 2-year oral rat and hamster carcinogenicity studies with CCX168.

Hamster Carcinogenicity Study
In the 2-year carcinogenicity study, Syrian Golden hamsters received CCX168 (avacopan) by oral gavage at doses of 0 (vehicle control: PEG [(b) (4) v:v]), 0 (water control), 10, 30, and 100 mg/kg/day.

Hamsters were determined to be a pharmacologically relevant species.

Prior concurrence for doses used in this study was obtained from the Executive Carcinogenicity Assessment Committee.

A potential vehicle-related effect on survival occurred for male vehicle-control and drug-treated groups. This did not appear to impact the ability of the study to assess the carcinogenic potential of CCX168 as males were treated up to Week 98 and females up to Week 92.

There were no CCX168-related neoplastic findings in either male or female hamsters.

Rat Carcinogenicity Study
In the 2-year carcinogenicity study, Sprague Dawley rats received CCX168 (avacopan) by oral gavage at doses of 0 (vehicle control: PEG (b) (4) [(b) (4) v:v]), 0 (water control), 10, 30, and 100 mg/kg/day.

The rat is not a pharmacologically relevant species.

Prior concurrence for doses used in this study was obtained from the Executive Carcinogenicity Assessment Committee.

Treatment with CCX168 had no effects on survival in male or female rats up to 97 and 92 weeks, respectively.

There were no CCX168-related neoplastic findings in either male or female rats.

Toxicokinetic analysis conducted on Day 28 indicated that the Cmax and AUC0-24 exposure decreased from 30 (MD) to 100 mg/kg/day (HD) such that the highest systemic exposures were achieved in the mid-dose group at 30 mg/kg/day. Therefore, to assess the relationship of findings to treatment with CCX168, the 30 mg/kg/day group was also analyzed as the high dose group.

Executive CAC Conclusions
Hamster:

- The Committee concurred that the two-year hamster study was adequate, noting prior Exec CAC approval of the protocol.
- The Committee determined that there were no drug-related neoplasms in the 2-year hamster study in either males or females.

Rat:

- The Committee concurred that the two-year rat study was adequate, noting prior Exec CAC approval of the protocol.
- The Committee determined that there were no drug-related neoplasms in the 2-year rat study in either males or females.

Karen Davis Bruno, PhD
Chair, Executive CAC

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/s/

ROBEENA M AZIZ
02/25/2021 11:12:38 AM

KAREN L DAVIS BRUNO
02/25/2021 11:24:21 AM

Appendix 7

IND 120784: Review of Pharmacology and TK/ADME studies (Dr. Timothy W. Robison, Dated in DARRTS March 1, 2021)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND ASSESSMENT AND EVALUATION

Application Number*:	120784
Supporting Document Number/s:	7
CDER Receipt Date:	June 16, 2014
Sponsor:	ChemoCentryx, Inc.
Product:	Avacopan
Pharmacologic Class:	"Complement 5a receptor (C5aR) Antagonist"
Indication:	Treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA])
Therapeutic area:	Rheumatology
Clinical Review Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Pharm/Tox Division	Division of Pharm/Tox for Immunology and Inflammation (DPT-II)
Reviewer/Team Leader:	Timothy W. Robison, Ph.D., D.A.B.T
Project Manager:	Susie Choi
Purpose of Review:	Study Report Review
	Click here to enter text.
Alternative Assays:	Click here to enter text.
Reviewer Completion Date:	Click here to enter a date.

Template Version: Sep 11, 2020

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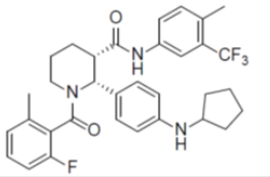
Executive Summary (Clinical Relevance)

Nonclinical Summary

Drug Information+

Type of Product:	Small molecule
Code/ Generic Name:	Avacopan (CCX-168)
Chemical Name (optional):	3-Piperidinecarboxamide, 2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]-, (2R,3S)-
CAS# or UNII (if available):	CAS:1346623-17-3 UNII:Click here to enter text.
Structure or Biochemical Description:	Avacopan Drug Substance Structural Formula 
Molecular Formula/ Molecular Weight:	$C_{33}H_{35}F_4N_3O_2$ / 581.6435 Da
Proposed 505(b)(2): If Yes, Listed Drug:	N Click here to enter text.
Biosimilar: If Yes, Reference Product:	N Click here to enter text.

Pharmacology/ Toxicology Summary *(Tables may be modified/ deleted)*

Pharmacology (primary & secondary/ MoA)

Key Findings:

CCX168 and its metabolite, CCX168-M1, are antagonists of C5a binding to its receptor, C5aR. Humans, monkeys, and hamsters were determined to be pharmacologically relevant species. C5aR displays a relatively low level of amino acid sequence conservation between species. The rodent versions of C5aR are only ~70% identical to human C5aR, with many amino acid changes occurring in the transmembrane and extracellular regions important for C5a binding. One trans-membrane domain residue, a tryptophan in transmembrane domain 5, was identified as crucial for C5a receptor antagonist binding in gerbil (Waters et al, 2005), and appears to contribute to the species-specific activity observed with small-molecule inhibitors of C5a receptors, since the amino acid is conserved with human, cynomolgus monkey, and hamster C5aR, but not other commonly used nonclinical animal species including mice, rats, rabbits, and dogs. Mice, rats, rabbits, and dogs were determined to not be pharmacologically relevant species.

PK/ ADME/ TK:

Key Findings:

Metabolite profiling study in Sprague-Dawley rats following with oral administration of [^{14}C]-CCX168

- CCX168 was well absorbed and extensively metabolized after oral administration. Most of the radioactive dose was recovered in feces in the form of numerous metabolites.
- Urine was a minor route of elimination for the radioactive dose; the amount of intact drug in urine was negligible.
- The extent of absorption was estimated to be ~80%. The recovered parent drug in feces accounted for approximately 20% of the total dose.
- CCX168 was the most abundant component in rat plasma, accounting for 50 – 65% of total plasma radioactivity.
- Seven metabolites were detected in the plasma samples. Mono-oxidation metabolite M1 was the most abundant, accounting for 9.24% - 15.0% of the total plasma radioactivity.
- The remaining metabolites were minor, present at <10% of the total plasma radioactivity.
- No significant covalent plasma protein binding was indicated because extraction recovery from plasma samples was high.
- Metabolism, rather than direct renal and biliary elimination of the intact drug, was the dominant route of CCX168 elimination. The primary route of elimination of the metabolites was through biliary excretion into feces.
- 33 and 25 components were found in male and female rats, respectively. The major metabolic pathways were oxidation and de-alkylation of CCX168.

Metabolite profiling study in Cynomolgus monkeys with oral administration of [^{14}C]-CCX168 to cynomolgus monkeys:

- CCX168 was extensively metabolized in cynomolgus monkeys. Multiple components were observed in monkey plasma. The parent compound only accounted for 12.7% of total radioactivity in plasma. M1, a mono-oxidation metabolite, accounted for 12.8% of the plasma radioactivity. Unknown polar metabolites contributed to 26.1% of the plasma radioactivity.
- Nearly all of the CCX168-related materials in plasma and feces were extractable from pooled samples across time points, suggesting no major reactive metabolites were involved.
- Fecal elimination was the primary route of elimination for the radioactive dose while urine elimination was minimal.
- Metabolism, rather than direct renal and biliary elimination of the intact drug, was the dominant route of CCX168 elimination. The primary route of elimination of the metabolites was through biliary excretion into feces.
- 25 components were found in plasma, urine or feces. Most of the metabolites were products of oxidation and/or de-alkylation of CCX168.

1 Background

1.1 Regulatory History

A Pre-IND meeting was held with the Sponsor. See preliminary comments and final meeting minutes dated April 17, 2014 and May 20, 2014, respectively.

1.2 Relevant INDs, NDAs, BLAs or DMFs

IND 120784
NDA 214487

1.3 Previous Reviews Referenced

Application	Reviewer	Date in DARRTS	Notes
IND 120784	Matthew Whittaker	11-09-2017	Review of 6-month toxicology study with rats
IND 120784	Dong Zhao	11-14-2017	Review of 13-week toxicology study with hamsters
IND 120784	Stephanie J Quinn	11-09-2017	ECAC meeting minutes
IND 120784	Matthew Whittaker	08-22-2019 (Comments were conveyed on 08-13-2019)	Early termination criteria for 104-week carcinogenicity study with rats

3 Studies Submitted

3.1 Studies Reviewed

Primary Pharmacology:

- IN VITRO ACTIVITY OF C0335273 AGAINST MOUSE, RAT, RABBIT AND CYNOMOLGUS MONKEY C5AR (Study Report No. PC0484_168_a)
- In Vitro Effects of CCX168 and CCX168-M1 on Hamster and Rabbit C5aR (Study Report No. PC0627_168_a)

Secondary Pharmacology:

- CHEMOKINE RECEPTOR SELECTIVITY OF CCX168 (Study number: PC0348-168b)
- ACTIVITY OF CCX168 ON GLUCOCORTICOID RECEPTOR (Study number: PC464-168)
- BIOCHEMICAL SELECTIVITY PROFILE OF C0335273 (CCX168-M1; Study number: PC0486-1680

Pharmacokinetics/ADME/Toxicokinetics:

- Hamster Pharmacokinetic and Formulation Tolerability Study Following Oral Administration of CCX168 (PC0646-168)
- IN VITRO BLOOD / PLASMA PARTITIONING OF CCX168 (MOUSE, RAT, DOG, AND HUMAN) AND EFFECT ON DEPENDENT PK CHARACTERISTICS IN MICE, RATS AND DOGS (PC0364-168a)
- EVALUATION OF BINDING OF CCX168 AND METABOLITE CCX168-M1 TO HUMAN ALBUMIN (PC0681-168)
- EVALUATION OF BINDING OF CCX168 AND METABOLITE CCX168-M1 TO HUMAN α1-ACID GLYCOPROTEIN (AAG) (Study Report No. PC0685_168)
- METABOLITE PROFILING OF CCX168 IN IN VITRO SYSTEMS OF VARIOUS SPECIES (Study Report No. PC0369_168)
- METABOLITE FORMATION FOLLOWING INCUBATION OF CCX168 WITH RAT LIVER S9 (Study Report No. PC0488_168)
- METABOLITE PROFILING IN SPRAGUE-DAWLEY RATS DOSED WITH [14C]-CCX168 (Study Report No. PC0641_168_a):
- METABOLITE PROFILING IN CYNOMOLGUS MONKEYS DOSED WITH [14C]-CCX168 (Study Report No. PC0645_168_a)

4 Pharmacology

4.1 Primary Pharmacology

Mechanism of action

IN VITRO ACTIVITY OF C0335273 AGAINST MOUSE, RAT, RABBIT AND CYNOMOLGUS MONKEY C5AR (Study Report No. PC0484_168_a): C0335273 is a putative metabolite of CCX168 designated as CCX168-M1. Certain leukocytes, including neutrophils and monocytes, express C5aR, which mediates their chemotaxis to and activation by the anaphylotoxin, C5a. C5aR displays a relatively low level of amino acid sequence conservation between species. The rodent versions of C5aR are only ~70% identical to human C5aR, with many amino acid changes occurring in the transmembrane and extracellular regions important for C5a binding. The present study evaluated the potencies of C0335273 on C5aR from mice, rats, rabbits and cynomolgus monkeys. Chemotaxis assays were performed with primary immune cells from each species. Leukocytes were isolated from peripheral blood of cynomolgus monkeys and rabbits. For C57BL/6 mice or Sprague-Dawley rats, a 3% aqueous solution of thioglycolate was injected into the peritoneal cavity to elicit primary macrophages and neutrophils.

hC5a induced chemotaxis of neutrophils in cynomolgus blood (EC_{50} value of ~0.05 nM); C0335273 caused a rightward shift in the dose-response curve of hC5a in the assay, exhibiting an A2 value of 1 nM. A repeat of the assay using isolated Cynomolgus monkey leukocytes in 100% cynomolgus plasma and C0335273 caused a rightward shift in the dose-response curve of C5a in this assay, also exhibiting an A2 value of 2.6 nM. mC5a induced chemotaxis of elicited mouse leukocytes in 100% mouse plasma (EC_{50} value of

0.1 nM); however, addition of 10 µM C0335273 had no effect suggesting that it was not an antagonist of mouse C5aR. Similarly, mC5a induced chemotaxis of elicited rat leukocytes in 100% rat plasma (EC50 value of 2 nM), but addition of 1 µM C0335273 had no effect on the C5a dose-response curve, indicating that it was not an antagonist of rat C5aR. C5a induced chemotaxis of isolated rabbit leukocytes in normal chemotaxis buffer (EC_{50} value of 0.05 nM), but addition of C0335273 (500 nM) had no effect on the C5a dose-response curve, indicating that it was not an antagonist of rabbit C5aR. C0335273 inhibited cynomolgus monkey C5aR with a potency (A2 value) of 2.6 nM nM; however, C0335273 did not inhibit mouse, rat, or rabbit C5aR.

Table 1 Summary of C0335273 Potencies Against Mouse, Rat, Rabbit and Cynomolgus Monkey C5aR

Table 1: Summary of C0335273 Potencies Against Mouse, Rat, Rabbit and Cynomolgus Monkey C5aR

Species	*Cell Type*	*Buffer*	*Inhibition of Chemotaxis (A_2 value)*
Mouse	Thioglycollate-elicited peritoneal lavage leukocytes	100% plasma	>1000 nM
Rat	Thioglycollate-elicited peritoneal lavage leukocytes	100% plasma	>1000 nM
Rabbit	Blood Leukocytes	Chemotaxis buffer (HBSS)	>500 nM
Cynomolgus	Blood Leukocytes	Whole blood or 100% plasma	2.6 nM

In Vitro Effects of CCX168 and CCX168-M1 on Hamster and Rabbit C5aR (Study Report No. PC0627_168_a): One trans-membrane domain residue, a tryptophan in transmembrane domain 5, was identified as crucial for C5a receptor antagonist binding in gerbil (Waters et al, 2005), and appears to contribute to the species-specific activity observed with small-molecule inhibitors of C5a receptors, since the amino acid is conserved with human, cynomolgus monkey, and hamster C5aR, but not other commonly used nonclinical animal species including mice, rats, rabbits, and dogs. A series of in vitro experiments characterized the activity of CCX168 and its metabolite CCX168-M1 in hamster and rabbit cells. Hamster and rabbit whole blood were either used directly in the chemotaxis assay or else leukocytes were isolated.

Both CCX168 and CCX168-M1 displaced the binding of [^{125}I]-C5a to freshly isolated hamster leukocytes with similar sub-nanomolar potencies. CCX168 competed [^{125}I]-C5a from hamster C5aR with an IC_{50} of 0.9 nM, and the CCX168-M1 competed for hamster C5aR binding with an IC_{50} of 0.3 nM.

CCX168 was tested for its ability to block C5a-induced chemotaxis of hamster leukocytes in a whole blood migration assay. Since blood contains a large number of leukocytes, and since a large number of these cells express functional C5aR, C5a causes chemotaxis of

leukocytes in this assay. C5a induced chemotaxis of leukocytes in hamster blood, and conducting this assay in the presence of CCX168 (100 nM or 1,000 nM) caused a rightward shift in the dose-response curve of C5a in this assay, exhibiting a potency (A2 value) of 14 nM. The assay was repeated using isolated hamster leukocytes in chemotaxis buffer with a measured CCX168 potency of 3 nM.

When CCX168-M1 was similarly tested for its ability to block C5a-induced chemotaxis of hamster leukocytes in a whole blood migration assay, CCX168-M1 caused a rightward shift in the dose-response curve of C5a in this whole blood assay with a potency (A2) of 10 nM. When the assay was repeated using isolated hamster leukocytes in chemotaxis buffer, CCX168-M1 caused a rightward shift in the dose-response curve of C5a with a potency (A2) of 5 nM.

CCX168 and CCX168-M1 were tested for their ability to block C5a-induced chemotaxis of rabbit leukocytes in a whole blood migration assay. In this experiment, CCX168 and CCX168-M1 were tested at concentrations of 1,000 nM and 10,000 nM, in contrast to the 500 nM used previously. CCX168 and CCX168-M1 caused a rightward shift in the dose-response curve of C5a with potencies (A2) of 4,000 nM and 3,000 nM, respectively.

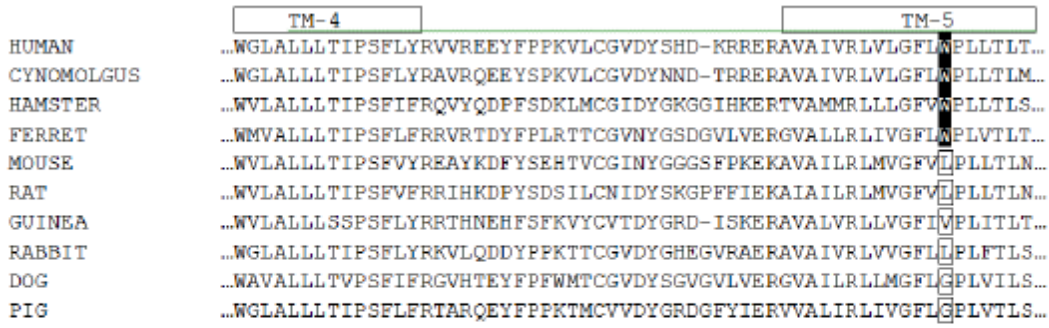
Table 2 Summary of CCX168 and CCX168-M1 Potencies against Hamster and Rabbit C5aR

Table 1: Summary of CCX168 and CCX168-M1 Potencies against Hamster and Rabbit C5aR

Assay	Cell type	CCX168	CCX168-M1 (C0335273)
Radioligand binding	Hamster leukocytes	IC_{50} = 0.9 nM	IC_{50} = 0.3 nM
Chemotaxis	Hamster leukocytes	A_2 = 3 nM	A_2 = 5 nM
Chemotaxis	Hamster leukocytes in whole blood	A_2 = 14 nM	A_2 = 10 nM
Chemotaxis	Rabbit leukocytes in whole blood	A_2 = 4,000 nM	A_2 = 3,000 nM

Figure 1 Alignment of C5aR amino acid sequences from ten species

Figure 1: Alignment of C5aR amino acid sequences from ten species



Sequence alignment of amino acids from ten C5aR orthologs is shown, focused on the region from trans-membrane region 4 (TM4) to trans-membrane region 5 (TM5). A tryptophan amino acid (W) - highlighted in TM5 in human, cynomolgus, hamster, and ferret sequences - has been found to be important for antagonist potency.

4.2 Secondary Pharmacology

<u>CHEMOKINE RECEPTOR SELECTIVITY OF CCX168</u> (Study number: PC0348-168b): The C5aR antagonist CCX168 was evaluated by chemotaxis, radioligand binding, and receptor signaling assays for its effects on other chemokine and related receptors. Cells or cell lines used were as follows: human neutrophils and lymphocytes and THP-1, MOLT-4, U937, L1.2, and Baf3 cell lines. Assessments includes chemotaxis assays, calcium mobilization assays, and radioligand binding assays. CCX168 exhibited no significant cross reactivity against CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CCR12, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, CXCR7, C5L2, C3aR, ChemR23, GPR1 or FPR. IC_{50} values were ≥6700 nM.

ACTIVITY OF CCX168 ON GLUCOCORTICOID RECEPTOR (Study number: PC464-168): The C5aR antagonist CCXI 68 was evaluated in a human glucocorticoid radioligand binding assay using Human Hela 53 cells with 3 nM [^{3}H] Dexamethasone. No significant effects were noted at the screening concentration of 10 µM.

BIOCHEMICAL SELECTIVITY PROFILE OF C0335273 (CCX168-M1; Study number: PC0486-168): C0335273 has been proposed as a metabolite of CCX168, a small molecule antagonist of the human C5a receptor (hC5aR). C0335273 was evaluated against a panel of 73 pharmacologically relevant receptors and membrane-associated proteins, including a selection of 17 chemokine or related receptors. IC_{50} exceeded 10 µM.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Disproportional Metabolite(s): N
Unique Human Metabolite(s): N

Summary of PK/ADME

Absorption

Hamster Pharmacokinetic and Formulation Tolerability Study Following Oral Administration of CCX168 (PC0646-168):

Methods: Administration of CCX-168 by oral gavage to male and female hamsters and subsequent systemic exposures were assessed using 12 vehicles. Doses ranged from 50 to 300 mg/kg/day using male and female hamsters. For BID dosing, doses were separated by 8 hours. A study with pregnant hamster was also conducted with administration from GDs 6 to 12. Blood samples were collected at time points ranging from 0.5 to 24 hours postdose. Plasma samples were analyzed for CCX168 and CCX168-M1.

Results: Maximum systemic exposures to CCX168 and metabolite CCX168-M1 were achieved when CCX168 was formulated in PEG (b) (4) (v/v (b) (4)). No significant gender differences were noted following administration of 100 mg/kg/day. Administration of 100 mg//kg/day (either 100 mg/kg QD or 50 mg/kg BID) was associated with the maximum systemic exposures achieved in this study. Increasing the dose to 300 mg/kg/day led to a decrease in systemic exposure to CCX168 and CCX168-M1.

Table 3 Summary of Selected Toxicokinetic Parameters of CCX168 and CCX168-M1 in Hamsters following a Single Oral Dose

Text Table 13
Summary of Selected Toxicokinetic Parameters of CCX168 and CCX168-M1 in Hamsters Following a Single Oral Dose

Group	Dose (mg/kg/day)	Formulation[a]	CCX168 $AUC_{0\text{-}24hr}$ (ng•hr/mL)	CCX168-M1 $AUC_{0\text{-}24hr}$ (ng•hr/mL)	CX168 C_{max} (ng/mL)	CCX168-M1 C_{max} (ng/mL)
1	100	a	37,400	3,060	4,260	280
2	300	b	20,700	1,500	2,090	75
3	100	a	26,800	1,880	3,780	142
4	300	b	18,400	1,430	1,000	79
5[e]	100	a	39,900	3,370	4,490	260
6[e]	100	a	24,400	2,460	2,000	119
7	100	c	4,660	648	320	32
8	100	d	14,900	1,570	1,260	100
9	50	a	28,900	2,430	3,280	224
10[f]	100	a	42,700	4,470	5,600	325
11[f]	200	a	30,100	2,820	4,170	166

[a] PEG (b) (4) (v/v (b) (4)).
[b] PEG (b) (4) Cremophor (v/v (b) (4)).
[c] (b) (4)
[d] PEG (b) (4)
[e] Animals is dose groups 5 and 6 were males; all other dose groups employed female animals.
[f] Dose regimens of 50 BID. and 100 BID. were employed for dose groups 10 and 11 respectively. All other dose groups were administered CCX168 QD.

Distribution

IN VITRO BLOOD / PLASMA PARTITIONING OF CCX168 (MOUSE, RAT, DOG, AND HUMAN) AND EFFECT ON DEPENDENT PK CHARACTERISTICS IN MICE, RATS AND DOGS (PC0364-168a)

Methods: This study assessed partitioning of CCX168 and C0335273 (the reference material for metabolite CCX168-M1 (also abbreviated as M1)) into red blood cells of several species (human, mouse, and rat) by incubating the test compound (final concentration of 5 µM) in fresh blood and an equivalent amount of reference plasma in duplicate for 60 minutes at 37°C. Samples were analyzed by LC-MS/MS.

Results The blood to plasma ratios for CCX168 and C0335273 (the reference material for metabolite M1) in all species tested are less than 1, suggesting that both compounds have limited penetration into red blood cells. The blood clearance and volume of distribution values of CCX168 in mice, rats and dogs were also calculated based on the corresponding plasma parameters and the blood to plasma ratios; both PK parameters were moderately higher than the corresponding plasma parameters.

Table 4 Blood Partitioning Values for CCX168

Table 1: Average Blood Partitioning Values for CCX168
(n=2; Study No. 09_BP_001)

Species	H (hematocrit)	$K_{RBC / PL}$	$K_{B / PL}$
Human	0.518	0.424	0.702
Mouse	0.508	0.452	0.722
Rat	0.553	0.600	0.779
Dog	0.465	0.267	0.659

Table 5 Blood Partitioning Values for C0335273

Table 2: Average Blood Partitioning Values for C0335273
(n=2; Study Nos. 10_BP_006, 10_BP_007, and 10_BP_008)

Species	H (hematocrit)	$K_{RBC / PL}$	$K_{B / PL}$
Human	0.47	0.30	0.67
Rat	0.30	0.76	0.93
Dog	0.48	0.37	0.70

Table 6 Estimated Pharmacokinetic Parameters from Partitioning Values for CCX168

Table 3: Estimated Pharmacokinetic Parameters from Partitioning Values for CCX168

Species	$K_{B/PL}$	CL_P (ml/min/kg)	CL_B (ml/min/kg)	MRT (h)	Estimated V_{ss} (L/kg)	[5]Q_H (mL/min/kg)	Estimated ER
Mouse	0.722	26.6	36.8	0.9	2.0	90	0.41
Rat	0.779	21.2	27.2	1.4	2.3	55.2	0.49
Dog	0.659	11.9	18.1	6.4	6.9	30.9	0.59

EVALUATION OF BINDING OF CCX168 AND METABOLITE CCX168-M1 TO HUMAN ALBUMIN (PC0681-168)

Methods: This study evaluated the binding of CCX168 and metabolite CCX168-M1 to human albumin. An equilibrium dialysis method was used with a 4-hour equilibration at

37°C. Samples were analyzed using LC-MS/MS to determine the bound and free concentrations by quantification against a standard curve.

Results: Both CCX168 and metabolite CCX168-M1 at 5 µM and 10 µM were found to be bound to human albumin at 99.9% or greater. The corresponding unbound fraction (fu) was 0.1% or lower.

Table 7 In vitro Albumin Binding (% bound) and Fraction Unbound (fu) Results of CCX168 and Metabolite CCX168 M1 after 4-hour Equilibrium Dialysis Incubation

Table 3: In vitro Albumin Binding (% bound) and Fraction Unbound (f_u) Results of CCX168 and Metabolite CCX168 M1 after 4-hour Equilibrium Dialysis Incubation

Compound ID		Test Article Concentration: 5 µM		Test Article Concentration: 10 µM	
		% Bound	f_u	% Bound	f_u
CCX168	Average	>99.9%	<0.1%	>99.9%	<0.1%
	SD	N/A	N/A	N/A	N/A
CCX168-M1	Average	99.9%	0.1%	99.9%	0.1%
	SD	0.01%	0.01%	0.004%	0.004%
Warfarin	Average	99.1%	0.9%	99.1%	0.9%
	SD	0.04%	0.04%	0.11%	0.11%

EVALUATION OF BINDING OF CCX168 AND METABOLITE CCX168-M1 TO HUMAN α1-ACID GLYCOPROTEIN (AAG) (Study Report No. PC0685_168)

Methods: This study evaluated of the binding of CCX168 and metabolite CCX168 M1 to human α1-acid glycoprotein (AAG). A standard equilibrium dialysis method was used with a 4-hour equilibration at 37 °C. Samples were analyzed using LC-MS/MS to determine the bound and free concentrations by quantification against a standard curve.

Results: CCX168 at 5 µM and 10 µM was bound to human AAG at >99.9%. The corresponding unbound fraction (fu) was <0.1%. Metabolite CCX168-M1 at 5 µM and 10 µM bound to human AAG at approximately 99%. The corresponding unbound fraction (fu) was approximately 1%.

Table 8 In vitro α1-Acid Glycoprotein Binding (% bound) and Fraction Unbound (fu) Results for CCX168 and Metabolite CCX168-M1 after 4-hour Equilibrium Dialysis Incubation

Table 3: In vitro α1-Acid Glycoprotein Binding (% bound) and Fraction Unbound (f_u) Results for CCX168 and Metabolite CCX168-M1 after 4-hour Equilibrium Dialysis Incubation

Compound ID		Test Article Concentration: 5 µM		Test Article Concentration: 10 µM	
		Bound	f_u	Bound	f_u
CCX168	Average	>99.9%	<0.1%	>99.9%	<0.1%
	SD	N/A	N/A	N/A	N/A
CCX168-M1	Average	99.3%	0.7%	98.9%	1.1%
	SD	0.045%	0.045%	0.077%	0.077%
Verapamil	Average	87.5%	12.5%	85.9%	14.1%
	SD	0.51%	0.51%	1.67%	1.67%

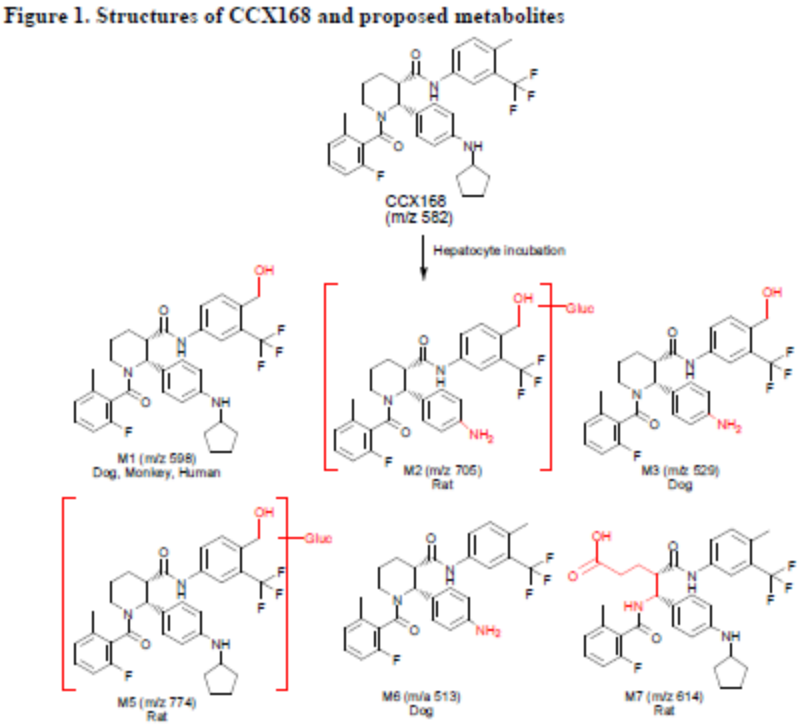
Metabolism

METABOLITE PROFILING OF CCX168 IN IN VITRO SYSTEMS OF VARIOUS SPECIES (Study Report No. PC0369_168)

Methods: This study compared the in vitro metabolite profiles of CCX168 following incubation with cryo-preserved hepatocytes from rats, dogs, monkeys and humans, and to identify the key metabolites. Incubations were carried out at a CCX168 concentration of 20 µM at 37ºC for 24 hours and were analyzed by LC-MS/MS.

Results: Only one metabolite (M1) was observed after incubation of CCX168 with human or cynomolgus monkey cryo-preserved hepatocytes. This metabolite was also observed in dog hepatocyte incubation. The metabolite was not observed in the rat hepatocyte incubation; however, several other metabolites were observed. MS/MS analysis suggested that M1 was attributed to hydroxylation of the benzylic position in the trifluoromethyl aniline moiety of CCX168.

Figure 2 Structures of CCX168 and proposed metabolites



METABOLITE FORMATION FOLLOWING INCUBATION OF CCX168 WITH RAT LIVER S9 (Study Report No. PC0488_168)

Methods: This study evaluated the formation of selected metabolites of CCX168 following incubation in Aroclor 1254-induced rat liver S9 fraction, which is routinely used as an exogenous metabolic activation system for the evaluation of mutagenicity of xenobiotics in the Ames test. The final concentrations of 0.2 and 2 µM CCX168 were incubated with induced rat liver S9 at 0.5 mg/mL protein concentration at 37°C for up to 4 hours. Aliquots of the incubation were analyzed for CCX168 turnover and formation of selected CCX168 metabolites (CCX168-Ml and CCX168-M6) by LCMS/MS.

Results: CCX168 is rapidly metabolized when incubated with Aroclor-1254 induced rat liver S9, and metabolites CCX168-M1 and CCX168-M6 are also formed rapidly, reaching maximum levels at 30 minutes.

Figure 3 CCX168 Turnover in 0.2 and 2 µM CCX168 Incubation with Aroclor-1254 Induced Rat Liver S9

Figure 1. CCX168 Turnover in 0.2 and 2 µM CCX168 Incubation with Aroclor-1254 Induced Rat Liver S9

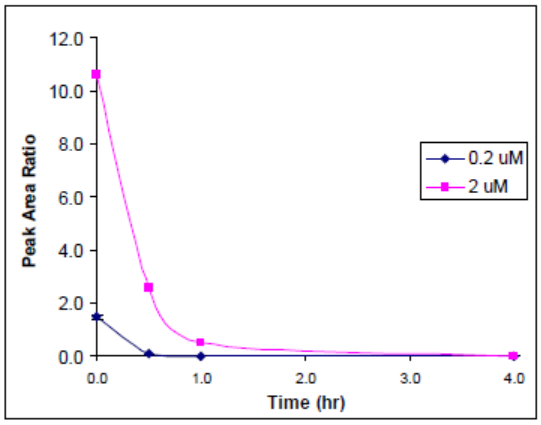
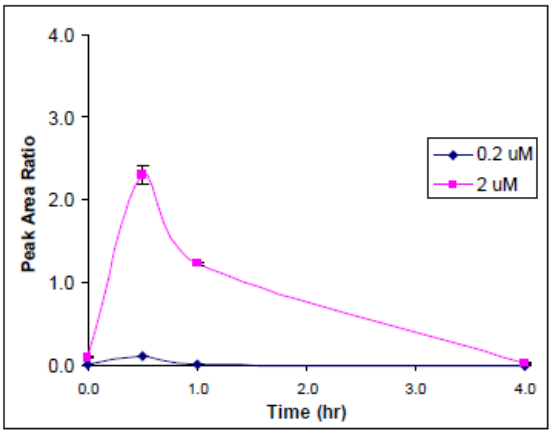


Figure 4 CCX168-M1 Formation in 0.2 and 2 µM CCX168 Incubation with Aroclor-1254 Induced Rat Liver S9

Figure 2. CCX168-M1 Formation in 0.2 and 2 µM CCX168 Incubation with Aroclor-1254 Induced Rat Liver S9



<u>METABOLITE PROFILING IN SPRAGUE-DAWLEY RATS DOSED WITH [^{14}C]-CCX168</u> (Study Report No. PC0641_168_a):

<u>Methods</u>: The metabolite profiling arm of the rat mass balance study, with oral administration of [^{14}C]-CCX168 to Sprague-Dawley rats, was provided as a supplement to the (b) (4) report "Pharmacokinetics, Distribution, Metabolism, and Excretion of [^{14}C]-CCX168 Following A Single Oral (15 mg/kg) Administration to Male and Female Rats" ((b) (4) No. 8301657, ChemoCentryx Study No. PC0641_168).

Based upon previous findings of no significant inter-animal differences, plasma, urine, feces and bile samples were pooled across animals, as well as across time points, while samples from males and females were kept separated.

Pooled plasma and fecal samples were extracted using acetonitrile containing 10% methanol and 0.25% DMSO. Urine and bile samples were used directly without extraction. Metabolites were separated using a HPLC system and radioactivity was measured. Metabolites were identified using a Thermo (San Jose, CA) LTQ ion trap mass spectrometer or an AB Sciex (Foster City, CA) API Q-Trap 4000 mass spectrometer which were operated in the positive electrospray ionization (ESI) mode; MS/MS spectra were collected through data-dependent MSn scanning.

Results:

Plasma metabolite profile: Plasma metabolite profiles were qualitatively similar between males and females. A total of 8 components were detected. CCX168 was the predominant component in HPLC profiles accounting for 52% (male) and 65% (female) of the total plasma radioactivity. Structures of four metabolites with abundancy >3% were proposed, most of which were oxidation and/or dealkylation products. M1, the most abundant circulating metabolite at 9.24% (male) and 15.02% (female) of total plasma radioactivity, was identified as a mono-oxidation metabolite with hydroxylation on the methyl group of the C ring. M15 was a subsequent oxidation product of M1 on the E ring. M6 and M3 were dealkylation products of the cyclopentyl ring. M3 was a subsequent oxidative product of M6 on the 4-methyl group of the C ring.

Urine metabolite profile: Urine was a negligible pathway for CCX168 elimination, accounting for only 1% – 3% of the total radioactive dose. While overall urine metabolite profiles were similar between males and females, although relative abundance of each component was slightly different. Most of the urine components were polar metabolites. Structural identifications were not pursued for the urine metabolites because these components were very minor (each at less than 1% of the total dose).

Fecal metabolite profile: The majority of radioactivity was eliminated through the feces (>90% of total dose). The overall fecal metabolite profiles were similar between males and females, although the relative abundance of each observed component was slightly different. A total of 15 and 13 components were observed in male and female fecal samples, respectively. Structures of five metabolites were proposed. M15, a bis-oxidation metabolite on the C and E rings, was the most abundant component eliminated through feces, accounting for 11.6% (male) and 16.5% (female) of the total dose. M1 was not abundant in the fecal samples (<4% of total dose). M25, the further oxidation product of M15, accounted for 7.1% (male) and 5.8% (female) of the total dose. M6 was relatively minor (<1% of total dose), but its subsequent metabolite M3 arising from further oxidation on the C ring accounted for 9.1% (male) and 11.5% (female) of the total dose. No phase 2 metabolites were detected in the fecal samples, despite being observed in a significant amount in bile samples, indicating that hydrolysis by gut microflora occurred after bile was secreted into the GI system.

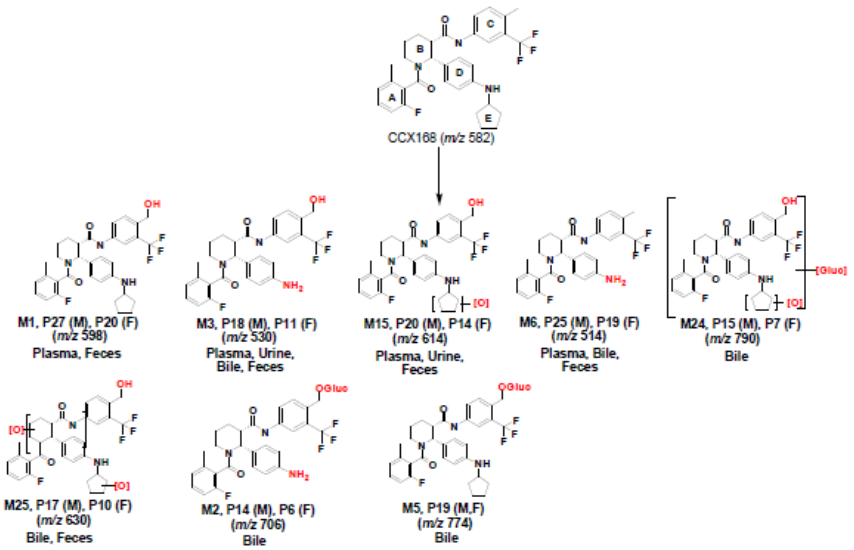
Intact CCX168 accounted for 19.9% and 18.8% of the total dose in fecal samples from male and female rats, respectively. Absorption of CCX168 in the gastrointestinal tract was estimated to be at least 80%. Since the fecal metabolites were primarily oxidative products of CCX168, liver metabolism was likely the major clearance pathway for CCX168.

Bile metabolite profile: Around 27.2% and 24.6% of total radioactivity was eliminated through bile in male and female bile duct-cannulated rats, respectively. The metabolite profiles were qualitatively similar across the two genders, except that P9 and P13 were significantly higher in the male bile HPLC profiles. CCX168 was extensively metabolized in liver and eliminated through bile. A total of 16 and 10 components were detected in male and female bile samples, respectively; most components were oxidation metabolites and subsequent conjugates. M3 and its glucuronic acid conjugate metabolite, M2, combined accounted for 20.6% and 38.0% of total radioactivity in male and female rat bile, respectively. M24, the glucuronic acid conjugate of M15, accounted for another 3.3% (male) and 3.8% (female) of total radioactive dose. Other metabolites, including phase I and phase II metabolites, were relatively minor and only accounted for <2% of total dose.

While the eliminated metabolites in the bile accounted for more than 20% of total radioactivity, the amount of intact parent compound in bile was negligible, indicating that bile elimination is a minor elimination pathway for intact CCX168.

Figure 5 Proposed rat metabolites of CCX168

Figure 1: Proposed Rat Metabolites of CCX168



P# denotes Peak identifier and M# denotes Metabolite identifier in Figure 3, Figure 4, Figure 5, Figure 6, Figure 7, Figure 8, Figure 9, and Figure 10.

METABOLITE PROFILING IN CYNOMOLGUS MONKEYS DOSED WITH [^{14}C]-CCX168 (Study Report No. PC0645_168_a)

Methods: The metabolite profiling arm of the cynomolgus monkey mass balance study, with oral administration of [^{14}C]-CCX168 to cynomolgus monkeys was provided as a supplement to the (b) (4) report "Pharmacokinetics, Metabolism, and Excretion of [14C]-CCX168 Following A Single Oral (15 mg/kg) Administration to Male and Female Primates" ((b) (4) No. 8301658, ChemoCentryx Study No. PC0645_168). Based on a previous finding that no significant inter-animal differences were observed in the same study, plasma, urine or fecal samples were pooled across animals as well as across time points.

Pooled plasma and fecal samples were extracted using acetonitrile containing 10% methanol and 0.25% DMSO. Urine and bile samples were used directly without extraction. Metabolites were separated using a HPLC system and radioactivity was measured. Metabolites were identified using a Thermo (San Jose, CA) LTQ ion trap mass spectrometer or an AB Sciex (Foster City, CA) API Q-Trap 4000 mass spectrometer which were operated in the positive electrospray ionization (ESI) mode; MS/MS spectra were collected through data-dependent MSn scanning.

Results:

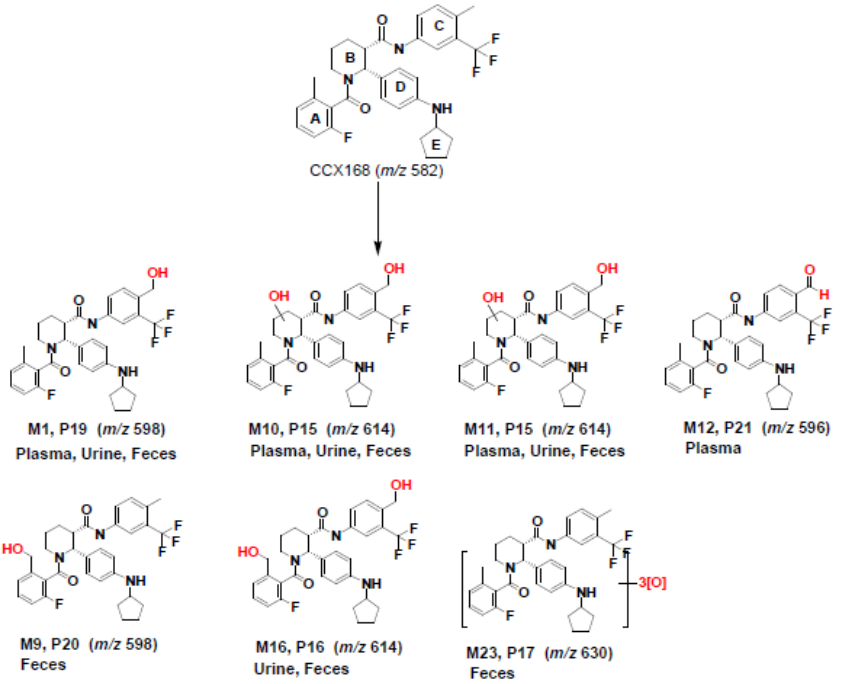
Plasma metabolites: A total of ten components were detected in the plasma radiometric HPLC profile. CCX168 accounted for 12.7% of the total plasma radioactivity. Structures of four of the nine metabolites were proposed to be oxidation and dealkylation metabolites. M1, one of the major circulating components (≥10% total radioactivity), was identified as a mono-oxidation metabolite with hydroxylation on the methyl group of the C ring. M10 and M11 were identified as further oxidation metabolites of M1 on the B ring. M12 was a further dehydrogenation metabolite of M1; it was also formed in the in vitro liver subcellular system (microsomal incubation).

Urine metabolites: Urine was a negligible pathway for CCX168 elimination, accounting for only 1% – 6% of the total radioactive dose. Overall metabolite profiles were similar between the two genders. Significant amounts of polar metabolites were observed at early retention times (Peaks P1, P3, P4 and P5). In addition, M1, M10, M11, M16 and CCX168 were also detected; the likely source of these metabolites was fecal contamination due to diarrhea.

Fecal metabolites: Approximately 26% of radioactivity was recovered in monkey fecal samples. Like the urine profiles, the overall fecal metabolite profiles were similar between males and females. Seventeen components were observed in fecal samples. CCX168 was the most abundant component and M1 was the second most abundant component, accounting for 31% and 14.6% of the fecal radioactivity, respectively. M10 and M11 were further oxidative metabolites from M1 on the Bring and together accounted for 9% of the fecal radioactivity. Other metabolites, including M9, M16 and M23, were all oxidation products and each represented no greater than 5% of the fecal radioactivity. No phase II metabolites were detected in the fecal samples.

Figure 6 Proposed Cynomolgus Monkey Metabolites of CCX168

Figure 1: Proposed Cynomolgus Monkey Metabolites of CCX168



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TIMOTHY W ROBISON
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TIMOTHY W ROBISON
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I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	214487
Supporting document/s:	SDN #1
Applicant's letter date:	July 7, 2020
CDER stamp date:	July 7, 2020
Product:	Avacopan (CCX168)
Indication:	Treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA])
Applicant:	ChemoCentryx, Inc.
Review Division:	Division of Rheumatology and Transplant Medicine (DRTM) Division of Pharm/Tox for Immunology and Inflammation (DPT-II)
Reviewer:	Ijeoma Uzoma, Ph.D.
Supervisor/Team Leader:	Timothy W. Robison, Ph.D., D.A.B.T.
Division Director:	Nikolay Nikolov, MD
Project Manager:	Susie Choi, PharmD

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 214487 are owned by ChemoCentryx Inc. or are data for which ChemoCentryx Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 214487 that ChemoCentryx Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 214487.

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1 Executive Summary

9.2 1.1 Introduction

ChemoCentryx Inc. submitted a 505(b)(1) NDA on July 7, 2020 in support of marketing approval for Avacopan (CCX168). CCX168 is a small molecule inhibitor of complement component 5a receptor (C5aR), that is being developed as an oral treatment for adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. Avacopan is a competitive antagonist of the human complement component 5a receptor (C5aR) that does not have agonist activity at C5aR. Avacopan is proposed as a hard gelatin capsule, administered at a clinical dose of 30 mg twice daily (BID) for treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]). This review evaluates the nonclinical pharmacology and toxicology program to support the safety of avacopan for marketing approval.

9.3 1.2 Brief Discussion of Nonclinical Findings

Pharmacology studies demonstrated that CCX168 is a competitive antagonist of the complement component 5a receptor (C5aR) that does not have agonist activity at C5aR. In *in vitro* studies, CCX168 displaced human C5a from the C5a receptor with an average IC_{50} of 0.45 nM. In functional chemotaxis assays, using human peripheral blood leukocytes (neutrophils and monocytes), pretreatment with CCX168 inhibited C5a-mediated chemotaxis of leukocytes with an A2 of 1.7 nM. In addition, pretreatment with CCX168 inhibited of upregulation of the neutrophil surface CD11b adhesion molecule and inhibited C5aR-mediated calcium mobilization in neutrophils and monocytes in response to stimulation with hC5a.

Pharmacology studies demonstrated that CCX168-M1, a methyl hydroxylation metabolite, was also active as a competitive antagonist of C5aR with comparable potency to the parent drug (M1 inhibited hC5aR-mediated chemotaxis with an A2 of 3 nM using human peripheral blood leukocytes). In clinical studies with ANCA patients, the M1 metabolite was found to constitute approximately 30-50% of the total systemic exposure at steady state. Therefore, the metabolite, CCX168-M1, could contribute to potential systemic pharmacodynamic activity of avacopan.

In a murine ANCA disease model, using human C5aR knock-in transgenic mice injected with anti-myeloperoxidase (MPO) antibody, treatment with CCX168 at 5 mg/kg BID and 37.5 mg/kg QD significantly reduced the incidence of glomerular crescent formation and necrosis in the kidneys and reduced urinary leukocytes, erythrocytes, and total protein.

Several GLP-compliant pivotal repeat-dose toxicology studies were conducted with CCX168 for up to 13-weeks in hamster, 26-weeks in rats, and 44 weeks in monkey.

In the 13-week oral toxicity study in hamster, animals received 0 (vehicle), 10, 30, 100 and 1000 (500 mg/kg BID) mg/kg/day CCX168. It is noted that the hamster is a pharmacologically relevant species for CCX168. No CCX168-related adverse findings

were identified during the dosing or recovery period. Administration of CCX168 at doses up to 1000 mg/kg/day of for 13-weeks was well tolerated. CCX168 exposure was saturated at doses ≥ 100 mg/kg/day. Based upon the observed saturation, the NOAEL was 100 mg/kg/day, the lowest dose where the saturation was first observed.

In the pivotal 6-month chronic oral toxicity study in rats, animals received 0 (vehicle), 5, 15, 100 and 200 (100 mg/kg BID) mg/kg/day CCX168. It is noted that the rat is not a pharmacologically relevant species for CCX168. There were no treatment-related toxicities at any of the doses tested. CCX168 exposure was saturated at doses ≥ 100 mg/kg/day. Based upon the observed saturation, the NOAEL was 100 mg/kg/day, the lowest dose where the saturation was first observed.

In the pivotal 44-week chronic oral toxicity study in monkeys, animals received either 0 (vehicle control article) and CCX168 doses of 5 or 15 mg/kg QD, or 30 (15 mg/kg BID) mg/kg/day of CCX168 over the first 25 weeks of the study and doses of 7.25 or 22.5 mg/kg QD, or 45 (22.5 mg/kg BID) mg/kg/day from Week 26 to Week 44. The monkey was a pharmacologically relevant species. No CCX168 treatment related findings were observed. The NOAEL was considered 30 mg/kg/day (Weeks 1- 25) and 45 mg/kg/day (Weeks 26-44).

Genetic Toxicology and Carcinogenicity
Avacopan was negative for genotoxicity in a standard battery of genetic toxicology tests that consisted of the in vitro Ames bacterial reverse mutation test, in vitro mouse lymphoma assay, and in vivo rat micronucleus assay. Metabolite CCX168-M1 was judged negative for mutagenicity in the Ames test for bacterial gene mutation based on confirmation that CCX168-M1 was formed upon incubation of CCX168 with S9. No treatment-related tumors were identified in 2-year oral studies with SD rats and hamsters that were conducted to assess the carcinogenic potential of CCX168.

Reproductive and Developmental Toxicology
Avacopan did not affect fertility or reproductive performance in male and female hamsters treated with oral doses of avacopan up to 1000 mg/kg/day. In embryo-fetal development (EFD) studies with pregnant hamsters and rabbits dosed orally during the period of organogenesis, avacopan did not cause fetal harm or malformations at maternal doses up to 1000 and 200 mg/kg/day, respectively. Supernumerary ribs, a non-adverse variation, were observed in hamster fetuses at 1000 mg/kg/day. In a pre- and postnatal development (PPND) study in pregnant hamsters dosed from gestation day (GD) 6 to lactation day (LD) 20, avacopan had no adverse developmental effects on pups at maternal doses up to 1000 mg/kg/day. Avacopan and the CCX168-M1 metabolite were present in plasma of the offspring of lactating hamsters on LD 15.

Phototoxicity
While CCX168 absorbed UV light at 290 nm with a molar extinction coefficient of 2989 L mol^{-1} cm^{-1}. CCX168 was negative in a Neutral Red Uptake Phototoxicity Assay in BALB/c 3T3 Mouse Fibroblasts. This assay has a high rate of false positive, so the negative assay indicated that there was minimal concern for potential phototoxicity.

9.4 1.3 Recommendations

1.3.1 Approvability

From the nonclinical perspective, NDA 214487 is recommended for approval. There are no outstanding nonclinical issues.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

Nonclinical sections of the product label will be evaluated in a separate review.

2 Drug Information

9.5 2.1 Drug

CAS Registry Number: 1346623-17-3

Trade Name: Avacopan

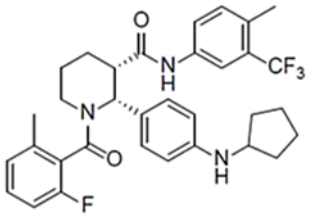
Code Name: CCX168

Chemical Name: 3-Piperidinecarboxamide, 2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]-, (2R,3S)-

Molecular Formula/Molecular Weight: $C_{33}H_{35}F_4N_3O_2$ / 581.6435 Da

Structure or Biochemical Description:

Avacopan Drug Substance Structural Formula



Pharmacologic Class: Complement 5a receptor (C5aR) Antagonist

9.6 2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 120784
DMF (b) (4)

9.7 2.3 Drug Formulation

Table 1 Composition of Avacopan 10 mg Hard Capsule

Component	Function	Quality Standard	10 mg Capsule	
			(mg)	% w/w
Avacopan	Drug Substance	In-House	10.0	(b) (4)
Polyoxyl-40 hydrogenated castor oil (b) (4)				(b) (4)
Polyethylene glycol 4000 (PEG-4000) (b) (4) (b) (4)				
Hard gelatin capsule, light orange opaque/ yellow opaque, Size 0				
Gelatin sealing band				
Total				(b) (4) (b) (4)

Table 2: Composition of Size 0 Light Orange Opaque and Yellow Opaque Bicolor Hard Gelatin Capsule Shell

Component	Function	Quality Standard	Quantity per Empty Capsule Cap or Body	
			(mg)	% (w/w)
				(b) (4)

Table 3 Composition of Clear Gelatin Sealing Solution

Component	Function	Quality Standard	10 mg Capsule	
			(mg)	% (w/w)
Gelatin	[redacted]	[redacted]	[redacted]	(b) (4)
Polysorbate 80				
				(b) (4)

9.8 2.4 Comments on Novel Excipients

None

9.9 2.5 Comments on Impurities/Degradants of Concern

Three impurities are controlled as specified impurities in the avacopan drug substance: (b) (4)

(b) (4) a (b) (4) impurity, (b) (4) was qualified by the 13-week repeat dose hamster toxicology study (No. PC0677_168). In an email communication dated December 8, 2020, CMC reviewer Dr. Caroline Strasinger asked whether Drug Product limit for the only identified impurity (b) (4) was qualified from a toxicology perspective. The limit is set at (b) (4)% and according to the Applicant is supported up to (b) (4)% based on PDE limits.

Sponsor's safety assessment of the level of [redacted] impurity

Table 3: Qualification of [redacted] in Avacopan Drug Substance

[redacted]

The lifetime permissible daily exposure (PDE) [redacted] is calculated to be [redacted] mg/day given the results of the 13-week hamster safety study. Based upon a NOAEL of 1,000 mg/kg/day and [redacted]% (a/a) [redacted] contained in the batch of avacopan drug substance used in the study, the daily dose [redacted] was [redacted] mg/kg/day. The chronic oral PDE [redacted] supports a drug product specification of up to [redacted]% based on a maximum daily dose of 60 mg avacopan per day in an adult ([redacted] mg/60 mg x 100% = [redacted]%).

$$\text{PDE (C0332414)} = \frac{\text{NOAEL x Weight Adjustment}}{\text{F1 x F2 x F3 x F4 x F5}} = \frac{\text{[redacted] mg/kg/day x 60 kg}}{5 \times 10 \times 5 \times 1 \times 1} = \frac{\text{[redacted] mg/day}}{250} = \text{[redacted] mg/day}$$

Human weight adjustment = 60 kg

F1 = species factor (hamster, 5)

F2 = individual variability factor (10)

F3 = short-term toxicity variability factor (3-mo. rodent study, 5)

F4 = fetal toxicity associated with maternal toxicity (1)

F5 = variable factor applied if no-effect level not established (1)

(Excerpted from Sponsor's submission)

The NOAEL in the 13-week hamster study (No. PC0677_168) was 1000 mg/kg/day and the level of [redacted] in the nonclinical batch used in that study was [redacted]% (a/a), resulting in a qualification level of [redacted] mg/kg/day. The human equivalent dose (HED) was calculated to be [redacted] mg/kg/day or [redacted] mg/day. The highest content level of [redacted] in the drug substance was [redacted]% (a/a) resulting in a daily exposure of [redacted] mg/day. For the clinical dose of 60 mg/day with a limit of [redacted]% [redacted] the daily exposure would be [redacted] mg/day. The Sponsor's calculation a PDE of [redacted] mg/kg based on the NOAEL in the hamster toxicology study appears to be acceptable based upon the Lifetime PDE in the ICH M7 (R1) Guidance. Therefore, the limit of [redacted]% is qualified from the nonclinical perspective.

The ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To limit Potential Carcinogenic Risk Guidance lists the Lifetime PDE [redacted] at [redacted] µg/day (based on the NOEL from a 2-year rat carcinogenicity study) which exceeds the Sponsor's proposed PDE.

[redacted] is not considered genotoxic (Class 5). Please refer to the ICH M7(R1) guidance for discussion of results mutagenicity, genotoxicity, and carcinogenicity studies [redacted]

[redacted] impurity is controlled to a release specification [redacted]

[redacted] was demonstrated [redacted] (Study No. PC0741_168). The Sponsor proposes to control the level at [redacted]%. In an email (dated December 23, 2020) from the API CMC reviewer, Dr. Sukhamaya Bain noted that the stability result [redacted] was NMT [redacted]%. Dr. Bain asked whether the limit of NMT [redacted]% is acceptable.

From the nonclinical perspective, [redacted] the Sponsor would need to provide the level [redacted] that was present in the tox batch from a toxicology study of 13 weeks or longer to qualify the impurity at [redacted]%. There is insufficient nonclinical data to support the specification of NMT [redacted]%, although the concern is low [redacted]

Potential Genotoxic Impurities (PGIs)
In accordance with ICH M7(R1), the Sponsor used in silico analyses using rule-based systems (DEREK Nexus and Leadscope Expert Alerts) and statistical-based systems (Leadscope Model Applier and EPA T.E.S.T) to classify PGIs for mutagenic risk (Class 1-5).

A total of 14 structures were identified as Class 3 PGIs in in silico analyses; however, the Sponsor noted that each of the class 3 PGIs were not observed in any batch of avacopan drug substance and achieved minimum purge ratios. Therefore, Sponsor has proposed Option 4 as outlined in ICH M7(R1) as the most appropriate PGI control strategy. The Sponsor's justification for Option 4 appears reasonable. These PGI impurities will not be listed on any specifications.

9.10 2.6 Proposed Clinical Population and Dosing Regimen

Avacopan (CCX168) has been developed for treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) at a dose of 30 mg BID. The Sponsor's target AUC concentration for the 30 mg BID dose for CCX168 is 2 x $AUC_{0\text{-}12hr}$ = 6932 ng*hr/mL and for CCX168-M1 is 2 x $AUC_{0\text{-}12hr}$ = 2566 ng*hr/mL.

9.11 2.7 Regulatory Background

A summary of the regulatory background for the avacopan development program in described below.

At the time of the PIND the Division agreed that the hamster was an appropriate pharmacologically relevant rodent species for nonclinical studies (See IND 120784 meeting minutes dated April 17, 2014). It was noted that hamster toxicology studies (e.g., the proposed developmental/reproductive toxicology studies and the 13-week dose-ranging study to support the carcinogenicity assessment) may be valuable in characterizing the toxicity of CCX168, and a full program of general toxicology studies in the hamster might be considered. During a telecon between FDA and ChemoCentryx Inc. on April 21, 2014, the Division further clarified that the 13-week hamster toxicology study may assist in characterizing the toxicity of CCX168, such as by identifying target organs of toxicity. A 6-month repeat dose toxicology study in hamster would not be required (See IND 120784 meeting minutes dated May 20, 2014).

The Sponsor submitted SPAs for the 2-year rat carcinogenicity study on October 10, 2017 (SDN 83) and the 2-year hamster carcinogenicity study on October 20, 2017 (SDN 85). The proposed carcinogenicity study protocols were presented to the Executive Carcinogenicity Assessment Committee (ECAC) on November 7, 2017. The ECAC agreed with the Division's/Sponsor's proposed doses for the 2-year rat and hamster carcinogenicity studies (See SPA Agreement in DARRTS, Dated November 9, 2017).

At the End of Phase 2 meeting, the Sponsor asked about the timing of completion of the carcinogenicity studies (see meeting minutes dated August 9, 2016, IND 120784). The Applicant's nonclinical question, the Division's response, and the meeting discussion are reproduced below.

End of Phase 2 meeting (August 9, 2016)

Question 2: Does the Division agree that it is acceptable to complete nonclinical carcinogenicity studies (rat and hamster) post-approval?

FDA Response to Question 2:
Yes, we agree that it would be acceptable to conduct carcinogenicity studies in rats and hamsters post-approval.

Nonclinical IR (August 14, 2020)

1. *Submit the final reports of the 2-year carcinogenicity studies in hamsters and rats to the NDA as they become available.*
2. *To facilitate statistical review of these studies, submit the tumor data sets along with study reports. The tumor data sets should be in conformance to the electronic format specified in Study Data Specifications, Version 2.0 (July 18, 2012). This document is available at:*

http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf).

Sponsor clarification (*August 14, 2020*):
We are acknowledging receipt of IR #1 (Reference ID: 4657154) and requesting a clarification. Our understanding, based on the Nonclinical Pre-NDA meeting (Reference ID: 4550563) as well as the EOP2 meeting (Reference ID: 3969901), was that the two-year carcinogenicity studies reports could be submitted post-approval.
Could you please clarify if there is a change in this agreement, as it impacts the timelines we have in place with our vendor? We appreciate the courtesy of a response by Monday, August 17, 2020 so that we can reach out to the vendor as soon as possible.

FDA response (August 17, 2020):
There is no change in the agreement. Your NDA will likely have a longer review clock (12 months) so if you are able to submit the carcinogenicity studies relatively early in the review cycle (around month 3 or 4), we could potentially review them. However, we could still review the studies as PMRs as well. You will get formal confirmation of review clock for NDA 214487 in the 74-day letter.

Sponsor response (August 21, 2020):
The sponsor proposes the following submission dates for Carcinogenicity study in Rats ([(b) (4)] Study No. 8374142; ChemoCentryx Study No. PC0675_168 and Hamster ([(b) (4)] Study No. 8374143; ChemoCentryx Study No. PC0674_168).

The 2-year final carcinogenicity studies in rat and hamster were submitted to the NDA on December 2, 2020.

3 Studies Submitted

9.12 3.1 Studies Reviewed

Primary Pharmacology

Title	Study Number	IND/NDA	Review Date
In vitro effects of CCX168 on mouse, rat, and cynomolgus monkey C5aR	PC0347_168_a	NDA 214487	Current Review
In vitro evaluation of CCX168 as an antagonist of Human C5aR	PC0346_168_a	NDA 214487	Current Review
EFFECTS OF CCX168 IN AN IN VIVO MECHANISM BASED MODEL IN CYNOMOLGUS MONKEYS	PC0351_168_a	NDA 214487	Current Review

EFFECTS OF CCX168 IN A MOUSE MODEL OF ANTI-MPO INDUCED GLOMERULONEPHRITIS	PC0480_168_b	NDA 214487	Current Review
EX-VIVO EFFECTS (HC5AR KI MICE) OF CCX168 ON C5A-INDUCED BLOOD LEUKOCYTE CD11B UPREGULATION	PC0481_168_a	NDA 214487	Current Review
IN VITRO ACTIVITY OF C0335273 AS AN ANTAGONIST OF HUMAN C5AR	PC0463_168a	NDA 214487	Current Review
IN VITRO ACTIVITY OF C0335273 AGAINST MOUSE, RAT, RABBIT AND CYNOMOLGUS MONKEY C5AR	PC0484_168_a	IND 120784	3/1/2021
In Vitro Effects of CCX168 and CCX168-M1 on Hamster and Rabbit C5aR	PC0627_168_a	IND 120784	3/1/2021

Secondary Pharmacology

Title	Study Number	IND/NDA	Review Date
Evaluation of CCX168 against a broad panel of biochemical targets	PC0349-168	NDA 214487	Current Review
CHEMOKINE RECEPTOR SELECTIVITY OF CCX168	PC0348-168b	IND 120784	3/1/2021
ACTIVITY OF CCX168 ON GLUCOCORTICOID RECEPTOR	PC0464-168	IND 120784	3/1/2021
BIOCHEMICAL SELECTIVITY PROFILE OF C0335273	PC0486_168	IND 120784	3/1/2021

Safety Pharmacology

Title	Study Number	IND/NDA	Review Date
Effect of CCX168 on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells	PC0380_168	IND 120784	7/15/2014
Effects of C0335273 on Cloned hERG Potassium Channels Expressed in Mammalian Cells	PC0490_168_a	IND 120784	7/15/2014
Evaluation of Respiratory Function Following Single-Dose Oral Administration of CCX168 in Sprague Dawley Rats	PC0376_168_a	IND 120784	7/15/2014
Neuropharmacological Profile (NPP) of CCX 168 Following Single-Dose Oral Administration in Sprague Dawley Rats	PC0375_168	IND 120784	7/15/2014
Evaluation of Cardiovascular Function Following Oral Administration of CCX168 in	PC0377_168	IND 120784	7/15/2014

Conscious Telemetered Male Cynomolgus Monkeys			
Evaluation of Renal Function Following Single-Dose Oral Administration of CCX168 in Sprague Dawley Rats	PC0485_168	IND 120784	7/15/2014

Pharmacokinetics/ADME/Toxicokinetics

Title	Study Number	IND/NDA	Review Date
PK Evaluation of CCX168 in SD Rat	PC0365_168_a	NDA 214487	Current Review
PK Evaluation of CCX168 and its metabolite CCX168-M1 in rats following 7 days of QD and BID Oral gavage dosing of CCX168	PC0639_168	NDA 214487	Current Review
Evaluation of non-specific protein binding of CCX168 and M1 in mouse, rat, hamster, rabbit, dog, cyno, and human plasma	PC0632_168	NDA 214487	Current Review
Investigation of CCX168 metabolites produced by in vitro systems of multiple species following incubation of CCX168	PC0623_168_a	NDA 214487	Current Review
Characterization of metabolic pathways of CCX168 and CCX168-M1	PC0711_168	NDA 214487	Current Review
Hamster Pharmacokinetic and Formulation Tolerability Study Following Oral Administration of CCX168	PC0648-168	IND 120784	3/1/2021
IN VITRO BLOOD / PLASMA PARTITIONING OF CCX168 (MOUSE, RAT, DOG, AND HUMAN) AND EFFECT ON DEPENDENT PK CHARACTERISTICS IN MICE, RATS AND DOGS	PC0364_168_a	IND 120784	3/1/2021
EVALUATION OF BINDING OF CCX168 AND METABOLITE CCX168-M1 TO HUMAN ALBUMIN	PC0681_168	IND 120784	3/1/2021
EVALUATION OF BINDING OF CCX168 AND METABOLITE CCX168-M1 TO HUMAN α1-ACID GLYCOPROTEIN (AAG)	PC0685_168	IND 120784	3/1/2021

METABOLITE PROFILING OF CCX168 IN IN VITRO SYSTEMS OF VARIOUS SPECIES	PC0369_168	IND 120784	3/1/2021
METABOLITE FORMATION FOLLOWING INCUBATION OF CCX168 WITH RAT LIVER S9	PC0488_168	IND 120784	3/1/2021
METABOLITE PROFILING IN SPRAGUE-DAWLEY RATS DOSED WITH [14C]-CCX168	PC0641_168_a	IND 120784	3/1/2021
METABOLITE PROFILING IN CYNOMOLGUS MONKEYS DOSED WITH [14C]-CCX168	PC0645-168a	IND 120784	3/1/2021

Repeat Dose Toxicology

Title	Study Number	IND/NDA	Review Date
13-WEEK GENERAL TOXICOLOGY AND 4-WEEK T-CELL DEPENDENT ANTIBODY PRODUCTION STUDY OF CCX168 IN SPRAGUE-DAWLEY RATS FOLLOWING DAILY ORAL ADMINISTRATION	PC0356_168	IND 120784	7/15/2014
A 13-Week Toxicity and Toxicokinetic Study of CCX168 by Oral Gavage in Hamsters with a 4-Week Recovery Period	PC0677_168	IND 120784	11/14/2017
20-WEEK GENERAL TOXICOLOGY STUDY OF CCX168 IN CYNOMOLGUS MONKEYS FOLLOWING DAILY ORAL ADMINISTRATION	PC0357_168	IND 120784	7/15/2014
26-Week Oral Gavage Toxicity and Toxicokinetic Study with CCX168 in Rats with a 6-Week Recovery Phase	PC0655_168	IND 120784	11/9/2017
44-Week Nasogastric Intubation (Weeks 1-5) and Oral Gavage (Weeks 6-44) Toxicity and Toxicokinetic Study with CCX168 in Cynomolgus Monkeys with a 6 Week Recovery Phase	PC0654_168	NDA 214487	Current Review

Genetic Toxicology

Title	Study Number	IND/NDA	Review Date
Evaluation of CCX168 in a bacterial reverse mutation assay with a confirmatory assay	PC0378_168	IND 120784	11/9/2017
Evaluation of CCX168 in a L5178Y TK+/- mouse lymphoma forward	PC0379_168	IND 120784	11/9/2017

mutation assay with a confirmatory assay			
Evaluation of the effects of CCX168 on bone marrow micronucleus formation	PC0320_168	IND 120784	11/9/2017

Carcinogenicity

Title	Study Number	IND/NDA	Review Date
CCX168: 104 Week Oral (Gavage) Administration Carcinogenicity Study in the Rat	PC0675_168	NDA 214487	3/8/2021
CCX168: 104 Week Oral (Gavage) Administration Carcinogenicity Study in the Hamster	PC0674_168	NDA 214487	3/8/2021

Reproductive Toxicology

Title	Study Number	IND/NDA	Review Date
Fertility and Early Embryonic Development Study of CCX168 in Hamsters following Oral Gavage Administration	PC0670_168	NDA 214487	Current Review
An Embryo-fetal Development Toxicity Study of CCX168 in Hamsters following Oral Gavage Administration	PC0671_168	NDA 214487	Current Review
An Embryo-Fetal Developmental Study of CCX168 by Oral (Stomach Tube) in Rabbits	PC0672_168	NDA 214487	Current Review
An Oral (Gavage) Prenatal/Postnatal Developmental Toxicity Study of CCX168 in Hamsters, Including a Postnatal Behavioral/Functional Evaluation	PC0673_168	NDA 214487	Current Review

Phototoxicity

Title	Study Number	IND/NDA	Review Date
Effects of CCX168 in a Neutral Red Uptake Phototoxicity Assay in BALB/c 3T3 Mouse Fibroblasts	PC0663_168	NDA 214487	Current Review

9.13 3.2 Studies Not Reviewed

Pharmacology

Title	Study Number
Effects of CCX168 in an In Vivo mechanism in hC5aR Knock-In Mice	PC0350_168
ASSESSMENT OF (b) (4) IN IN VITRO C5AR-MEDIATED CALCIUM MOBILIZATION ASSAY	PC0741_168

Effect of CCX168 on human lymphocyte proliferation	PC0465_168

Pharmacokinetics/ADME/Toxicokinetics

Title	Study Number
EVALUATION OF BINDING OF CCX168 AND METABOLITE CCX168-M1 TO HUMAN ALBUMIN	PC0632_168
Permeability of CCX168 in CACO-2 Cell Monolayer	PC0361_168_a
OPTIMIZATION OF CCX168 TOXICOLOGY FORMULATION	PC0482_168
PHENOTYPING OF DRUG METABOLIZING ENZYMES THAT ARE RESPONSIBLE FOR THE IN VITRO METABOLISM OF CCX168	PC0373_168
EVALUATION OF STEAD STATE PLASMA LEVELS OF CCX168 METABOLITES IN VARIOUS SPECIES FOLLOWING ORAL ADMINISTRATION OF CCX168 AMENDMENT 1	PC0487_168_a
CYP450 INHIBITION CCX168 IN HUMAN LIVER MICROSOMES	PC0360_168
EVALUATION OF THE CYP450 TIME DEPENDENT INHIBITION POTENTIAL OF CCX168 IN VITRO	PC0372_168
AN IN VITRO INVESTIGATION INTO THE METABOLISM-DEPENDENT INHIBITION OF HUMAN CYTOCHROME P450 3A4 BY CCX168	PC0622_168
STUDY TO INVESTIGATE CYTOCHROME P450 TIME DEPENDENT INHIBITION (IC50) SHIFT) POTENTIAL OF TEST COMPOUNDS CCX168 AND CCX168-M1	PC0710_168
CYP450 INHIBITION PROFILE OF C0335273 IN HUMAN LIVER MICROSOMES	PC0489_168
EVALUATION OF THE CYP450 TIME-DEPENDENT INHIBITION POTENTIAL OF CCX168-M1 IN VITRO	PC0634_168
CYP INDUCTION EVALUATION OF C0335273	PC0491_168
Evaluation of P450 induction potential of Test Article in Human Hepatocytes	PC0635_168_a
In vitro Interaction Studies of CCX168 and CCX168-M1 with human BCRP and MDR1 Efflux (ABC) Transporters and with human MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3 and OCT2 Uptake Transporters	PC0712_168
EFFECTS OF CCX168 IN PREDNISONE AND PREDNISOLINE FREE FRACTION IN HUMAN PLASMA	PC0466_168
EFFECTS OF CCX168 AND C0335273 ON 11β-HYDROXYSTEROID DEHYDROGENASES	PC0469_168

General Toxicology

Title	Study Number
7-DAY DOSE-RANGE FINDING TOXICITY STUDY OF CCX168 IN SD RATS (30 AND 100 MG/KG)	PC0374_168
7-DAY ORAL GAVAGE TOXICITY AND TOXICOKINETIC STUDY OF CCX168 IN GOLDEN SYRIAN HAMSTERS	PC0657_168
ESCALATING DOSE RANGE-FINDING STUDY WITH CCX168-A IN CYNOMULGUS MONKEYS	PC0383_168

4-Week Nasogastric Intubation Toxicity and Toxicokinetic Study with CCX168 in Cynomolgus Monkeys with a 2-Week Recovery Phase	PC0385_168
Effects of CCX168 Administered by Oral Gavage on T-Cell Dependent Antibody Response to KLH in Fisher Rats	PC0496_168

9.14 3.3 Previous Reviews Referenced

Application	Reviewer	Date in DARRTS	Notes
IND 120784	Dr. Matthew Whittaker	7-15-2014	30 Day Safety Review 13-week rat and 20-week review
IND 120784	Dr. Matthew Whittaker	11-09-2017	Review of 6-month toxicology study with rats and genetic toxicology studies
IND 120784	Dr. Dong Zhao	11-14-2017	Review of 13-week hamster toxicology study
IND 120784	Dr. Karen Davis-Bruno	11-09-2017	ECAC meeting minutes
IND 120784	Dr. Matthew Whittaker	08-22-2019 (Comments were conveyed on 08-13-2019)	Early termination criteria for 104-week carcinogenicity study with rats
NDA 214487	Dr. Karen Davis-Bruno	2-25-2021	ECAC meeting minutes
IND 120784	Dr. Timothy W. Robison	3-1-2021	Pharmacology and TK/ADME

4 Pharmacology

9.15 4.1 Primary Pharmacology

In vitro pharmacology

Title: In Vitro Evaluation of CCX168 as an Antagonist of Human C5aR
Study No. PC0346_168_a

The C5a anaphylatoxin exerts inflammatory effects by activating the C5a receptor (C5aR) that is expressed on immune cells, primarily on neutrophils. In this study, CCX168 was evaluated for its ability to inhibit C5a-mediated effects on various human cell types under different conditions.

Ligand Binding Assay: U937 cells were stimulated with cAMP and incubated with 0.1 nM of ^{125}I-C5a in binding buffer in the presence of various concentrations of CCX168 for 3 hours.

Calcium mobilization assay in human neutrophils: Human neutrophils or monocytes were incubated with 2 µM indo-1 AM (cell-permeant dye that can be used to measure intracellular ionized calcium concentration). Fluorescence of indo-1 AM (excitation at 350 nm and dual emission at 400 and 490 nm) was monitored. CCX168 was added to the cells, then hC5a (or other chemokines) were added ~25 seconds later.

Calcium mobilization assay in U937 cells: U937 cells were incubated for 45 min with 2 µM Fluo-4 AM. Fluorescence was monitored (excitation at 494 nm and emission at 516 nm). CCX168 was added to the cells, then hC5a (or other chemokines) were added 1-2 minutes later.

Results:
In the radioligand binding assays, CCX168 was tested for displacement of ^{125}I-hC5a from the C5a receptor on U937 cells. The average IC_{50} of CCX168 was 0.45 nM.

In the calcium mobilization assay in U937 cells, the A2 value was 0.1 nM.

In the C5aR-mediated calcium mobilization assay in human neutrophils and monocytes, CCX168 inhibited C5aR-mediated calcium mobilization with an IC_{50} value of 0.2 nM for human neutrophils and 0.4 nM for human monocytes. No calcium mobilization was detected in neutrophils or monocytes in the time window (1-2 minutes) between the addition of CCX168 and prior to the addition of C5a.

Therefore, it was concluded that CCX168 is a potent antagonist of the human C5a receptor and that CCX168 does not have agonist activity at C5aR on neutrophils or monocytes.

Chemotaxis Studies: This section summarizes the methods and results of a series of in vitro studies which characterized the activity of CCX168 and the M1 metabolite at the C5aR, with respect to inhibition of C5a mediated chemotaxis of primary neutrophils or leukocytes (neutrophils and monocytes) in whole blood from human and multiple nonclinical species.

- In vitro effects of CCX168 on Mouse, Rat, and Cynomolgus Monkey C5aR (Study No. PC0347_168_a)
- In Vitro Effects of CCX168 and CCX168-M1 on Hamster and Rabbit C5aR (Study No. PC0627_168_a)
- C0335273(M1) In vitro activity C0335273 against mouse, rat, rabbit, and mouse C5aR (Study No. PC0484_168)
- In Vitro Evaluation of CCX168 as an Antagonist of Human C5aR (Study No. PC0346_168_a)
- In Vitro Evaluation of C0335273 as an Antagonist of Human C5aR (Study No. PC0463_168_a)

To determine the potencies of CCX168 for mouse, rat, monkey, hamster, and human C5aR in a physiological model, chemotaxis assays were performed with primary cells

from each species in plasma, whole blood, or chemotaxis buffer. The immune cells used in the assays were either leukocytes (neutrophils and monocytes) in peripheral blood (human, cynomolgus monkey, and hamster) or thioglycollate-elicited peritoneal lavage leukocytes, a mixture of neutrophils and macrophages (rat and mouse). Isolated neutrophils from humans and monkeys were used in some studies. The cells were exposed to a range of concentrations of C5a in the presence or absence of CCX168. The results are presented as A2 values. An A2 value indicates the concentration of CCX168 that results in a two-fold rightward shift of the dose-response curve for C5a-mediated chemotaxis and correlates with 50% receptor occupancy by a competitive antagonist such as CCX168.

Human and Monkey: It is noted that peripheral blood from primates is composed of a large proportion of neutrophils (approximately 70% of white blood cells) which express functional C5aR. Peripheral blood leukocytes (neutrophil and monocytes) were tested using whole blood obtained from humans and monkeys. Human and monkey neutrophils were isolated for some studies.

Rodent: Macrophages and neutrophils were harvested from rodent (C57BL/6 mice or Sprague-Dawley rats) peritoneal cavity following injection with thioglycollate (10 ml/kg) in the peritoneal cavity.

Hamster and Rabbit: Peripheral blood leukocytes were either used directly in the chemotaxis assay or leukocytes were isolated using a standard hypotonic red blood cell lysis procedure, followed by resuspension in the chemotaxis buffer.

Chemotaxis Assays: Using a standard cell migration plate system, CCX168 was added to the peripheral blood leukocytes or isolated leukocytes suspended in chemotaxis buffer or peripheral blood (noted in Table 4) and placed into wells on a porous membrane. C5a was diluted with chemotaxis buffer and plated in the lower wells of a ChemoTX plate. The plates were then incubated at 37°C for 90 – 180 minutes. To measure migration, CyQUANT (DNA intercalating agent) was added to the lower wells. The amount of fluorescence corresponded to the number of migrated cells.

Chemotaxis Results: CCX168 and CCX168-M1 inhibited C5aR function in human, cynomolgus monkey, and hamster peripheral blood leukocytes with A2 values less than 18 nM (see Table 4). Both CCX168 and CCX168-M1 were found to be inactive or minimally active (A2 > 1,000 nM) with rat, mouse, and rabbit C5aRs (Table 4).

Table 4: In vitro potency (A2 values) of CCX168 and its M1 metabolite for inhibition of C5a mediated chemotaxis in leukocytes of multiple species.

Species	Leukocyte Medium	CCX168 A_2 Value	CCX168-M1 A_2 Value
Human	Leukocytes in whole blood	1.7 nM	3 nM

Cynomolgus monkey	Neutrophils in whole blood	18 nM	1 nM
Cynomolgus monkey	Leukocytes in 100% plasma	--	2.6 nM
Hamster	Leukocytes (in Whole blood)	14 nM	10 nM
Hamster	Leukocytes (in Chemotaxis buffer)	3 nM	5 nM
Rabbit	Leukocytes (in Chemotaxis buffer)	--	>500 nM
Rabbit	Leukocytes (in Whole blood)	4000 nM	3,000 nM
Mouse	Thioglycollate-elicited peritoneal lavage leukocytes in mouse plasma	>1,000	>1,000
Rat	Thioglycollate-elicited peritoneal lavage leukocytes in rat plasma	>1,000	>1,000

Radioligand binding assay in hamster: Leukocytes isolated from hamster blood were incubated with 0.1 nM of [^{125}I]-C5a in binding buffer in the presence of various concentrations of CCX168 or CCX168-M1 for 3 hours.

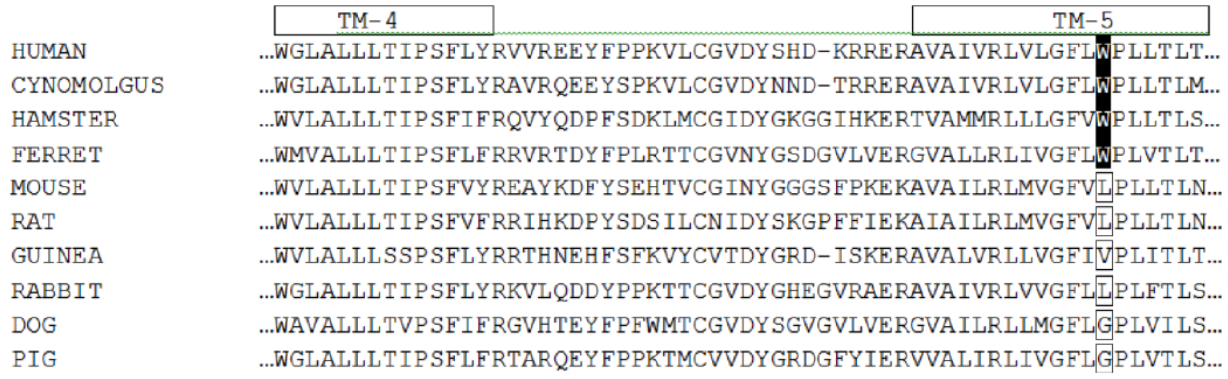
Both CCX168 and CCX168-M1 antagonized the binding of [^{125}I]-C5a to freshly isolated hamster leukocytes with similar sub-nanomolar potencies. CCX168 inhibited binding of [^{125}I]-C5a to C5aR with an IC_{50} of 0.9 nM. CCX168- M1 inhibited hamster C5aR binding with an IC_{50} of 0.3 nM.

Conclusions:
CCX168 and M1 have comparable potency in antagonizing the binding of C5a to C5aR expressed on human neutrophils or leukocytes as measured by chemotaxis assays (CCX168 A2 of 1.7 nM; CCX168-M1 A2 of 3 nM). CCX168 and CCX168-M1 inhibited binding of C5a to C5aR expressed on leukocytes of cynomolgus monkeys (CCX168 A2 value of 18 nM; CCX168-M1 A2 of 2.6 nM) and hamsters (CCX168 A2 value of 14 nM; CCX168-M1 of A2 10 nM) with similar potencies. Therefore, the cynomolgus monkey and hamster were considered pharmacologically relevant species. Based on the lack of affinity of CCX168 and CCX168-M1 for C5aRs (A2 > 1,000 nM) expressed on leukocytes from mice, rats, and rabbits, these species were determined to not be pharmacologically relevant.

C5aR amino acid sequence alignment (provided by the sponsor) identified a potential key residue located within the 5th transmembrane region (TM-5) of C5aR with regard to species specific binding of CCX168 or M1. The amino acid sequences for human,

cynomolgus, and hamster C5aR all contain a tryptophan residue at this location, while other species have variable amino acid residues (Figure 1). The sequence alignment data are consistent with the pharmacological relevance of the nonclinical species based on CCX168 in vitro activity in C5aR-mediated chemotaxis assays.

Figure 1: Amino acid sequence alignment of the C5a receptor for 10 species shows a potential key residue in the TM-5 region that may influence CCX168 and M1 binding



Title: In vitro Activity of C0335273 as an Antagonist of Human C5aR(Study No. PC0463_168_a)

C0335273 (CCX168-M1) was identified as a putative metabolite of CCX168. Whether C0335273 has activity against the human C5aR was assessed in multiple models: 1) U937 human cell line in a hC5a-mediated chemotaxis assay, 2) in an hC5a-mediated chemotaxis assay of blood neutrophils in freshly isolated human blood, and 3) in an hC5a-mediated neutrophil CD11b upregulation assay using freshly isolated human blood.

Chemotaxis assays were conducted with human U937 cells or using human neutrophils (in whole blood). C0335273 was added to the U937 cells or to human whole blood. Separately, recombinant human or human C5a was diluted with chemotaxis buffer and 29 µL was added in the lower wells of a ChemoTX plate. Next, a 3-5 µm (pore size) polycarbonate membrane was placed onto the plate. Then 20 µL of the cells/CCX168 mixture was transferred onto each well of the membrane. The plates were then incubated at 37°C for 90 – 180 minutes. Membranes were then removed and CyQUANT (DNA intercalating agent) was added to the lower wells. The amount of fluorescence corresponded to the number of migrated cells.

CD11b upregulation assay: C0335273 or an equivalent volume of DMSO was added to freshly isolated human whole blood. Human whole blood was pipetted to 96-well plates containing 11 uL of different concentrations of hC5a to stimulate neutrophils. The plate was incubated for 30 min on ice. After incubation, FACS lysing solution was added

and the plate was centrifuged twice at 400 g for 5 min at 4 °C to isolate neutrophils. The cells were suspended in 200 ul cold PBS containing 2% FBS and 1.5% paraformaldehyde for fixation. The cells were then analyzed by flow cytometry by measuring the mean fluorescence intensity of CD11b antibody staining of Gr-1+ neutrophils.

Results:

C0335273 inhibited C5aR-mediated chemotaxis in buffer:

Treatment of U937 cells with 5 nM and 50 nM C0335273 resulted in a rightward shift of the chemotaxis dose response curves for hC5a (Figure 2Figure 2, A). The A2 value for C0335273 for inhibition of U937 cell chemotaxis in normal buffer was calculated to be 0.3 nM (Table 5).

C0335273 inhibited hC5a-induced chemotaxis neutrophils in human whole blood:

Treatment of human neutrophils in whole blood with 10 nM and 100 nM C0335273 resulted in a rightward shift of the chemotaxis dose response curves for hC5a (Figure 2, B). The A2 value for C0335273 for inhibition of neutrophil chemotaxis in human whole blood was calculated to be 3 nM (Table 5).

C0335273 inhibited hC5a-induced upregulation of neutrophil CD11b in human whole blood:

In the absence of an antagonist, stimulation of C5aR with hC5a causes a dose-dependent increase in the neutrophil surface expression of CD11b. Treatment of human whole blood with 10 nM and 100 nM C0335273 resulted in a rightward shift of the dose response curves for hC5a induced upregulation of neutrophil CD11b (Figure 2Figure 2, C). The A2 value for C0335273 for inhibition of hC5a-induced upregulation of neutrophil CD11b was calculated to be 7 nM (Table 5).

Figure 2: CCX168-M1 Metabolite (C0335723) inhibits hCRa-mediated chemotaxis and CD11b-upregulation on neutrophils

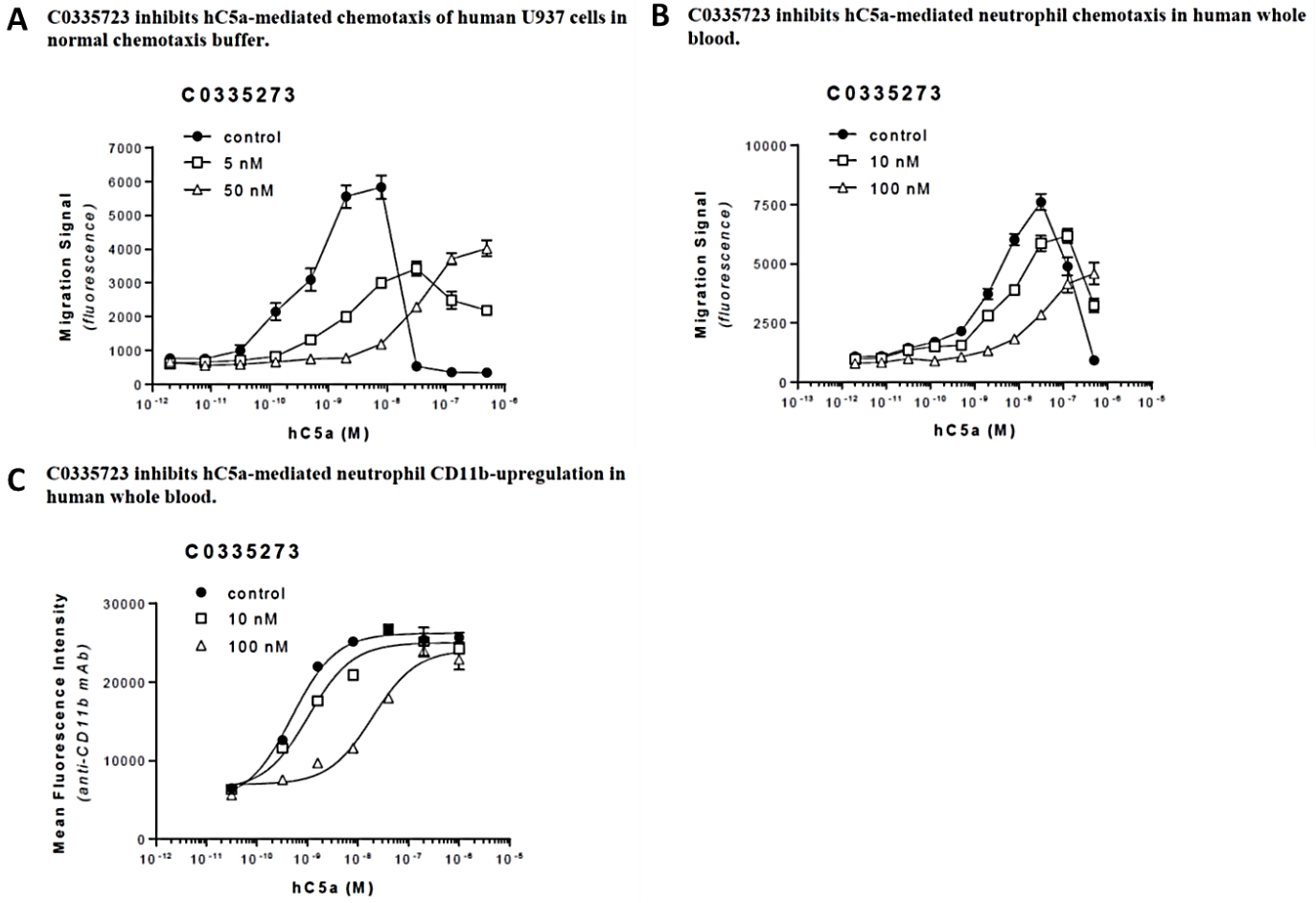


Table 5: Summary of C0335273 results against human C5aR

Assay	Replicates	Potency
Chemotaxis, U937, normal buffer	n=2	A_2 = 0.3 nM
Chemotaxis, neutrophils, human whole blood	n=4	A_2 = 3 nM
CD11b-upregulation, neutrophils, human whole blood	n=2	A_2 = 7 nM

In vivo Pharmacology

Title: Effects of CCX168 in an in vivo Mechanism Based Model in Cynomolgus Monkeys (Study no. PC0351_168_a)

CCX168 is a potent antagonist of cynomolgus monkey C5aR-mediated chemotaxis of blood leukocytes (in whole blood or 100% plasma) with an A_2 of 18 nM and an A_{10} of

162 nM, indicating that the cynomolgus monkey is a pharmacologically relevant species for use with CCX168.

In this crossover study design, monkeys were dosed orally with vehicle (Day 1), CCX168 at 3 mg/kg (Day 8), and 30 mg/kg (Day 15). Subsequently monkeys were administered a C5a-induced neutropenia challenge with an intravenous injection of hC5a at 2, 10, or 50 µg/kg at 90 minutes and 220 minutes. Blood samples were collected on Day 1, Day 8 and Day 15 from each animal at immediately before (baseline measurement) and at 75, 90, 91, 95, 100, 205, 220, 221, and 230 minutes post dose. Blood samples were analyzed for neutrophils counts and plasma analysis of test compound levels.

Table 6: Study Design for CCX168 inhibition of C5a induced neutropenia in monkey

Dosing:

Phase	Number of Males	Test Article	Dose Route	Target Dose Level (mg/kg)[a]	Target Dose Concentration (mg/mL)	Target Dose Volume (mL/kg)	C5a Dose (90 minutes)	C5a Dose (220 minutes)
Day 1	1	Vehicle	oral	0	0	2	A	B
	2	Vehicle	oral	0	0	2	A	B
	3	Vehicle	oral	0	0	2	B	C
	4	Vehicle	oral	0	0	2	B	C
Day 8	1	Vehicle	oral	0	0	2	B	B
	2	Dose 1 CCX1368	oral	30	15	2	B	B
	3	Dose 1 CCX1368	oral	30	15	2	B	B
	4	Dose 1 CCX1368	oral	30	15	2	B	B
Day 15	1	Dose 2 CCX1368	oral	3	1.5	2	B	B
	2	Dose 2 CCX1368	oral	3	1.5	2	B	B
	3	Vehicle	oral	0	0	2	B	B
	4	Dose 2 CCX1368	oral	3	1.5	2	B	B

Dosing of CCX1368: Dose 1: 30mg/Kg CCX1368, Dose **2:** 3 mg/Kg CCX1368
Dosing of human C5a: will be dosed as a 30ug/ml solution of hC5a in sterile saline, to be dosed IV to a final dose of either: **Dose A:** 2ug/Kg, **Dose B:** 10ug/Kg, **Dose C:** 50ug/Kg.

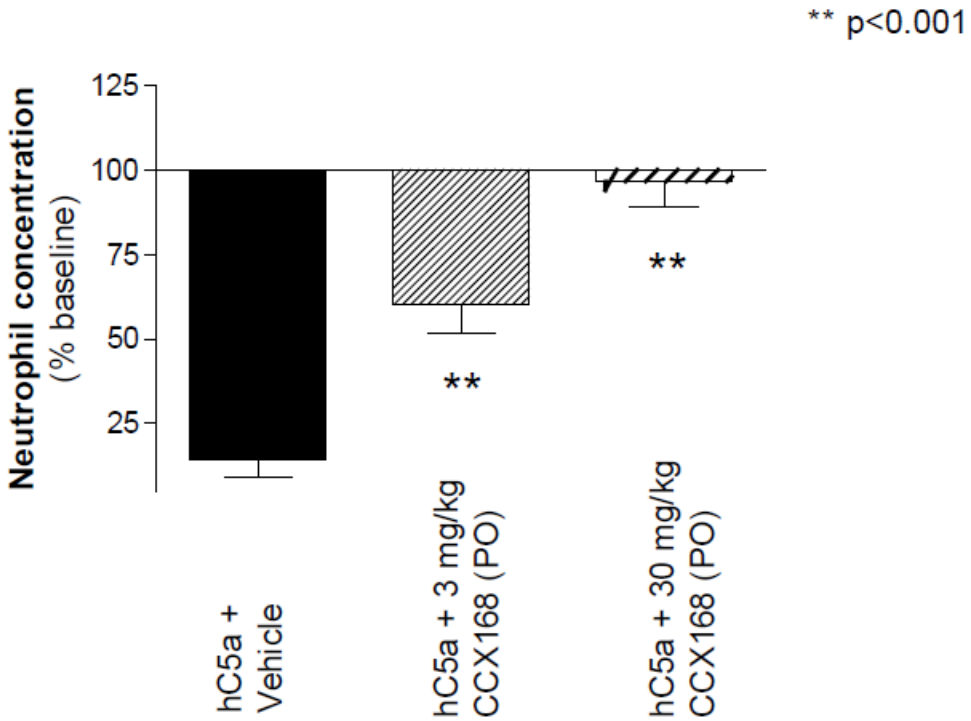
Results:

It was determined that IV injection of 10 µg/kg hC5a produced maximal neutropenia in cynomolgus monkeys. Therefore, the data reported refer the results from study groups where hC5a was administered at 10 µg/kg. In the cynomolgus monkey, IV administration of C5a at 10 µg/kg results in the immediate, but transient, adhesion of

neutrophils to blood vessel walls and, thereby reducing the neutrophil concentration in blood.

Pretreatment with CCX168 at 3 mg/kg resulted in greater than 50% reduction of the hC5a response which was associated with a CCX168 plasma concentration of 38 nM. Pretreatment with CCX168 at 30 mg/kg resulted in 100% inhibition of C5a-induced neutropenia ($p<0.001$), which was associated with a CCX168 plasma concentration of 230 nM.

Figure 3: Inhibition of C5a-induced neutropenia in cynomolgus monkey by CCX168



Conclusion:

- Oral dosing of CCX168 ameliorates hC5a-induced neutropenia in cynomolgus monkeys.
- Coverage in plasma of the cynomolgus whole blood A2 (18 nM), as determined in vitro, results in >50% inhibition of neutropenia in vivo.
- Coverage in plasma of the cynomolgus whole blood A10 (162 nM), as determined in vitro, results in complete inhibition of neutropenia in vivo.

Title: Effects of CCX1168 in a Mouse Model of Anti-MPO Induced Glomerulonephritis (Study No. PC0480_168_b)

Anti-neutrophil cytoplasmic antibodies (ANCA) disease, a small vessel vasculitis that is characterized by pauci-immune necrotizing crescentic glomerulonephritis and which is triggered by autoantibodies against neutrophil cytoplasm-expressed proteins, such as

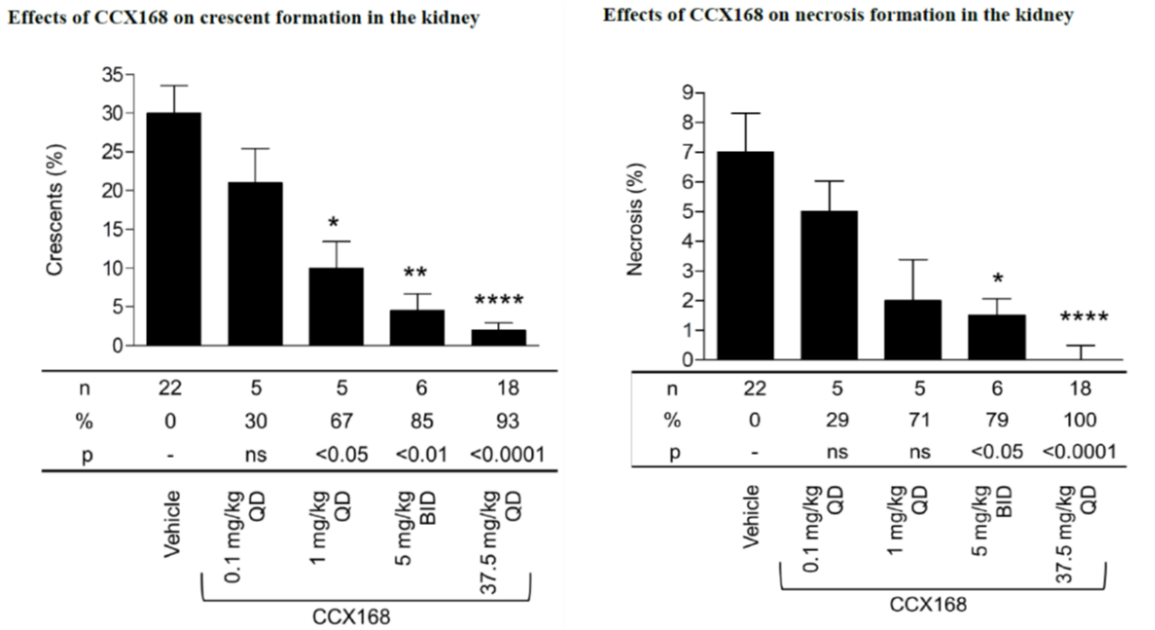
myeloperoxidase (MPO) or proteinase 3 (PR3). ANCAs are thought to induce blood vessel inflammation by causing neutrophils to lyse, releasing granule components which kill nearby endothelial cells. The granule components include factors which activate the alternative complement pathway, which in turn recruits more neutrophils and primes them for respiratory burst. Complement C5a is critical in this process: in a mouse model of ANCA-induced glomerulonephritis, antibody-mediated blockade of C5a prevents disease; moreover, C5a receptor (C5aR) knockout mice are resistant to disease in this model.

Human C5aR knock-in mice: CCX168 is a potent antagonist of human C5aR, but does not antagonize mouse C5aR. To test CCX168 in the ANCA-induced glomerulonephritis model, a mouse line was generated in which the mouse C5aR gene is replaced with the human C5aR gene. Neutrophils from these hC5aR knock-in mice are activated by C5a in a functional assay, a C5a-mediated neutrophil CD11b-upregulation assay, conducted in whole blood. Pretreatment with CCX168 inhibited neutrophil CD11b-upregulation. CCX168 at 38 nM caused a ten-fold reduction in responsiveness to C5a (an A10 value of 38 nM). Further, human C5aR knock-in mice develop glomerular necrosis and display kidney crescent (fibrocellular deposit) formation. Therefore, this model is appropriate to evaluate CCX168 for activity against kidney injury.

Methods: On day 0, ten-week-old female hC5aR KI mice were injected in the tail vein with 50 mg/kg anti-myeloperoxidase (MPO) antibody. The mice were dosed orally with CCX168 at doses of 0.1, 1 or 37.5 mg/kg once daily or CCX168 or vehicle control once daily, or 5 mg/kg CCX168 twice daily from Day -1 to Day 6. On days 6, urine samples were collected and analyzed for markers of kidney dysfunction including protein levels, red blood cells and white blood cells. Mice were euthanized on day 6 and blood was collected to measure plasma concentrations of CCX168. The kidneys were harvested and fixed in formalin for sectioning followed by histopathological examination. Specifically, the kidney tissues were analyzed for glomerular necrosis and crescent formation.

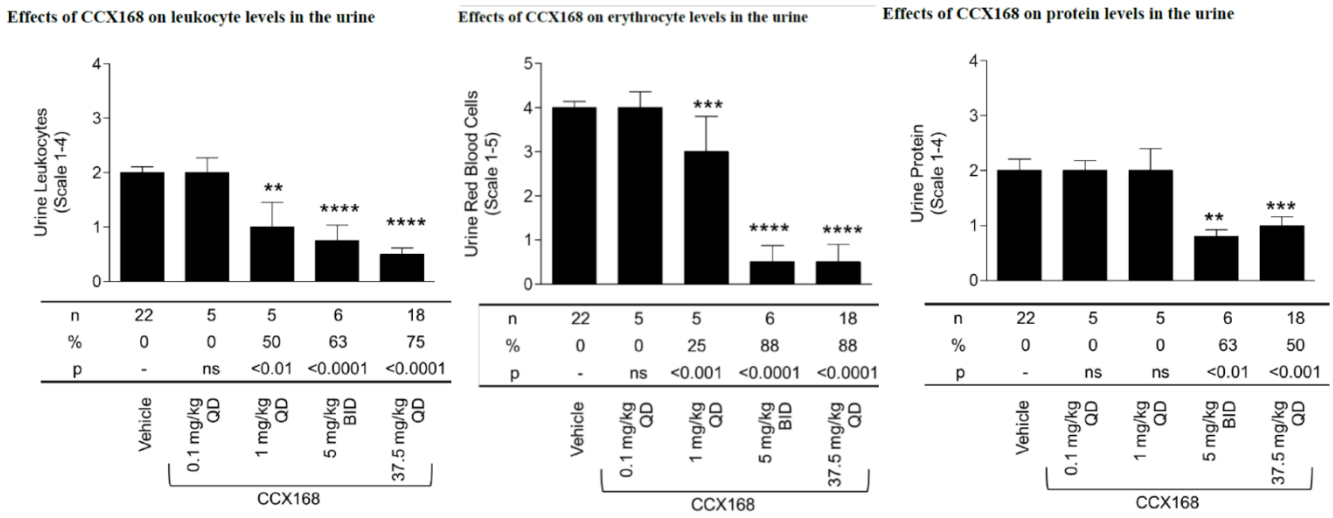
Results:
In a model of anti-MPO ANCA disease in hC5aR knock-in mice, administration of CCX168 at 5 mg/kg BID and 37.5 mg/kg QD resulted in significant reduction in the incidence of glomerular crescent formation and necrosis, relative to vehicle treated mice (Figure 4). CCX168 treatment resulted in dose-dependent decreases in urinary leukocytes and erythrocytes. Treatment-related reduction in total urine protein was noted, although the relationship to the dose was not clear (Figure 5).

Figure 4: Effect of CCX168 on ANCA-related kidney disease in hC5aR knock-in mice



Oral CCX168 dose-dependently inhibited kidney crescent formation and kidney necrosis in a mouse model of ANCA associated glomerulonephritis (Study PC0480_168_b)

Figure 5: : Effect of CCX168 on ANCA-related kidney disease in hC5aR knock-in mice



Oral CCX168 treatment reduced urinary leukocytes, erythrocytes, and total protein in a model of anti-MPO ANCA disease in hC5aR knock-in mice.

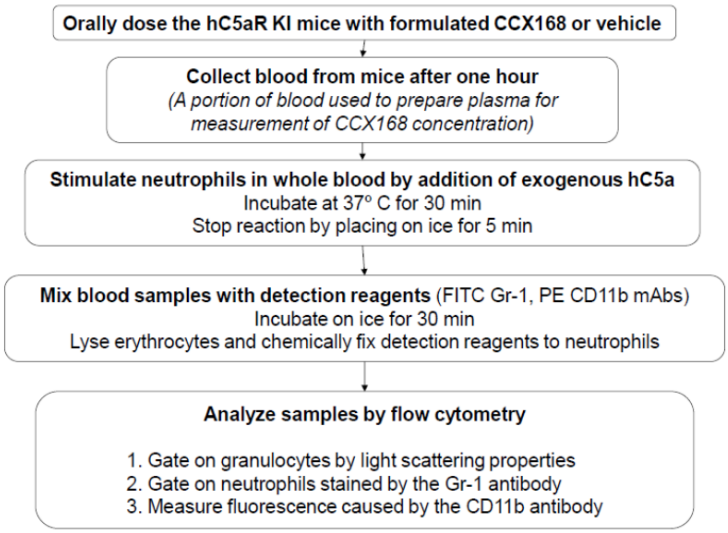
Title: Ex-vivo effects (hC5aR Knock-In Mice) of CCX168 on C5a-induced blood leukocyte CD11B Upregulation

Study No. PC0481_168_a

hC5aR mice were treated with different doses of CCX168. The concentration of CCX168 in the plasma was measured and the extent of hC5aR inhibition was determined using the CD11b upregulation assay. The plasma CCX168 concentration needed to provide adequate inhibition of hC5aR was determined so that it could be used in conjunction with the animal model to provide sufficient hC5aR inhibition needed to ameliorate disease in the model.

hC5aR-KI mice were treated with CCX168 at doses from 0.1 up to 5 mg/kg, or vehicle. One-hour post CCX168 treatment, blood was collected by cardiac puncture and was processed to measure plasma concentrations of CCX168 and assay the level of inhibition of CD11b upregulation. In the CD11b upregulation assay, 100 ul of blood was transferred to each well of a 96-well plate containing 11 µl of different concentrations of hC5a to stimulate neutrophils. The plate was incubated for 30 min on ice. After incubation, FACS lysing solution was added and the plate was centrifuged twice at 400 g for 5 min at 4 °C to isolate neutrophils. The cells were suspended in 200 ul cold PBS containing 2% FBS and 1.5% paraformaldehyde for fixation. The cells were then analyzed by flow cytometry by measuring the mean fluorescence intensity of CD11b antibody staining of Gr-1+ neutrophils.

Figure 6: Flow chart of sample collection and processing

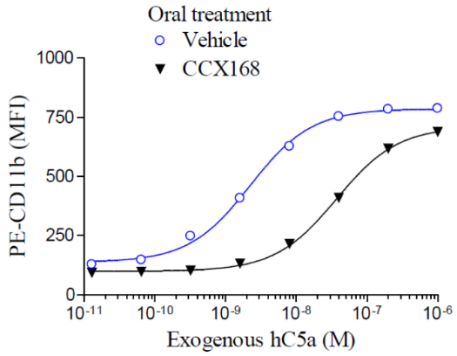


In the CD11b assay, the EC_{50} values for hC5a-mediated CD11b upregulation on neutrophils from CCX168-treated versus vehicle treated mice were determined. The data indicate that higher plasma concentrations of CCX168 yielded greater shifts in the EC_{50} of hC5a-mediated CD11b upregulation on neutrophils relative to vehicle-treated mice (Figure 7). The Sponsor's calculations indicate a CCX168 plasma concentration of 4.75 nM was required for 2-fold shift the EC_{50} value 2-fold and a plasma concentration of 38 nM was required for a 10-fold shift the EC_{50} value. However, A2 and A10 values

did not display a dose-responsive relationship. Thus, the Sponsor's calculations were unclear.

Figure 7: CCX168 inhibition of hC5a-mediated CD11b upregulation on neutrophils

A. CCX168-mediated reduction in sensitivity of neutrophils to hC5a-mediated CD11b upregulation



B. Comparison of CCX168 vs Vehicle treatment in changes in EC50 values for hC5a-mediated CD11b upregulation

Plasma CCX168	Animals per group	VEHICLE (A - C5a EC_{50})	CCX168 (A' - C5a EC_{50})	A_2	A_{10}
21 nM	n=7	1.4 nM	12 nM	2.9 nM	26 nM
43 nM	n=5	3.9 nM	37 nM	5.1 nM	46 nM
47 nM	n=5	2.2 nM	37 nM	3.0 nM	27 nM
61 nM	n=7	1.4 nM	36 nM	2.5 nM	22 nM
426 nM	n=6	2.1 nM	138 nM	6.6 nM	59 nM
584 nM	n=6	2.1 nM	148 nM	8.6 nM	78 nM

Figure 7: A) Neutrophils from vehicle- or CCX168-treated mice (1 hour following an oral dose of 0.15 mg/kg CCX168 or 2 ml/kg vehicle) were exposed to a range of concentrations of hC5a in the CD11b assay, and the CD11b mean fluorescence intensities (MFI) were plotted vs the hC5a concentrations. CCX168 treatment caused a rightward shift in the dose response curve. B) Summary of comparison of plasma concentrations of CCX168 to changes in EC_{50} values in the hC5a-mediated CD11b upregulation assay.

Conclusions: Treatment with CCX168 reduced the potency of exogenous hC5a to upregulate the adhesion molecule CD11b on blood neutrophils in hC5aR mice. A correlation between the plasma concentration of CCX168 and the extent of inhibition in the CD11b assay was established. The Sponsor contends that these data indicate that a plasma concentration of 38 nM CCX168 is required for 90% inhibition of hC5aR on hC5aR-KI mouse blood leukocytes. However, the Sponsor's calculation were unclear and veracity of their statements was considered questionable.

9.16 4.2 Secondary Pharmacology

Title: Chemokine Receptor Selectivity of CCX168 (Study No. PC0348_168_b)

CCX168 was tested at concentrations up to 10 µM for activity against human chemokine/chemotactic receptors. These included human CCR1 – CCR12; CXCR1-CXCR7, C5L2, C3aR, ChemR23, GPR1 and FPR1.

Methods:
Specific assays included: Chemotaxis assay methods were described under Section 4.1 (Study Nos. PC0347_168_a and PC0463_168_a).

Calcium mobilization: Cells were incubated with 2 µM indo-1/AM. Fluorescence was monitored (excitation at 350 nm and dual emission at 490 and 400 nm) using a PTI fluorimeter. CCX168 (10 µM) or an equivalent volume of DMSO was added to the cells, then the appropriate chemokine or chemoattractant agonist (100 nM) was added.

Radioligand binding: Cells (10^5/well) were incubated with 0.1 nM of [^{125}I]-labeled chemokine or chemoattractant plus various concentrations of CCX168. Following a 3-hour incubation period, cells were aspirated onto a filter and washed. Scintillation counting was performed.

Results: CCX168 showed no significant reactivity at any of these receptors evaluated in this study.

Title: Evaluation of CCX168 Against a Broad Panel of Biochemical Targets (Study No. PC0349_168)

The off-target selectivity of CCX168 was evaluated at 10 µM against a panel of 55 receptors and membrane associated proteins.

CCX168 at 10 µM did not achieve 50% inhibition against any receptors or membrane associated protein in the screening panel. It was noted that treatment with 10 µM CCX168 resulted in 42% inhibition of human Adenosine A2a, 33% inhibition of human Adenosine A3, and 59% inhibition of the sodium channel (site 2).

The Sponsor noted that CCX168 blocked C5a mediated cell migration with a potency of 0.25 nM; therefore, there was greater than 1000-fold selectivity for hC5aR relative to off-target activities assayed in this study.

Title: Biochemical Selectivity Profile of C0335273 (Study No. PC0486_168)

The off-target selectivity of C0335273 was evaluated in the following formats:

- C0335273 was evaluated at 10 µM in duplicate against the panel of 55 pharmacologically relevant targets in a radioligand binding assay format.
- C0335273 was evaluated at 10 µM in duplicate against the glucocorticoid receptor in a radioligand binding assay

Results: C0335273 exhibited weak activity at the human CB1 receptor (53% inhibition), sodium channel (site 2) (65% inhibition), and the $GABA_A$ receptor (51% inhibition).

Title: Activity of CCX168 on Glucocorticoid Receptor (Study No. PC0464_168)

CCX168 was evaluated at 10 µM against the glucocorticoid receptor in a radioligand binding assay

Result: CCX168, at a concentration of 10 µM, did not bind to the glucocorticoid receptor.

It is noted that neither CCX168 nor CCX168-M1 inhibited the glucocorticoid receptor or enzymes involved in metabolism of corticosteroids. This is a potentially relevant finding given that the current standard of care for ANCA associated vasculitis involves oral prednisone as well as administration of rescue corticosteroid treatment if necessary; however, the correlation of this in vitro assay to the in vivo setting was not clear.

9.17 4.3 Safety Pharmacology

See the nonclinical review of IND 120784 (Authored by Dr. Matthew Whittaker, Dated in DARRTS July 15, 2014) for additional details on safety pharmacology studies conducted with CCX168. The findings are summarized below.

CCX168 was evaluated in a standard battery of safety pharmacology studies.

- In vitro, CCX168 did not inhibit hERG channel current in HEK293 cells stably expressing hERG, at concentrations up to 6.9 µM. CCX168-M1 inhibited hERG channel currents by 38% at 3 µM. CCX168-M1 at concentrations of 10 and 15.8 µM resulted in a similar degree of inhibition.
- In a cardiovascular safety pharmacology studies in telemetered male cynomolgus monkeys (single oral doses of 0, 5, 15, 50 mg/kg CCX168), systolic, diastolic, and arterial blood pressure values were decreased by approximately 7 - 10% at 50 mg/kg relative to controls during the time period from 15 mins – 225 mins after dosing. No treatment related effects were observed on QTc interval.
- In a respiratory safety pharmacology in rats (single oral doses 0, 3.5, 19, 73 mg/kg CCX168), no treatment related effects were observed at any dose tested.
- No treatment related findings were observed in CNS or renal safety pharmacology studies with rats that received CCX168 at doses up to 100 mg/kg.
- Taken together, avacopan did not have any significant adverse effects on the cardiovascular, CNS, respiratory, and renal parameters that were evaluated.

5 Pharmacokinetics/ADME/Toxicokinetics

9.18 5.1 PK/ADME

Absorption

Title: Pharmacokinetic Evaluation of CCX168 in Sprague-Dawley Rats
Study No. PC0365_168_a

Pharmacokinetic profiles of CCX168 following intravenous and oral administration to naive Sprague-Dawley rats.

CCX168 was dosed intravenously at 0.5 mg/kg, orally at 2 mg/kg as a suspension in aqueous hydroxypropyl methylcellulose, and orally as a solution at 30 mg/kg and 100 mg/kg in PEG (b) (4)

Blood (0.2 mL) was sampled through the jugular vein or cardiac puncture (for terminal point only) at pre-dose, 2, 5, 10, 15, and 30 min, 1, 2, 4, 6, and 8 hours post-dose for IV dosing and at pre-dose, 5, 15, and 30 min, 1, 1.5, 2, 4, 6, 8, and 24 (24 h for 30 and 100 mg/kg dosing only) hours post-dose for oral dosing.

Results:
Following oral dosing of the neutral form of CCX168, the bioavailability was 27% with suspension dosing at 2 mg/kg. Bioavailability was higher with the oral solution formulation: 104% at 30 mg/kg and 55% at 100 mg/kg).

Following intravenous dosing, the half-life was 1.9 hours, the average total body clearance was 21.2 mL/min/kg (~38% of rat liver blood flow), and the volume of distribution of was 1.8 L/kg (exceeds the blood volume [0.054 L/kg] and was indicative of distribution into tissues)

Mean plasma concentrations and mean pharmacokinetic parameters following IV and oral dosing of CCX168 are shown in Table 7.

Table 7: Mean pharmacokinetic parameters of CCX168 in SD rats

Route (formulation)	**IV** (Lot 3A; solution in propylene glycol/*N,N'*-dimethyl acetamide/EtOH (31.6/31.6/36.8))[a]	**PO** (Lot 3A; suspension in 1% aqueous hydroxypropyl methylcellulose)[b]	**PO** (Lot 12A; solution in PEG400 – Solutol HS-15 (70/30))[c]	
Dose [mg/kg]	0.5 (N=2)	2 (N=2)	30 (N=3)	100 (N=3)
C_{max} [ng/mL]		152	2530 ± 256	3810 ± 555
$AUC_{0-\infty}$ [ng•h/mL]	397	434	24600 ± 7450	43300 ± 9730
$MRT_{0-\infty}$ [h]	1.4	2.7	7.0 ± 1.0	6.7 ± 0.2
CL [mL/min/kg]	21.2			
$t_{1/2}$ [h]	1.9	2.3	4.6 ± 0.8	4.1 ± 0.2
Vd_{ss} [L/kg]	1.8			
t_{max} [h]		1.0	1.5 ± 0.0	1.7 ± 0.3
F [%]		27	104 ± 31.8	55 ± 13

[a]Study No. 08-RPK-182; [b]Study No. 08-RPK-178; [c]Study No. 08-RPK-211.

Title: Pharmacokinetic Evaluation of CCX168 and its Metabolite CCX169-M1 in Rats Following 7 Days of QD and BID Oral Gavage Dosing of CCX168
Study No. PC0639_168

Methods: Male and female Sprague-Dawley rats (3/sex/group) were administered CCX168 by the oral route at dose levels of 100 or 300 mg/kg once daily (QD), and at 50, 100 or 300 mg/kg twice daily (BID) for 7 day. Blood samples were collected on Day 1 and Day 7 at predetermined time points and the plasma concentrations of CCX168 and its metabolite, CCX168-M1, were analyzed by LC-MS/MS. Pharmacokinetic parameters (C_{max} and AUC_{0-t} were derived)

Results: Pharmacokinetic analysis of CCX168 administered orally at doses of 100 and 300 mg/kg QD indicated exposures (AUC0-24) of CCX168 and CCX168-M1 were higher at 100 mg/kg than 300 mg/kg indicative of saturation of exposure. There was evidence of modest accumulation of exposure (AUC) from Day 1 to Day 7. Cmax was higher at 100 mg/kg than 300 mg/kg for CCX168 and CCX168-M1. Cmax decreased slightly from Day 1 to Day 7 for CCX168 and CCX168-M1.

Table 8: Mean Pharmacokinetic Parameters of CCX168 and CCX168-M1 with QD dosing in SD rats

CCX168

Dose:		100 mg/kg		300 mg/kg	
		Day 1	Day 7	Day 1	Day 7
C_{max} (ng/mL)	Male	6,250 ± 1,340	6,110 ± 580	4,000 ± 1,360	3,640 ± 1,010
	Female	5,150 ± 1,170	5,970 ± 1,980	3,450 ± 560	3,320 ± 502*
AUC_{0-24} (ng•h/mL)	Male	49,900 ± 17,500	98,400 ± 28,900	34,300± 17,900	53,900 ± 25,900
	Female	47,800 ± 4,000	112,000 ± 49,400	31,600 ± 5,550	54,600 ± 7,800*

CCX168-M1

Dose:		100 mg/kg		300 mg/kg	
		Day 1	Day 7	Day 1	Day 7
C_{max} (ng/mL)	Male	718 ± 173	631 ± 185	510 ± 233	464 ± 93.9
	Female	832 ± 48.5	678 ± 119	554 ± 129	506 ± 31.1*
AUC_{0-24} (ng•h/mL)	Male	8,550 ± 2,390	12,200 ± 4,340	6,310 ± 4,630	8,300 ± 1,550
	Female	11,100 ± 709	13,900 ± 1,710	7,120 ± 792	10,500 ± 1,030*

Pharmacokinetic analysis of CCX168 administered orally at doses of 50, 100, and 300 mg/kg BID indicated the maximum exposure (AUC0-24) of CCX168 and CCX168-M1 occurred at 100 mg/kg BID. The increase of exposure from 50 to 100 mg/kg BID was less than dose proportional. The exposure decreased from 100 mg/kg to 300 mg/kg BID indicative of saturation of exposure. There was evidence of accumulation from Day 1 to Day 7 (up to 2.3-fold).

Table 9: Mean Pharmacokinetic Parameters of CCX168 and CCX168-M1 with BID dosing in SD rats

CCX168

Dose:		50 mg/kg		100 mg/kg		300 mg/kg	
		Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
C_{max} (ng/mL)	Male	5,610 ± 511	5,600 ± 1,180	8,040 ± 4,330	6,240 ± 938	1,510 ± 275	1,830 ± 165
	Female	4,590 ± 295	6,860 ± 979	4,550 ± 708	6,830 ± 234	2,170 ± 631	2,280 ± 184*
AUC_{0-24} (ng•h/mL)	Male	53,200 ± 6,090	88,200 ± 5,850	91,400 ± 40,000	115,000 ± 35,000	10,400 ± 2,210	27,800 ± 2,980
	Female	46,200 ± 9,170	118,000 ± 10,400	52,500 ± 6,880	122,000 ± 5,040	17,400 ± 2,440	37,100 ± 249*

CCX168-M1

Dose:		50 mg/kg		100 mg/kg		300 mg/kg	
		Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
C_{max} (ng/mL)	Male	627 ± 250	559 ± 185	1,370 ± 600	944 ± 416	173± 30.5	183 ± 35.1
	Female	874 ± 137	865 ± 104	808 ± 115	763 ± 68.0	383 ± 38.6	428 ± 15.6*
AUC_{0-24} (ng•h/mL)	Male	8,120 ± 2,560	9,320 ± 3,030	20,500 ± 9,690	17,500 ± 7,520	1,710 ± 335	3,510 ± 569
	Female	13,500 ± 411	17,800 ± 1,690	13,200 ± 2,720	16,100 ± 1,470	5,210 ± 820	8,720 ± 209*

Distribution

Title: Evaluation of Non-Specific Protein Binding of CCX168 and M1 in mouse, rat, hamster, rabbit, dog, cynomolgus monkey, and human plasma
Study No. PC0632_168

Methods: Protein binding of CCX168 and CCX168-M1 in plasma from CD-1 mice, SD rats, rabbits, hamsters, dogs, and humans was determined using commercially available plasma samples. CCX168 and the M1 metabolite were tested at plasma concentrations of 2.5, 10, and 50 µM and subjected to equilibrium dialysis for 4 hours at 37°C.

Results: The mean percent bound values for CCX168 and M1 were >99.9% in plasma from SD rats, hamsters, cynomolgus monkey, and humans and >96.7% bound in plasma from CD-1 mice, rabbits, and dog.

Table 10: Summary of in vitro plasma protein binding of CCX168 and CCX168-M1 in plasma of various species

Species	Concentration (µM)	CCX168		CCX168-M1		Warfarin	
		f_u	% Bound	f_u	% Bound	f_u	% Bound
Human	2.5	< 0.001	> 99.9%	< 0.001	> 99.9%		
	10	< 0.001	> 99.9%	< 0.001	> 99.9%	0.010	99.0%
	50	< 0.001	> 99.9%	< 0.001	> 99.9%		
Cynomolgus monkey	2.5	< 0.001	> 99.9%	< 0.001	> 99.9%		
	10	< 0.001	> 99.9%	< 0.001	> 99.9%	0.007	99.3%
	50	< 0.001	> 99.9%	< 0.001	> 99.9%		
New Zealand white Rabbit	2.5	< 0.001	> 99.9%	0.001	99.9%		
	10	< 0.001	> 99.9%	< 0.001	> 99.9%	0.033	96.7%
	50	< 0.001	> 99.9%	< 0.001	> 99.9%		
Syrian Golden Hamster	2.5	< 0.001	> 99.9%	< 0.001	> 99.9%		
	10	< 0.001	> 99.9%	< 0.001	> 99.9%	0.006	99.4%
	50	< 0.001	> 99.9%	< 0.001	> 99.9%		
Sprague-Dawley Rat	2.5	< 0.001	> 99.9%	< 0.001	> 99.9%		
	10	< 0.001	> 99.9%	< 0.001	> 99.9%	0.005	99.5%
	50	< 0.001	> 99.9%	< 0.001	> 99.9%		
CD-1 Mouse	2.5	< 0.001	> 99.9%	< 0.001	> 99.9%		
	10	< 0.001	> 99.9%	< 0.001	> 99.9%	0.033	96.7%
	50	< 0.001	> 99.9%	< 0.001	> 99.9%		
Beagle dog	2.5	< 0.001	> 99.9%	< 0.001	> 99.9%		
	10	< 0.001	> 99.9%	< 0.001	> 99.9%	0.028	97.2%
	50	< 0.001	> 99.9%	< 0.001	> 99.9%		

Note: recorded as ChemoCentryx Study No. 14 PPB 01

Metabolism

Title: Investigation of CCX168 Metabolites Produced by In Vitro Systems of Multiple Species Following Incubation of [^{3}H]CCX168
Study No. PC0632_168_a

Methods: In vitro metabolism studies were conducted with liver microsomes from humans and several nonclinical species. Briefly, 1 µM [^{3}H]CCX168 was incubated with liver microsomes (rat, hamster, rabbit, monkey, and human) and hepatocytes (rat, hamster, rabbit, monkey, and human) from various species.

Microsomal incubation of CCX168:
CCX168 was incubated at 37°C with 1 mg/mL liver microsomes and 1 mM NADPH. Final compound concentrations were 50 µM for non-radiolabeled samples and 1 µM (25 µCi/mL) for radiolabeled samples. At 0 and 4 hours, the reaction was quenched to stop the reaction and extract the analytes.

Hepatocyte incubation of CCX168:
Cryo-preserved hepatocytes were thawed and were diluted to a final cell concentration of 1 – 2 million viable cells/mL. Final CCX168 compound concentrations were 50 µM for non-radiolabeled samples and 1 µM (25 µCi/mL) for radiolabeled samples. At 0 or 2 hours, the reaction was quenched and extract the analytes.

Results:

A total of twelve metabolites were detected in the microsomal incubation of the five species where CCX168-M1 was the major metabolite (**Table 11**). The human microsomal profile contained 10 metabolites. The unchanged parent compound accounted for the largest proportion of radioactivity among all metabolites detected.

The metabolism of CCX168 in hepatocytes was less extensive than in liver microsomes. CCX168-M1 and CCX168-M6 were the only metabolites detected in human, monkey and rat hepatocyte incubations. The unchanged parent compound accounted for the largest proportion of radioactivity among all metabolites detected.

All metabolites produced in human liver microsomes and hepatocytes were also formed by at least one animal species.

Table 11: In vitro metabolism of CCX168 in liver microsomes

Metabolite Identifier	Percentage of total radioactivity				
	Human	Monkey	Rabbit	Hamster	Rat
CCX168 (parent)	39.9	10.5	20.1	37.3	16.9
CCX168-M1	17.7	10.6	17.1	6.8	20.4
CCX168-M3	2.2	6.3	14.2	3.9	8.8
CCX168-M6	0.4	-	-	1.0	1.3
CCX168-M8	2.7	-	7.6	24.5	0.7
CCX168-M9	1.2	-	-	1.8	-
CCX168-M10	2.3	8.6*	21.6*	9.3	-
CCX168-M11	2.8			-	-
CCX168-M12	0.5	-	1.9	-	-
CCX168-M13	3.0	5.1	-	-	-
CCX168-M14	1.5	9.2	-	-	-
CCX168-M15	-	-	-	-	30.7

Table 12: In vitro metabolism of CCX168 in hepatocytes

Metabolite Identifier	Percentage of total radioactivity			
	Human	Monkey	Rabbit	Rat
CCX168 (parent)	92.5	76.9	54.9	88.3
CCX168-M1	0.4	5.1	5.6	0.6
CCX168-M3	-	-	2.4	-
CCX168-M6	0.8	2	4.8	0.3
CCX168-M11	-	-	3.1	-

Title: Characterization of Metabolic Pathways of CCX168 and CCX168-M1(Study No. PC0711_168)

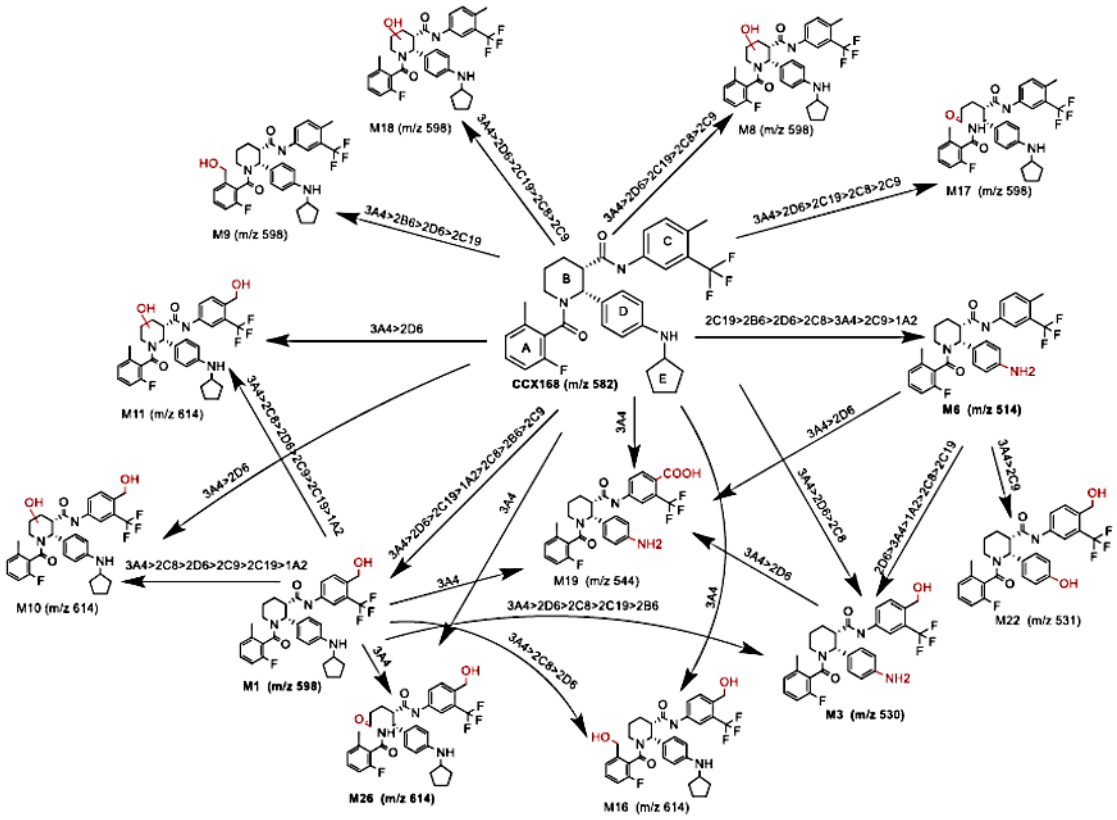
The human metabolic pathways of CCX168 and metabolite CCX168-M1 were characterized, including the CYP450 isozymes that are responsible for metabolic transformation of these molecules. The metabolic pathways involved in CCX168 transformation were assessed in systematic assays designed to determine the activity of recombinant CYP450 enzyme systems and pooled human liver microsomes on CCX168.

Methods:
Using Recombinant Cytochrome P450 Isozymes:
CCX168, reference standards for M1, M3, M6 and M26, and each positive control compound were separately incubated at 2 µM with each of the following recombinant CYP450 isozymes: CYP3A4, CYP1A2, 2C19, CYP2B6, CYP2C9, CYP2D6 and CYP2C8 (500 µL 50 mM phosphate buffer [pH 7.4] containing 20 pmol/mL and 4 mM NADPH). Reaction samples were collected at 0, 15 and 60 minutes and were then processed and plated for LC-MS/MS analysis.

Using Human Liver Microsomes:
CCX168 and reference standards for M1, M3, M6 and M26 were incubated separately at 2 µM with 1 mg/mL human liver microsomes pooled from 50 donors (500 µL 50 mM phosphate buffer [pH 7.4] and 2 mM NADPH). Reaction samples were collected at 0, 15 and 60 minutes and were then processed and plated for LC-MS/MS analysis.

Results: CYP3A4/5 was the primary isozyme involved in the in vitro metabolism of CCX168 and M1. The metabolic pathways and the corresponding CYP450 isozymes for CCX168 and CCX168-M1 involved were proposed based on metabolism results from in vitro incubation of CCX168 and reference standards for metabolites CCX168-M1, CCX168-M3, CCX168-M6 and CCX168-M26. The proposed biotransformation pathways and the CYP450 isozymes involved are shown in Figure 8.

Figure 8: Proposed Metabolic Pathways for CCX168 and Metabolite CCX168-M1



Note: The display order of the CYP450 isozymes in each pathway is based on the relative contribution to the formation of each metabolite.

6 General Toxicology

9.19 6.2 Repeat-Dose Toxicity

The Sponsor conducted oral toxicology studies up to 26 weeks in rats, 13 weeks in hamsters, and 44 weeks in monkeys.

- Review of the 26-week oral toxicology study in rats can be found in the review of IND 120784 dated November 9, 2017.
- Review of the 13-week oral toxicology study in hamsters can be found in the review of IND 120784 dated November 14, 2017.
- Review of the 20-week oral toxicology study in monkeys can be found in the review of IND 120784 dated July 15, 2014.

Study title: 44-Week Nasogastric Intubation (Weeks 1-5) and Oral Gavage (Weeks 6-44) Toxicity and Toxicokinetic Study with CCX168 in Cynomolgus Monkeys with a 6 Week Recovery Phase

Study no.:	PC0654_168
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 8, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lot # SD-112-9-0904; Purity 99.6%

Key Study Findings

- Monkeys received either 0 (vehicle-control article), 5 or 15 mg/kg QD, or 15 mg/kg BID (30 mg/kg/day) of CCX168 over the first 25 weeks of the study (Groups 1-5). At the beginning of the study, CCX168 and the vehicle were administered by nasogastric intubation (Weeks 1-5). Starting at Week 6, the route of administration was switched to oral gavage (Weeks 6-44). After reviewing interim toxicokinetic data, the Sponsor/Study Director chose to increase dose levels with the goal of increasing CCX168 exposure. Therefore, the doses were changed to 0 (vehicle control article), 7.25 or 22.5 mg/kg QD, or 22.5 mg/kg BID (45 mg/kg/day) of CCX168 for Groups 1-5, respectively, from Weeks 26-44. As a consequence of the increasing dose levels at Week 26, the dose volume changed from 1 mL/kg/day from Weeks 1-25 to 1.5 mL/kg/day from Weeks 26-44.
- No CCX168-related mortalities occurred during the treatment or recovery periods.
- No CCX168-related findings were noted for clinical signs, body weights, physical examinations, hematology, clinical chemistry, vital signs, pulse oximetry, ophthalmic exams, blood pressure, ECG parameters, neurological examinations, anti-KLH induced IgM or IgG antibody production, peripheral blood lymphocyte subset analyses, clinical chemistry, or macroscopic and microscopic examinations.
- Vehicle-related fecal abnormalities and minimally decreased body weight gain were noted in all groups including the controls, which increased after the Week 26.
- The NOAEL was considered as the High Dose (30 mg/kg/day (Weeks 1- 25) and 45 mg/kg/day (Weeks 26-44)). The AUC_{0-24} and C_{max} associated with the 45 mg/kg/day dose were 26400 ng·hr/mL and 2200 ng/mL, respectively, in males and 32200 ng·hr/mL and 2470 ng/mL, respectively, in females.

Methods

Doses:	Weeks 1 - 25 0, 5, 15 mg/kg QD 0, 15 mg/kg BID (30 mg/kg/d) Weeks 26-44 0, 7.25, 22.5 mg/kg QD 0, 22.5 mg/kg BID (45 mg/kg/day)
Frequency of dosing:	QD: 0, 5, 15 mg/kg (Weeks 1-25); 0, 7.25, 22.5 mg/kg (Weeks 26-44) BID: 15 mg/kg (30 mg/kg/day) (Weeks 1-25); 22.5 mg/kg (45 mg/kg/day) (Weeks 26-44)
Route of administration:	Nasogastric intubation (weeks 1- 5) Oral Gavage (weeks 6 – 44)
Dose volume:	Weeks 1-25: 0.5 mL/kg (1 mL/kg/day) Weeks 26-44: 0.75 mL/kg (1.5 mL/kg/day)
Formulation/Vehicle:	Polyethylene glycol (b) (4) v:v).
Species/Strain:	cynomolgus monkeys (*Macaca fascicularis*)
Number/Sex/Group:	Main study: 4/sex/group Recovery: 2/sex for Group 1 (vehicle control) and Group 5 (high dose)
Age:	2-3 years old
Weight:	Males: 2.4 to 2.9 kg Females: 2.4 to 3.4 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	There were no deviations that affected the interpretation of study findings nor compromised the integrity of the study

Experimental Design:

WEEKS 1 - 25					
	No. of Animals[a]		Dose Level	Dose Level	Dose Concentration[b]
Group	Male	Female	(mg/kg/dose)	(mg/kg/day)	(mg/mL)
1 (Vehicle control article)[c,d]	6	6	0	0	0
2 (Vehicle control article)[c,e]	4	4	0	0	0
3 (Low)[e]	4	4	5	5	5
4 (Mid)[e]	4	4	15	15	15
5 (High)[d]	6	6	15	30	30

a Animals designated for recovery sacrifice (two animals/sex in Groups 1 and 5, depending on survival) underwent at least 6 weeks of recovery following dosing.

b The test article, CCX168, was supplied as a free base anhydrate. Correction factors of 1.024 (only formulations prepared for use during Week 1 of the dosing phase) or 1.026 (all subsequent formulations using lot #112-9-0904) were applied to lot #112-9-0904; a correction factor of 1.021 was applied to lot #112-9-0923; a correction factor of 1.013 was applied to lot #112-9-0911; and a correction factor of 1.007 was applied to lot #D-14-030. Details of use on study are available in the methods. Correction factors describe the quantity of the provided lot containing 1000 mg of the neutral active test article, CCX168, compensating for chemical impurities, solvent, and water content.

c Groups 1 and 2 were given vehicle control article only (Polyethylene glycol [(b) (4) v:v]).

d Animals in Groups 1 and 5 were dosed twice daily, with approximately 8 hours between each dose.

e Animals in Groups 2, 3, and 4 were dosed once daily at the same time as the first daily dose for animals in Groups 1 and 5.

WEEKS 26 - 44					
	No. of Animals[a]		Dose Level	Dose Level	Dose Concentration[b]
Group	Male	Female	(mg/kg/dose)	(mg/kg/day)	(mg/mL)
1 (Vehicle control article)[c,d]	6	6	0	0	0
2 (Vehicle control article)[c,e]	4	4	0	0	0
3 (Low)[e]	4	4	7.25	7.25	5
4 (Mid)[e]	4	4	22.5	22.5	15
5 (High)[d]	6	6	22.5	45.0	30

a Animals designated for recovery sacrifice (two animals/sex in Groups 1 and 5, depending on survival) underwent at least 6 weeks of recovery following dosing.

b The test article, CCX168, was supplied as a free base anhydrate. A correction factor of 1.007 was applied to lot #D-14-030 and a correction factor of 1.015 was applied to lot #D-15-012. Details of use on study are available in section 3.2.1. Correction factors describe the quantity of the provided lot containing 1000 mg of the neutral active test article, CCX168, compensating for chemical impurities, solvent, and water content.

c Groups 1 and 2 were given vehicle control article only (Polyethylene glycol [(b) (4) v:v]).

d Animals in Groups 1 and 5 were dosed twice daily, with approximately 8 hours between each dose.

e Animals in Groups 2, 3, and 4 were dosed once daily at the same time as the first daily dose for animals in Groups 1 and 5.

Observations and Results

Mortality

Animals were checked twice daily, in the morning and evening, for mortality.

No CCX168-related mortality was noted during the study period. Two gavage-related deaths occurred: One female (Animal No. I05288) in the vehicle control group on Day 26 and one female (Animal No. I05300) in the 30 mg/kg/day group on Day 50. These animals were replaced. All remaining animals survived to their scheduled sacrifice.

Clinical Signs

Animals were checked twice daily, in the morning and evening, for mortality, abnormalities, and signs of pain or distress. Cageside observations were conducted for each animal once daily during the predose, dosing, and recovery phases. Detailed observations were conducted for each animal four times during the predose phase, prior to dosing on Day 1, and weekly (based on Day 1) throughout the dosing and recovery phases. Detailed observations were also collected on days of scheduled sacrifice.

No CCX168-related clinical signs were noted. Vehicle-related increases in abnormal fecal observations were noted including green discoloration, non-formed, or liquid feces in the control and CCX168 groups. It is noted that the incidence of these observations increased when the dose volume was increased at Week 26.

Body Weights

Body weights were recorded four times during the predose phase, before dosing on Day 1, and weekly up through Week 25 of the dosing phase. Beginning on Week 26 of the dosing phase body weights were recorded twice weekly until the end of the recovery phase.

No CCX168-related changes in body weight or body weight gain were noted. Vehicle related effects on body weight gain were noted. Following the increase in vehicle volume at Week 26, transient body weight loss for most animals, including the controls, was noted. In general animals did not gain as much body weight during the second half of the study (after Week 26). Weight gain was noted in the recovery phase, therefore, the vehicle related effects on body weight were considered reversible.

Ophthalmoscopy

Ophthalmic examinations were conducted on all anesthetized animals once during the predose phase and once during Week 43 of the dosing phase by a veterinarian using an indirect ophthalmoscope. The eyes were dilated with a mydriatic agent prior to examination.

No CCX168-related ophthalmic findings were noted.

Vital Signs

Body temperature, respiration rate, and heart rate were collected by technical staff on anesthetized animals once during the predose phase and approximately 4 and 24 hours following the first daily dose on Day 1 and during Weeks 34 and 44 of the dosing phase and once during Week 6 of the recovery phase.

No CCX168-related changes in vital signs were noted.

Pulse Oximetry

Pulse oximetry measurements were recorded by trained technical staff on anesthetized animals during Weeks 34 and 44 of the dosing phase approximately 4 and 24 hours following the first daily dose and once during Week 6 of the recovery phase.

No CCX168-related changes in blood oxygen saturation were noted.

Blood Pressure Measurements

Blood pressure measurements were recorded by trained technical staff on animals anesthetized with ketamine once during the predose phase, once on Day 1 and during Week 44 of the dosing phase approximately 4 and 24 hours following the first daily dose.

No CCX168-related changes in blood pressure were noted.

ECG

Electrocardiograms (ECGs) were recorded by technical staff on anesthetized animals once during the predose phase and approximately 4 and 24 hours following the first daily dose on Day 1, during Weeks 18 and 44 of the dosing phase, and during Week 6 of the recovery phase at the approximate 4 hour collection time from the dosing phase. Electrocardiograms were recorded using eight leads. Routine quantitative measurements of ECGs were made on a single lead. The heart rate-corrected QT (QTc) interval was calculated using the Bazett method. A qualitative review for rhythm abnormalities and disturbances of collected ECGs was performed.

No treatment-related ECG changes were noted.

Neurological Examination

Neurological examinations were conducted by trained technical staff once during Weeks 34 and 44 of the dosing phase and once during Week 6 of the recovery phase. Each animal was observed before removing the animal from the cage. After removing the animal from the home cage and placing it in a restraint device, the general condition of the animal was observed. The head and eyes were examined for unusual orientation and movements; reflexes were tested, and muscle tone was evaluated.

No CCX168-related findings were noted in the neurological assessment.

Hematology

Blood samples for hematology were collected from fasted animals via a femoral vein. Blood samples were collected twice during the predose phase; once during Weeks 8, 18, and 34 of the dosing phase; and prior to the terminal and recovery phase necropsies.

No CCX168-related changes were noted for hematology parameters.

Peripheral Blood Immunophenotyping

Blood was collected from fasted animals via a femoral vein for immunophenotyping twice during the predose phase, during Week 18, and prior to the terminal and recovery sacrifices.

Lymphocyte Subsets	Phenotype
total T cells	CD3+
helper T cells	CD3+ CD4+
cytotoxic T cells	CD3+ CD8+
B cells	CD3- CD20+
natural killer cells	CD3- CD16+

There were no CCX168-related effects on absolute values for peripheral blood immunophenotyping of lymphocytes (total T lymphocytes, helper T lymphocytes, cytotoxic T lymphocytes, B lymphocytes, or natural killer cells) during the dosing or recovery phases.

Clinical Chemistry

Blood samples for coagulation and clinical chemistry were collected from fasted animals via a femoral vein. Blood samples were collected twice during the predose phase; once during Weeks 8, 18, and 34 of the dosing phase; and prior to the terminal and recovery phase necropsies.

No CCX168-related changes were noted for coagulation or clinical chemistry parameters.

Urinalysis

Urine samples were collected once during the predose phase; during Weeks 18 and 34 of the dosing phase; and prior to the terminal and recovery necropsies.

No CCX168 changes were noted for urinalysis parameters.

Gross Pathology

Monkeys (4/sex/group) were sacrificed on Day 309 of the dosing phase. Remaining animals were sacrificed on Day 43 of the recovery period. Terminal body weights were recorded. For scheduled and unscheduled sacrifices examination of the external features of the carcass; external body orifices; abdominal, thoracic, and cranial cavities; organs; and tissues was performed.

No CCX168-related macroscopic findings were observed at the terminal or recovery

sacrifice.

Organ Weights

Organ weights, as indicated in the following table, were recorded at each scheduled sacrifice. Paired organs were weighed together (unless noted as missing).

No CCX168-related organ weight changes were noted at the terminal or recovery sacrifice.

Histopathology

Adequate Battery Yes

The following tissues from each animal were preserved in 10% neutral-buffered formalin unless otherwise indicated.

Organ/Tissue			Organ/Tissue		
adrenal (2)	W	P,E	mesenteric lymph nodes		P,E
animal identification			muscle (biceps femoris)		P,E
aorta		P,E	optic nerve (2)[a]		P,E
brain	W	P,E	ovary (2)	W	P,E
cecum		P,E	pancreas		P,E
cervix		P,E	pituitary gland	W	P,E
colon		P,E	prostate	W	P,E
dose site(s)		P,E	rectum		P,E
duodenum		P,E	salivary gland (mandibular [2])	W	P,E
epididymis (2)		P,E	sciatic nerve		P,E
esophagus		P,E	seminal vesicle		P,E
eye (2)[a]		P,E	skin and subcutis		P,E
femur with bone marrow (articular surface of the distal end)		P,E	spinal cord (cervical, thoracic, and lumbar)		P,E
gall bladder (drained)[b]	W	P,E	spleen	W	P,E
heart	W	P,E	sternum with bone marrow		P,E
ileum		P,E	stomach		P,E
jejunum		P,E	testis (2)[a]	W	P,E
kidney (2)	W	P,E	thymus	W	P,E
lacrimal gland		P,E	thyroid (2 lobes) with parathyroid	W	P,E
lesions		P,E	tongue		P,E
liver[b]	W	P,E	trachea		P,E
lungs with large bronchi	W	P,E	urinary bladder		P,E
mammary gland (females)		P,E	uterus	W	P,E
mandibular lymph nodes		P,E	vagina		P,E

E = Examined microscopically; P = Processed; W = Weighed.

a Collected in modified Davidson's fixative and stored in 10% neutral-buffered formalin.

b Organs weighed together. This applies to gall bladder and liver.

Peer Review No

Histological Findings

Tissues designated for microscopic examination (Table X) from each animal were embedded in paraffin, sectioned, and slides were prepared and stained with hematoxylin and eosin. Tissues listed in the table were examined microscopically from all animals by the principal investigator for anatomic pathology (unless noted as missing).

No CCX168-related microscopic findings were observed at the terminal or recovery sacrifice.

T-cell dependent antibody response (TDAR)/Anti-KLH IgM and IgG Analysis

Main study animals were given one dose of KLH (1 mL) by subcutaneous injection (interscapular region) on Day 285 of the dosing phase (24 days prior to the terminal sacrifice). Blood samples (approximately 0.5 mL) were collected via a femoral vein from animals predose on Day 1 of the dosing phase and on Days 285 (prior to KLH administration), 290, 295, 302, and 309 of the dosing phase (5, 10, 17, and 24 days, respectively, following KLH administration).

The recovery sacrifice animals were given one dose of KLH (1 mL) by subcutaneous injection into the interscapular region on Day 19 of the recovery phase. Blood samples (approximately 0.5 mL) were collected via a femoral vein from animals predose on Day 19 of the recovery phase, and on Days 24, 29, 36, and 43 of the recovery phase (5, 10, 17, and 24 days, respectively, following recovery phase KLH administration).

Serum samples were analyzed using a validated enzyme-linked immunosorbent assay (ELISA) method to assess the ability of the test article to interfere with the anti-KLH IgM and immunoglobulin IgG ELISA assays.

Treatment with CCX168 did not result in reduced anti-KLH IgM or IgG antibody production relative to vehicle controls. However, it was noted that the response to KLH immunization in control animals was minimal and lower than expected for this assay. The anti-KLH IgM and IgG antibody production was greater in CCX168 treated animals than in the untreated vehicle controls.

Toxicokinetics

Blood samples (approximately 2.0 mL) were collected via a femoral vein into tubes containing potassium (K2) EDTA on Days 1, 21, and 36 and during Weeks 18, 26, 34, and 42 of the dosing phase. Samples were collected predose and approximately 1, 2, 4, 8 (prior to the second daily dose when applicable), 9, 10, 12, and 24 hours postdose.

Exposure to CCX168 increased with the dose level on Day 1 (5 to 15 mg/kg/day), Day 36 (5 to 30 mg/kg/day), Week 18 (5 to 30 mg/kg/day), Week 26 (7.25 to 45 mg/kg/day), and Week 42 (7.25 to 45 mg/kg/day) (Table 13). CCX168 exposure increased in a dose proportional manner throughout the study. A modest increase in CCX168 exposure (less than 2-fold) was noted from Week 26 to Week 42 following the 2-fold increase in dose volume at Week 26. In general, there were no sex-related differences in AUC and Cmax (differences were less than 2-fold).

Exposure to CCX168-M1 increased with the dose level on Day 1 (5 to 15 mg/kg/day), Day 36 (5 to 30 mg/kg/day), Week 18 (5 to 30 mg/kg/day), Week 26 (7.25 to 45 mg/kg/day), and Week 42 (7.25 to 45 mg/kg/day) (Table 14). A modest increase in CCX168-M1 exposure (less than 2-fold) was noted from Week 26 to Week 42 following the 2-fold increase in dose volume at Week 26. In general, there were no sex-related differences in AUC and Cmax (differences were less than 2-fold). The mean CCX168-

M1 metabolite to parent ratios ranged from 0.27 to 0.79 and from 0.33 to 1.38 for Cmax and AUC0-24, respectively.

CCX168-M6 was not detected at 5 mg/kg via NG or oral dosing. Increases in exposure from 15 to 30 mg/kg/day ranged from 2- to 4-fold at Day 36 and Week 18 (Table 15). Increases in exposure from 7.25, 22.5, and 44 mg/kg/day were generally dose proportional at Week 26 and Week 42. Some accumulation was noted from Week 26 to Week 42. Exposures in females were higher; however, sex related differences in AUC and Cmax were less than 2-fold. The mean CCX168-M6 metabolite to parent ratios ranged from 0.0035 to 0.0115 and from 0.0076 to 0.0129 for Cmax and AUC0-24, respectively.

Table 13: Summary of CCX168 Pharmacokinetic Parameters in Monkey Plasma

Interval	Dose Group	Dose Level (mg/kg/dose)	Dose Level (mg/kg/day)	Sex	$C_{max\ 0\text{-}24}$ (ng/mL)	$AUC_{0\text{-}24}$ (ng·hr/mL)
Day 1	3	5	5	M	159	799
				F	109	531
				MF	134	665
	4	15	15	M	537	3240
				F	456	2980
				MF	496	3110
	5	15	30	M	377	3990
				F	406	3990
				MF	391	3990
Day 36	3	5	5	M	220	1380
				F	299	1490
				MF	259	1430
	4	15	15	M	704	5740
				F	905	7610
				MF	805	6670
	5	15	30	M	1130	16300
				F	1230	14100
				MF	1180	15200
Week 18	3	5	5	M	118	1030
				F	150	1200
				MF	134	1120
	4	15	15	M	387	3920
				F	608	6310
				MF	497	5110
	5	15	30	M	743	7750
				F	1010	11100
				MF	876	9430

Text Table 4.1 (Continued): Summary of the Mean CCX168 $C_{max\ 0-24}$ and AUC_{0-24} in Monkey Plasma

Interval	Dose Group	Dose Level (mg/kg/dose)	Dose Level (mg/kg/day)	Sex	$C_{max\ 0-24}$ (ng/mL)	AUC_{0-24} (ng·hr/mL)
Week 26	3	7.25	7.25	M	424	2480
				F	444	3100
				MF	434	2790
	4	22.5	22.5	M	999	9630
				F	1400	10900
				MF	1200	10200
	5	22.5	45.0	M	1310	17900
				F	1640	23000
				MF	1480	20500
Week 42	3	7.25	7.25	M	522	3930
				F	267	2880
				MF	394	3410
	4	22.5	22.5	M	1090	13700
				F	1710	19700
				MF	1400	16700
	5	22.5	45.0	M	2200	26400
				F	2470	32200
				MF	2330	29300

Table 14: Summary of CCX168-M1 Pharmacokinetic Parameters in Monkey Plasma

Interval	Dose Group	CCX168 Dose Level (mg/kg/dose)	CCX168 Dose Level (mg/kg/day)	Sex	$C_{max\ 0\text{-}24}$ (ng/mL)	$AUC_{0\text{-}24}$ (ng·hr/mL)
Day 1	3	5	5	M	82.1	867
				F	73.4	733
				MF	77.8	800
	4	15	15	M	241	2470
				F	259	2510
				MF	250	2490
	5	15	30	M	192	3040
				F	148	2110
				MF	170	2570
Day 36	3	5	5	M	127	1300
				F	131	1240
				MF	129	1270
	4	15	15	M	288	3540
				F	325	4120
				MF	306	3830
	5	15	30	M	464	8100
				F	394	6360
				MF	429	7230
Week 18	3	5	5	M	90.7	1030
				F	97.1	1130
				MF	93.9	1080
	4	15	15	M	194	2590
				F	227	3150
				MF	211	2870
	5	15	30	M	239	4050
				F	267	4590
				MF	253	4320

Text Table 4.2 (Continued): Summary of the Mean CCX168-M1 $C_{max\ 0-24}$ and AUC_{0-24} in Monkey Plasma

Interval	Dose Group	CCX168 Dose Level (mg/kg/dose)	CCX168 Dose Level (mg/kg/day)	Sex	$C_{max\ 0-24}$ (ng/mL)	AUC_{0-24} (ng·hr/mL)
Week 26	3	7.25	7.25	M	124	1390
				F	165	1790
				MF	144	1590
	4	22.5	22.5	M	318	4420
				F	295	3820
				MF	307	4120
	5	22.5	45.0	M	362	6510
				F	356	6370
				MF	359	6440
Week 42	3	7.25	7.25	M	213	2540
				F	140	2070
				MF	176	2310
	4	22.5	22.5	M	363	5430
				F	445	6790
				MF	404	6110
	5	22.5	45.0	M	538	9330
				F	548	9840
				MF	543	9590

Table 15: Summary of CCX168-M6 Pharmacokinetic Parameters in Monkey Plasma

Interval	Dose Group	CCX168 Dose Level (mg/kg/dose)	CCX168 Dose Level (mg/kg/day)	Sex	$C_{max\ 0-24}$ (ng/mL)	AUC_{0-24} (ng·hr/mL)
Day 1	3	5	5	M	1.16[a]	NA
				F	1.08[a]	NA
				MF	1.12	NA
	4	15	15	M	4.30	34.2
				F	2.97	23.0
				MF	3.63	28.6
	5	15	30	M	3.23	46.9
				F	3.96	58.2
				MF	3.56	50.7
Day 36	3	5	5	M	1.24[a]	NA
				F	1.81	NA
				MF	1.67	NA
	4	15	15	M	5.44	49.7
				F	6.55	65.4
				MF	6.00	57.5
	5	15	30	M	11.8	177
				F	14.1	210
				MF	13.0	193
Week 18	3	5	5	M	1.09[a]	NA
				F	1.69[a]	NA
				MF	1.39	NA
	4	15	15	M	3.72	36.6
				F	4.77	52.0
				MF	4.24	44.3
	5	15	30	M	5.50	76.8
				F	9.52	154
				MF	7.51	115

Text Table 4.3 (Continued): Summary of the Mean CCX168-M6 $C_{max\ 0-24}$ and AUC_{0-24} in Monkey Plasma

Interval	Dose Group	CCX168 Dose Level (mg/kg/dose)	CCX168 Dose Level (mg/kg/day)	Sex	$C_{max\ 0-24}$ (ng/mL)	AUC_{0-24} (ng·hr/mL)
Week 26	3	7.25	7.25	M	1.50	NA
				F	1.62	7.98[a]
				MF	1.57	7.98[a]
	4	22.5	22.5	M	7.48	84.2
				F	7.81	91.0
				MF	7.64	87.6
	5	22.5	45.0	M	10.5	160
				F	15.1	243
				MF	12.8	202
Week 42	3	7.25	7.25	M	2.44	26.1
				F	1.99	33.0
				MF	2.21	28.8
	4	22.5	22.5	M	7.82	107
				F	13.1	196
				MF	10.4	151
	5	22.5	45.0	M	19.0	289
				F	28.2	462
				MF	23.6	375

NA = Not applicable.
a Value is not a mean and is presented for informational purposes only.

Dosing Solution Analysis

Homogeneity Analysis: Quadruplicate samples (1.00 mL each) were taken from the top, middle, and bottom strata of the 5, 15, and 30 mg/mL formulations prepared for administration on Days 1 and 176 of the dosing phase and from the 15 and 30mg/mL formulations prepared for administration on Day 8 of the dosing phase. The acceptable limited for homogeneity was ±7% of the overall mean.

Concentration Verification: Quadruplicate samples (1.00 mL each) were taken from the middle of the vehicle control article and each test article formulation prepared for administration on Days 1 and 43 and during Weeks 18, 26, 31, and 44 of the dosing phase (see Protocol Deviations). Samples collected from the middle of formulations prepared at the homogeneity interval were used for concentration verification. The acceptable limit was 90 to 110% of the target concentration.

All test article samples met the specifications for homogeneity and concentration verification analysis.

7 Genetic Toxicology

Genotoxicity studies evaluating CCX168 were reviewed previously under IND 120784. The test item was negative in all assays including the in vitro bacterial mutagenicity

study (Ames test), in vitro mammalian cell mutagenicity study (mouse lymphoma forward-mutation assay), and in vivo rat bone marrow micronucleus study. Metabolite CCX168-M1 was judged negative for mutagenicity in the Ames test for bacterial gene mutation based on confirmation that CCX168-M1 was formed upon incubation of CCX168 with S9.

See the nonclinical review under IND 120784 for a detailed review of the genetic toxicology studies conducted with CCX168 (Authored by Dr. Matthew Whittaker, Dated in DARRTS November 9, 2017).

8 Carcinogenicity

Carcinogenicity studies are evaluated in a separate review and presented to the Executive Carcinogenicity Assessment Committee (see nonclinical review dated March 8, 2021 and ECAC Meeting Minutes dated February 25, 2021).

No treatment-related tumors were identified in 2-year oral studies with SD rats and hamsters that were conducted to assess the carcinogenic potential of CCX168.

9 Reproductive and Developmental Toxicology

9.20 9.1 Fertility and Early Embryonic Development

Study title: Fertility and Early Embryonic Development Study of CCX168 in Hamsters following Oral Gavage Administration

Study no.:	PC0670-168
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 23, 2016 February 29, 2016 (start of dosing)
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lot: D-15-012; 99.0% purity

Key Study Findings

- Sexually mature male and female hamsters received CCX168 at doses of 0, 10, 30, and 100 mg/kg once daily (QD) or 0 and 500 mg/kg BID (0 and 1000 mg/kg/day, respectively) before cohabitation (28 days for males and 15 days for females), during cohabitation/mating, and through gestation day 12 in females and up to dosing day 50 to 53 in males.

- Administration of CCX168 was well-tolerated in male and female hamsters when administered daily during the pre-mating, cohabitation, and postmating or gestation periods.
- There were no changes of mating or fertility indices attributed to administration of the test article in either the male or female hamsters.
- There were no effects on reproductive organ weights or sperm motility, count, or density in the male hamsters, and there were no effects on estrous cyclicity or ovarian or uterine observations in the female hamsters.
- There were also no gross external observations apparent in the fetuses.
- The paternal and maternal NOAELs for general and reproductive toxicity of CCX168 was 1000 mg/kg/day.

Methods

Doses:	QD: 0 (Vehicle),10, 30, or 100 mg/kg BID: 0 (Vehicle) and 500 mg/kg (1000 mg/kg/day)
Frequency of dosing:	Daily or twice daily
Dose volume:	QD- 5 mL/kg/day BID- 2.5 mL/kg/dose (5 mL/kg/day)
Route of administration:	Oral gavage
Formulation/Vehicle:	Polyethylene (b) (4) (b) (4) (V:V (b) (4))
Species/Strain:	Hamster/Crl:LVG(SYR)
Number/Sex/Group:	CCX168 dose groups: 25 Controls: 17
Satellite groups:	none
Study design:	From the 13-week toxicology study with hamsters, doses of 100 mg/kg/day and 1000 mg/kg/day (500 mg/kg BID) were anticipated to produce maximal systemic exposure to the test article. Additionally, the dose of 1000 mg/kg/day represented the limit dose (ICH M3(R2) and S5(R3) Guidances) for evaluation in reproductive toxicology studies. Previously, doses up to 1000 mg/kg/day administered orally to pregnant female hamsters for 7 days produced no adverse effects. Doses up to 200 mg/kg/day were well tolerated in 7-day pilot study in male and female hamsters. Males were given the test article or vehicle control article formulation once daily in Groups 1-4 or twice daily (approximately 8 hours apart) in Groups 5 and 6 via oral gavage beginning 28 days before cohabitation, during cohabitation and continuing through the day prior to scheduled euthanasia (Days 50 to 53 of study [DSs 50 to 53]). Females were given the test or control article once daily in Groups 1-4 or twice daily (approximately 8 hours apart) in Groups 5 and 6 beginning 15 days before cohabitation with males, during cohabitation and continuing until Day 12 of Presumed Gestation (GD 12). Females that did not mate after the completion of the 16-day cohabitation period and presumed

not pregnant were euthanized at the discretion of the Study Director.

Deviation from study protocol: No deviations were noted that were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions.

Experimental Design:

Experimental Design - QD (Once Daily)

Group No.	Test Material	Dose Level (mg/kg/day)[a]	Concentration (mg/mL)	Dose Volume (mL/kg/day)	No. of Animals	
					Males	Females
1	Control Article	0	0	5	17	17
2	CCX168	10	2	5	25	25
3	CCX168	30	6	5	25	25
4	CCX168	100	20	5	25	25

[a] Hamsters were dosed once daily at approximately the same time as the first daily dose for animals in Groups 5 and 6. Dose calculations were corrected for purity, water and solvent content using a correction factor of 0.985.

Experimental Design - BID (Twice Daily)

Group No.	Test Material[a]	Dose Level (mg/kg/dose)	Dose Level (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg/dose)[b]	No. of Animals	
						Males	Females
5	CCX168	0	0	0	2.5	17	17
6	CCX168	500	1000	200	2.5	25	25

[a] Hamsters were dosed twice per day (approximately 8 hours apart).
[b] Total dose volume/day = 5 mL/kg.

Observations and Results

Mortality

The hamsters were assessed for viability at least twice daily.

No treatment related deaths occurred.

One male was euthanized early in each of Group 1 (0 mg/kg/day), Group 2 (10 mg/kg/day) and Group 5 (0 mg/kg/day; BID) and two males were euthanized early in Group 3 (30 mg/kg/day) due to adverse clinical signs including body weight loss, dehydration, and soft/liquid feces. The adverse clinical signs did not exhibit a dose-response relationship to the test article (lack of dose-response).

Table 16: Mortality Data in the CCX168 FEED Study In Hamsters

Dose Level (mg/kg/day)	0 (Group 1)	10 (Group 2)	30 (Group 3)	30 (Group 3)	0 (Group 5)
Hamster Number	1202	1221	1243	1247	1305
Doses Administered	38	16	21	8	34
Mode of Death	UE	UE	UE	UE	UE
Day of Death	DS 38	DS 16	DS 21	DS 8	DS 18
Clinical Observations					
Appeared Normal	-	-	-	-	-
Ungroomed Coat	DS 36	-	-	-	DSs 12 to 18
Soft or Liquid Feces	DS 36	DSs 9, 10 and 13 to 16	DSs 15 and 16	-	DSs 12 to 17
Swelling - right testis	-	DS 4	-	-	DS 4
Swelling - testes	-	-	-	-	DS 3
Ungroomed coat – underside	-	DSs 9 to 16	-	-	-
Mild and/or moderate dehydration	-	DSs 9 to 16	-	DS 8	DSs 16 to 18
Hunched posture	-	DSs 14 to 16	-	-	DSs 17 and 18
Vocalization	-	-	DS 21	-	-
Gasping	-	-	DS 21	-	-
Red anal-genital area	-	-	-	-	DSs 17 and 18
Bodyweights					
Body weight change (grams)	-22% (-34g) DSs 26 to 38	-32% (-42g) DSs 1 to 16	-4% (-5g) DSs 17 to 21	-15% (-18g) DSs 1 to 8	-33% (-41g) DSs 1 to 18
Necropsy Observations					
All tissues appear normal	X	X	-[a]	X	X

- = Finding not present; DS = Day of Study; NA = Not applicable; FD = Found Dead; UE = Unscheduled Euthanized; UR = Unremarkable
a. Necropsy observations were not recorded.

Clinical Signs

The hamsters were observed for general appearance twice (males) or four times (females) during the acclimation period, daily before each dose during the dose period and daily during the postdose period (including the day of scheduled euthanasia).

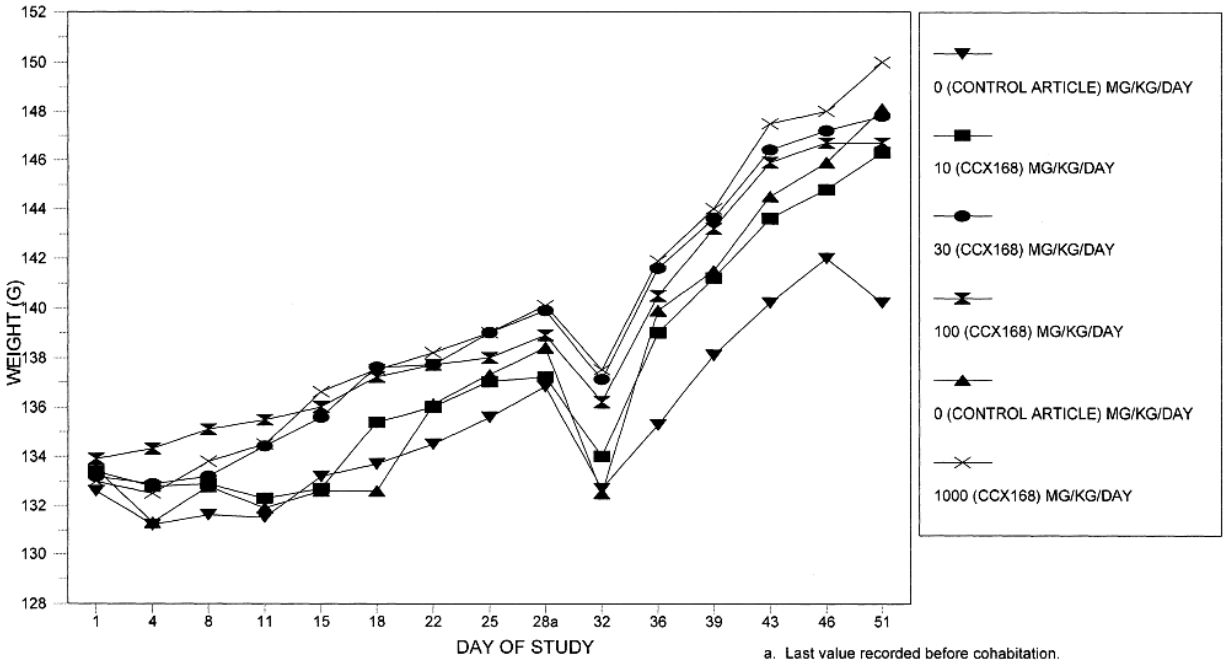
No treatment related clinical signs were noted

Body Weight

Body weights were recorded twice (males) or four times (females) during the acclimation period, including on the day of randomization, daily during the dosing period and on the day of euthanasia.

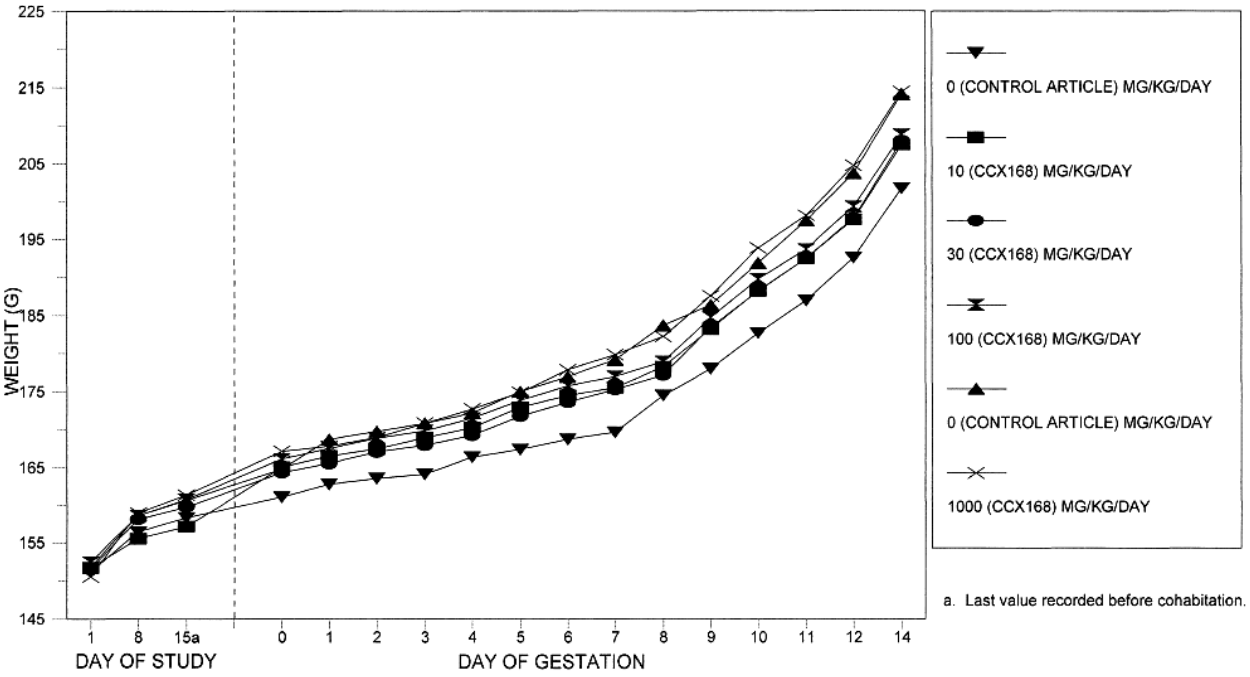
No treatment related changes in body weight gains were noted.

Figure 9: Body Weight changes in male hamster treated with CCX168 (FEED Study)



a. Last value recorded before cohabitation.

Figure 10: Body Weight changes in female hamster treated with CCX168 (FEED Study)



Feed Consumption

Food consumption values for the males were recorded at least twice weekly during the dose period through the week prior to scheduled euthanasia. Food consumption values for the females were recorded twice weekly during the dose period, and on GDs 0, 3, 7, 10, 12 and 14 (the amount of feed that remained was recorded at each interval).

No treatment related changes in food consumption were noted in males or females.

Estrous Cycle Evaluations

Estrous cycles were evaluated by examining the vaginal discharge and/or by samples obtained by vaginal lavage for 14 consecutive days before initiation of dose administration, for 14 consecutive days beginning with the day after the first administration and then until spermatozoa are observed in a smear of the vaginal contents and/or a copulatory plug is observed in situ during the cohabitation period.

No treatment related changes in the estrous cycle in females was noted.

Cohabitation/Mating and Fertility

The cohabitation period consisted of up to 16 days for each pairing after being observed to be compatible.

There were no treatment related effects on mating or the following fertility parameters:

- numbers of days in cohabitation,

- mating index (number of pregnancies per number of hamsters in cohabitation)
- fertility index (number of pregnancies per number of hamsters that mated)
- hamsters with confirmed mating dates during the first week of cohabitation (vs week 2), and

Table 17: Summary of Cohabitation, Mating and Fertility Performance in CCX168 treated male hamsters

Male Hamsters		CCX168 Dose Groups (mg/kg/day)					
Mating/Fertility Parameters	**N**	**Control**	**10**	**30**	**100**	**Control**	**1000**
Hamsters in cohabitation and included in analysis [a]	N	16	23	23	24	16	25
Days in Cohabitation	(mean)	2.9	2.7	2.3	2.3	3.2	2.6
Mating Index	N (%)	16 (100)	23 (100)	23 (100)	24 (100)	15 (93.8)	25 (100)
Fertility Index [b]	N/N (%)	15/16 (93.8)	23/23 (100)	22/23 (95.6)	24/24 (100)	14/15 (93.3)	24/25 (96)
Mated with Females							
Days 1-7	N (%)	15 (93)	23 (100)	23 (100)	24 (100)	15 (100)	25 (100)
Days 8-14	N (%)	1 (6.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[a] Animals were excluded due to euthanization due to adverse clinical signs or lack of an available female for cohabitation
[b] Number of pregnancies/number of hamsters that mated

Table 18: Summary of Cohabitation, Mating and Fertility Performance in CCX168 treated female hamsters

Female Hamsters		CCX168 Dose Groups (mg/kg/day)					
Mating/Fertility Parameters	**N**	**Control**	**10**	**30**	**100**	**Control**	**1000**
Hamsters in cohabitation	N	17	24	25	24	17	25
Days in Cohabitation	(mean)	2.9	2.7	2.3	2.3	2.6	2.6
Mating Index	N (%)	17 (100)	24 (100)	25 (100)	24 (100)	17 (100)	25 (100)
Fertility Index [a]	N/N (%)	16/17 (94.1)	24/24 (100)	24/25 (96)	24/24 (100)	16/17 (94.1)	24/25 (96)
Mated by first male							
Days 1-7	N (%)	15 (93)	24 (100)	25 (100)	24 (100)	16 (100)	25 (100)
Days 8-14	N (%)	1 (6.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[a] Number of pregnancies/number of females that mated

Toxicokinetics

Blood samples (0.4 mL) were collected from male hamsters on Day 50 (0-24 hours) from the jugular vein after being anesthetized under isoflurane/oxygen.

The increase in exposure (AUC_{0-t}) to CCX168 in male hamsters on Day 50 was dose proportional from 10 to 30 mg/kg/day, whereas the increase in exposure from 30 to 100 mg/kg/day was less than dose proportional. The increase in exposure (AUC_{0-t}) from 100 to 1000 mg/kg/day was less than dose proportional and suggested saturation of exposure occurred at ≥ 100 mg/kg/day. The increase in Cmax was less than dose proportional from 10 to 100 mg/kg/day. Cmax decreased from 100 to 1000 mg/kg/day.

The increase in exposure (AUC_{0-t}) to CCX168-M1 in male hamsters on Day 50 was dose proportional from 10 to 100 mg/kg/day. The increase in exposure (AUC_{0-t}) to CCX168-M1 from 100 to 1000 mg/kg/day was less than dose proportional and suggested exposure is approaching saturation at ≥ 100 mg/kg/day. The increase in Cmax was less than dose proportional from 10 to 1000 mg/kg/day. The exposure levels of the M1 metabolite were 11, 14, 16, and 15% of the AUC of the parent at 10, 30, 100, and 1000 mg/kg/day, respectively.

Table 19: Toxicokinetic analysis of CCX168 in male hamsters on Day 50

Toxicokinetic Parameters for CCX168 in the Plasma of DS 50 Male Hamsters

Dose	C_{max} (ng/mL)	AUC_{0-t} ng.hr/mL	MRT_{0-t} (hr)	T_{max} (hr)
10 mg/kg/day	1,371	6,321	4.6	2.0
30 mg/kg/day	2,617	18,379	5.1	1.0
100 mg/kg/day	4,707	39,249	7.3	1.0
500 mg/kg/dose (1000 mg/kg/day)	4,143	47,339	10.0	4.0

Table 20: Toxicokinetic analysis of CCX168-M1 in male hamsters on Day 50

Toxicokinetic Parameters for CCX168-M1 in the Plasma of DS 50 Male Hamsters

Dose	C_{max} (ng/mL)	AUC_{0-t} ng.hr/mL	MRT_{0-t} (hr)	T_{max} (hr)	AUC% (M1/CCX168)
10 mg/kg/day	107	670	5.5	2.0	11
30 mg/kg/day	317	2,489	6.1	4.0	14
100 mg/kg/day	532	6,195	7.9	4.0	16
500 mg/kg/dose (1000 mg/kg/day)	690	7,795	10.7	4.0	15

Dosing Solution Analysis

Duplicate (1 mL) sets of top, middle, and bottom samples for the sampling time points were analyzed. Concentration results were considered acceptable if mean sample concentration results were within or equal to ± 10% of nominal concentration. Each individual sample concentration result was considered acceptable if it was within or equal to ± 15% of nominal concentration. For homogeneity, the criteria for acceptability were a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

All homogeneity and concentration analysis results met the protocol specified acceptance criteria.

Necropsy

Terminal procedures for males:
Males were subjected to scheduled euthanasia by carbon dioxide asphyxiation on Days 51 to 54. To assess the potential toxicity of the test article on the male reproductive system, following euthanasia, males underwent sperm evaluations, necropsy, tissue collection, and organ weight analysis.

Terminal procedures for females:
Females were subjected to scheduled euthanasia by carbon dioxide asphyxiation on Gestation Day 14. To assess the potential toxicity of the test article on the female reproductive system, following euthanasia, females underwent ovarian/uterine examinations, necropsy, tissue collection, and organ weight analysis.

Representative samples of the tissues identified in Table 21 were collected from all hamsters and preserved in 10% neutral buffered formalin.

Table 21: Tissues collected from CCX168 treated hamsters in FEED Study

Tissue	Weighed	Collected	Comment
Cervix	X	X	Collected and weighed with uterus and oviduct. All nonpregnant animals.
Epididymides	X	X	Individual weighed. All male hamsters. The remaining portion of the left epididymis (corpus and caput) and right epididymis was fixed in 10% neutral buffered formalin for possible future evaluation.
Epididymis, left cauda	X	X	For unscheduled and found dead animals, retained as described for the epididmides.
Gland, mammary	-	X	Both male and female.
Gland, pituitary	X	X	-
Gland, prostate	X	X	-
Gland, seminal vesicle	X	X	Weighed with and without fluid.
Esophagus	-	X	Infused with 10% neutral buffered formalin. Animals found dead or euthanized before scheduled termination.
Gross lesions/masses	-	X	All animals.
Heart	-	X	Animals found dead or euthanized before scheduled termination.
Kidney	-	X	Animals found dead or euthanized before scheduled termination.
Liver	-	X	Animals found dead or euthanized before scheduled termination.
Lung	-	X	Infused with 10% neutral buffered formalin. Animals found dead or euthanized before scheduled termination.
Ovaries	-	X	All female hamsters.
Oviduct	X	X	Collected and weighed with uterus and cervix. All nonpregnant animals.
Spleen	-	X	Animals found dead or euthanized before scheduled termination.

Tissue	Weighed	Collected	Comment
Stomach	-	X	Animals found dead or euthanized before scheduled termination.
Testes	X	X	Individually weighed. All male hamsters. Preserved in Modified Davidson's fixative. Rinsed and retained as per Testing Facility Standard Operating Procedures.
Trachea	-	X	Infuse with 10% neutral buffered formalin. Animals found dead or euthanized before scheduled termination.
Uterus	X	X	Collected and weighed with cervix and oviduct. All nonpregnant animals.
Vagina	-	X	-

X = Procedure conducted; - = Not applicable.

Gross Pathology Assessment

A gross examination of the thoracic, abdominal and pelvic viscera was performed for all male and female hamsters.

No treatment-related macroscopic changes were noted in males or females.

No organ weight changes noted in males or females.

Ovarian and Uterine Examinations and Litter Observations

Following caesarian section of pregnant females on gestation day 14, the reproductive tract was dissected from the abdominal cavity. The uterus was opened, and the contents were examined. The fetuses were removed from the uterus and placed in individual containers. The uterus was examined for numbers and distribution of corpora lutea, implantation sites, placentae (size, color, and shape), live and dead fetuses, and early and late resorptions. Fetuses were examined for sex, body weight, and percent male fetuses per litter.

In pregnant females that were subjected to caesarian section on gestation day 14, there were no CCX168-related effects on uterine contents in the treated females for the following parameters: confirmed pregnancies, corpora lutea, implantations, preimplantation loss, early resorptions, litter sizes (live fetuses/litter), post-implantation loss, dead fetuses, or late resorptions.

Table 22: Summary of Uterine Examinations and Litter Observations from CCX168 Treated Females

Female Hamsters	CCX168 Dose Groups (mg/kg/day)					
Uterine Contents	**Control**	**10**	**30**	**100**	**Control**	**1000**
Pregnant/Mated (%)	15/16 (93.8)	24/24 (100)	24/24 (100)	24/24 (100)	15/16 (93.8)	24/25 (96)
Copora lutea (mean)	16.5	17.1	16.9	18	18.3	17.5
Implantation	15.9	17	16.6	17.8	17.9	17.3
Preimplantation loss (%)	5.7	0.5	1.7	0.9	2.4	0.9
Early resorptions (mean in parentheses)	5 (0.7)	12 (0.5)	26 (1.1)	9 (0.4)	6 (0.4)	14 (0.6)

Live fetuses/litter (mean)	15.2	16.4	15.3	17.2	17.5	16.7
Post-implantation loss (%)	3.7	3.9	8	3.1	2.3	3.8
Dead fetuses (mean)	0.0 (0/15)	0.0 (1/24)	0.0 (0/24)	0.0 (1/24)	0.0 (0/15)	0.0 (1/24)
Late resorptions	5	2	5	3	0	1
Late resorptions (mean)	0.3	0.1	0.2	0.1	0.0	0.0

Male Reproductive Assessments

To assess the potential toxicity of the test article on the male reproductive system, sperm motility and sperm concentration were evaluated for each male that survived to scheduled euthanasia.

Sperm Motility
Sperm motility was evaluated using computer-assisted sperm analysis (CASA). Motility was evaluated following dispersion, into an appropriate medium, using sperm from each vas deferens.

There were no treatment related effects on sperm motility in CCX168 treated males relative to controls.

Sperm Concentration
A homogenate was prepared from the left or right cauda epididymis for evaluation to determine sperm concentration (sperm per gram of tissue weight). Sperm concentration was evaluated using computer-assisted sperm analysis (CASA).

There were no treatment related effects on the mean cauda epididymal sperm count in CCX168 treated male relative to controls.

Fetal Examinations
Following caesarean deliveries on gestation day 14, fetuses were examined for sex and external abnormalities. Late resorptions and dead fetuses were examined for external abnormalities and sex to the extent possible. The body weight of each fetus was recorded. All fetuses were examined internally to determine sex.

There were no treatment-related effects on fetal body weights or on the sex of the fetuses. No treatment related gross external alterations were noted.

Table 23: Fetal Observations from CCX168-treated Female and Male Hamsters in FEED Study

Fetal Litter Observations	CCX168 Dose Groups (mg/kg/day)					
	Control	10	30	100	Control	1000
% Live male fetuses/litter	49.2	46.4	46.3	51.9	46.4	47.5

Live fetal body weights (g)/litter	1.78	1.8	1.85	1.78	1.91	1.83

9.21 Embryonic Fetal Development

Study title: An Embryo-fetal Development Toxicity Study of CCX168 in Hamsters following Oral Gavage Administration

Study no.:	PC0671_168
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 1, 2016 (March 15, 2016-start of dosing)
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lot # D-15-012, 99% purity

Key Study Findings

- This GLP-compliant oral EFD study in hamsters evaluated CCX168 at doses of 0 (vehicle), 10, 30, and 100 mg/kg/day and 0 and 500 mg/kg BID administered from GD 6-12.
- There was no maternal mortality in this study and no test article-related effects on body weight gain.
- No treatment-related effects on maternal performance or ovarian and uterine contents.
- No treatment-related fetal malformations were noted. An increase in a skeletal variation described as supernumerary ribs was noted in all litters and 40 fetuses in the 1000 mg/kg/day group relative to 14 fetuses of 9 litters in the BID control group and 22 fetuses of 10 litters in the daily dosing control group. This finding is considered a developmental delay and supernumerary ribs can resolve into the vertebral arch later in development. Although there is an apparent treatment related increase for this finding, this variation was not judged to be adverse.
- Toxicokinetic analysis identified that there was no increase in exposure (AUC0-24) from 100 to 1000 mg/kg/day and suggests saturation of exposure occurred at ≥ 100 mg/kg/day.
- The NOAEL for maternal and developmental toxicity was 1000 mg/kg/day. The increase in supernumerary ribs, a variation, was judged to be not adverse.

Methods

Doses:	QD dosing: 0, 10, 30, 100 mg/kg/day BID dosing: 0, 500 mg/kg (1000 mg/kg/day)
Frequency of dosing:	Daily or twice daily
Dose volume:	Dose Groups 0, 10, 30, 100 mg/kg/day: 5 mL/kg Dose group 0 and 500 mg/kg BID: 2.5 mL/kg/dose
Route of administration:	Oral gavage
Formulation/Vehicle:	Polyethylene glycol (b) (4) (b) (4) (v:v (b) (4))
Species/Strain:	Golden Syrian Hamster Crl:LVG(SYR) from (b) (4)
Number/Sex/Group:	Controls (QD and BID): 17/sex CCX168 treatment groups: main study 19/sex; TK study 9/sex
Satellite groups:	None
Study design:	Dose levels were selected based on prior repeat-dose toxicology and toxicokinetic evaluation in hamsters. The mid-high dose (100 mg/kg/day) and the high dose (1000 mg/kg/day) are anticipated to produce maximal systemic exposure to the test article. Additionally, the dose of 1000 mg/kg/day represents the limit dose (ICH M3(R2) and S5(R3) Guidances) for evaluation in reproductive toxicology studies. Previously doses up to 1000 mg/kg/day administered orally to pregnant female hamsters for 7 days produced no adverse effects. Female hamsters were mated with untreated male hamsters of the same source and strain. The cohabitation period was 6 days. Pregnancy was confirmed by the presence of spermatozoa in a smear of the vaginal contents and/or a copulatory plug observed in situ. The day of confirmed pregnancy was considered to be GD 0 and the pregnant females were assigned to individual housing. In the QD and BID portion of the study, hamsters were dosed daily by oral gavage on gestation day (GD) 6 through GD 12. The following parameters and end points were evaluated in this study: viability, clinical signs, body weights, body weight gains, food consumption, toxicokinetic parameters, gross necropsy findings, ovarian and uterine examinations (early and late resorptions,

implantation sites, corpora lutea, live and dead fetuses, etc.), and fetal examinations (sex, body weights, external, skeletal and visceral examinations).

Deviation from study protocol: No deviations were noted that were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions.

Experimental Design - QD (Once Daily)

Group No.	Test Material	Dose Level (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg/day)	No. of Animals	
					Main Study[b]	Toxicokinetic Study[a]
1	Control Article	0	0	5	17	3
2	CCX168	10	2	5	19	9
3	CCX168	30	6	5	19	9
4	CCX168	100	20	5	19	9

[a] Hamsters were dosed once daily at approximately the same time as the first daily dose for animals in Groups 5 and 6 (see Text Table 2). Dose calculations were corrected for purity, water and solvent content using a correction factor of 0.985.

Experimental Design - BID (Twice Daily)

Group No.	Test Material[a]	Dose Level (mg/kg/dose)	Dose Level (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg/dose)[b]	No. of Animals	
						Main Study[c]	Toxicokinetic Study[a]
5	CCX168	0	0	0	2.5	17	12
6	CCX168	500	1000	200	2.5	19	12

[a] Hamsters were dosed twice per day (approximately 8 hours apart).
[b] Total dose volume/day = 5 mL/kg.

Observations and Results

Mortality

The hamsters were assessed for viability at least twice daily during the study.

There were no treatment related deaths.

One hamster in the 10 mg/kg/day dose group delivered on GD 14 and one hamster in the 100 mg/kg/day dose group delivered on GD 13. These dams were euthanized early and were judged to be mistimed pregnancies based on fetal weights from the litters.

Clinical Signs

The hamsters were observed for general appearance at least once weekly during the acclimation period, daily before each dose during the dose period and daily during the postdose period. During the QD Phase, postdose observations were recorded at approximately 1 and 4 hours postdose. During the BID Phase, postdose observations were recorded at approximately 1 and 4 hours postdose (relative to the 1st daily dose) and at the end of the normal working day (after the 2nd daily dose).

There were no treatment related clinical signs.

Body Weight

Body weights were recorded at least once weekly during the acclimation period, on GD 0, and daily during the dose and postdose period. Body weights for most gestating hamsters were last measured on GD 14

There were no treatment related changes in body weight gains in pregnant hamsters in all CCX168 dosing groups.

Feed Consumption

Food consumption values were recorded on GD 6, 9, 12, and 15

Reductions in food consumption were noted from GD 6-12 and from GD 6-15. Over the interval of GD 6-12 reductions of -24.3%, -12.2%, -25%, -11.6% were and over the interval from GD 6-15 reduction of -12.6%, -20.7%, -24.7%, and 10.3% were noted for the 10, 30, 100, 1000 mg/kg/day groups, relative to the appropriate QD or BID control. While reductions were noted relative to controls, the relationship to the dose CCX168 level was not consistent. Body weight gains were unaffected suggesting that changes of food consumption had no impact.

Table 24: Food consumption changes in pregnant hamsters treated with CCX168 (treatment from GD 6 to GD 12)

Maternal Food Consumption (g/animal/day)	QD dosing- mg/kg/day				BID dosing - mg/kg/day	
	Control	10	30	100	Control	500 (1000)
GD 6-12	14.8	11.2	13	11.1	13.8	12.2
% Change of Control	0	**-24.3**	**-12.2**	**-25.0**	0.0	**-11.6**
GD 6-15	17.4	15.2	13.8	13.1	11.7	12.9
% Change of Control	0	**-12.6**	**-20.7**	**-24.7**	0.0	**+10.3**

Toxicokinetics

Blood samples (0.4 mL) were collected from the jugular vein after being anesthetized under isoflurane/oxygen from all hamsters assigned to the toxicokinetic portion of the study on DG 6 and DG 12 and placed into K_2EDTA tubes.

TK Sample Collection Schedule - Groups 1 through 4

Group No.	Subgroup	No. of Animals	Sample Collection Time Points (Approximate Time Postdose) on DG 6 and 12					
			0 hour[a]	1 hour	2 hour	4 hour	8 hour	24 hour
1	-	3	-	-	X	-	-	-
2	A	3	X	-	-	X	-	-
	B	3	-	X	-	-	X	-
	C	3	-	-	X	-	-	X
3	A	3	X	-	-	X	-	-
	B	3	-	X	-	-	X	-
	C	3	-	-	X	-	-	X
4	A	3	X	-	-	X	-	-
	B	3	-	X	-	-	X	-
	C	3	-	-	X	-	-	X

X = Sample collected; - = Not applicable.
[a] Sample was collected prior dose administration.

TK Sample Collection Schedule - Groups 5 and 6

Group No.	Subgroup	No. of Animals	Sample Collection Time Points (Approximate Time Postdose) on DG 6 and 12[a]								
			0 hour[b]	1 hour	2 hour	4 hour	8 hour[c]	9 hour	10 hour	12 hour	24 hour
5	A	3	X	-	-	-	X	-	-	-	X
	B	3	-	X	-	-	-	X	-	-	-
	C	3	-	-	X	-	-	-	X	-	-
	D	3	-	-	-	X	-	-	-	X	-
6	A	3	X	-	-	-	X	-	-	-	X
	B	3	-	X	-	-	-	X	-	-	-
	C	3	-	-	X	-	-	-	X	-	-
	D	3	-	-	-	X	-	-	-	X	-

X = Sample collected; - = Not applicable.
[a] Collection timepoints were based on the first dose of the day.
[b] Sample was collected prior to dose administration.
[c] Sample was collected prior to the second dose of the day.

The increase in exposure (AUC0-24) to CCX168 in pregnant hamsters on GD 12 was dose proportional from 10 to 30 mg/kg/day whereas the increase in exposure from 30 to 100 mg/kg/day was less than dose proportional. There was no increase in exposure (AUC0-24) from 100 to 1000 mg/kg/day and suggests saturation of exposure occurred at ≥ 100 mg/kg/day. The increase in Cmax was dose proportional from 10 to 30 mg/kg/day whereas the increase in Cmax from 30 to 100 mg/kg/day was less than dose proportional. Cmax decreased from 100 to 1000 mg/kg/day.

The increase in exposure (AUC0-24) to CCX168-M1 in pregnant hamsters on GD 12 was dose proportional from 10 to 30 mg/kg/day whereas the increase in exposure from 30 to 100 mg/kg/day was less than dose proportional. There was no increase in exposure (AUC0-24) from 100 to 1000 mg/kg/day and suggests saturation of exposure occurred at ≥ 100 mg/kg/day.

Table 25: Toxicokinetic Parameters for CCX168 in Pregnant Hamsters (treatment from GD 6 to GD 12)

Dose Group	Dose Level (mg/kg/dose)	Dose Level (mg/kg/day)	$C_{max\ First\ Dose}$ (ng/mL)	$C_{max\ Second\ Dose}$ (ng/mL)	$C_{max\ 0-24}$ (ng/mL)	DN $C_{max\ 0-24}$ [(ng/mL)/(mg/kg/day)]	$T_{max\ First\ Dose}$ (hr)	$T_{max\ Second\ Dose}$ (hr)	$T_{max\ 0-24}$ (hr)
				DG 6					
2	10	10	NA	NA	379	37.9	NA	NA	2.00
3	30	30	NA	NA	1400	46.8	NA	NA	2.00
4	100	100	NA	NA	3160	31.6	NA	NA	2.00
6	500	1000	863	1020	1020	1.02	2.00	9.00	9.00
				DG 12					
2	10	10	NA	NA	560	56.0	NA	NA	2.00
3	30	30	NA	NA	1840	61.4	NA	NA	1.00
4	100	100	NA	NA	3620	36.2	NA	NA	2.00
6	500	1000	1650	2150	2150	2.15	2.00	10.0	10.0

NA = Not applicable.
Notes: Animals in Groups 2 through 4 were dosed once daily.
Animals in Group 6 were dosed twice daily, with approximately 8 hours between doses.

Text Table 14
Toxicokinetic Parameters for CCX168 in the Plasma of Pregnant Hamsters: DG 6 and DG 12

Dose Group	Dose Level (mg/kg/dose)	Dose Level (mg/kg/day)	($ng \cdot hr/mL$) AUC_{0-8}	AUC_{8-24}	AUC_{0-t}	AUC_{0-24}	DN AUC_{0-t} [($ng \cdot hr/mL$)/(mg/kg/day)]	DN AUC_{0-24} [($ng \cdot hr/mL$)/(mg/kg/day)]	AUC_{0-inf} ($ng \cdot hr/mL$)	$t_{1/2}$ (hr)
					DG 6					
2	10	10	NA	NA	2420	2420	242	242	2540	5.48
3	30	30	NA	NA	8950	8950	298	298	NC	NC
4	100	100	NA	NA	20300	20300	203	203	23100	8.66
6	500	1000	3660	11200	14900	14900	14.9	14.9	NC	NC
					DG 12					
2	10	10	NA	NA	5290	5290	529	529	NA	12.0
3	30	30	NA	NA	19600	19600	652	652	NA	9.74
4	100	100	NA	NA	36600	36600	366	366	NA	NC
6	500	1000	10700	25700	36400	36400	36.4	36.4	NA	NC

NA = Not applicable; NC = Not calculated due to the lack of a distinct elimination phase.
Notes: Animals in Groups 2 through 4 were dosed once daily.
Animals in Group 6 were dosed twice daily, with approximately 8 hours between doses.

Table 26: Toxicokinetic Parameters for CCX168-M1 in Pregnant Hamsters (treatment from GD 6 to GD 12)

Toxicokinetic Parameters for CCX168-M1 in the Plasma of Pregnant Hamsters: DG 6 and DG 12

Dose Group	Dose Level (mg/kg/dose)	Dose Level (mg/kg/day)	(ng·hr/mL) AUC_{0-8}	(ng·hr/mL) AUC_{8-24}	(ng·hr/mL) AUC_{0-t}	(ng·hr/mL) AUC_{0-24}	DN AUC_{0-t} [(ng·hr/mL)/(mg/kg/day)]	DN AUC_{0-24} [(ng·hr/mL)/(mg/kg/day)]	AUC_{0-inf} (ng·hr/mL)	$t_{1/2}$ (hr)
					DG 6					
2	10	10	NA	NA	89.0	89.0	8.90	8.90	NC	NC
3	30	30	NA	NA	296	296	9.85	9.85	334	7.31
4	100	100	NA	NA	845	845	8.45	8.45	NC	NC
6	500	1000	143	433	576	576	0.576	0.576	NC	NC
					DG 12					
2	10	10	NA	NA	204	204	20.4	20.4	NC	NC
3	30	30	NA	NA	843	843	28.1	28.1	NC	NC
4	100	100	NA	NA	1610	1610	16.1	16.1	NC	NC
6	500	1000	420	1260	1680	1680	1.68	1.68	NC	NC

NA = Not applicable; NC = Not calculated due to the lack of a distinct elimination phase.
Notes: Animals in Groups 2 through 4 were dosed once daily.
Animals in Group 6 were dosed twice daily, with approximately 8 hours between doses.

Dosing Solution Analysis

Duplicate (1 mL) sets of top, middle, and bottom samples for the sampling time points were analyzed. Concentration results were considered acceptable if mean sample concentration results were within or equal to ± 10% of nominal concentration. Each individual sample concentration result was considered acceptable if it was within or equal to ± 15% of nominal concentration. For homogeneity, the criteria for acceptability were a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

All homogeneity and concentration analysis results met the protocol specified acceptance criteria.

Necropsy

Pregnant female hamsters in the toxicokinetic groups were euthanized on GD 13 after the last scheduled blood collection timepoint. Pregnancy status was recorded, and uteri of apparently nonpregnant hamsters were examined while being pressed between glass plates to confirm the absence of implantation sites. No tissues were collected for scheduled toxicokinetic animals. Carcass/tissues were discarded without further evaluation.

Main study female hamsters were euthanized on GD 15. Hamsters were euthanized by carbon dioxide asphyxiation. Live fetuses were euthanized by an intraperitoneal injection of sodium pentobarbital (390 mg/mL). A gross necropsy of the thoracic, abdominal and pelvic viscera was performed for each main study animal.

Terminal Procedures

Group No.	No. of Animals	Scheduled Euthanasia Day	Necropsy Procedures				Histology	Histopathology
			Ovarian/ Uterine Examination	Necropsy	Tissue Collection	Organ Weights		
1[a]	3	DG 13	Pregnancy Status	-	-	-	-	-
2[a]	9							
3[a]	9							
4[a]	9							
5[a]	12							
6[a]	12							
Unscheduled Deaths[b]			Pregnancy Status	X	-	-	-	-
1[c]	17	DG 15[d]	X	X	X	-	-	-
2[c]	19							
3[c]	19							
4[c]	19							
5[c]	17							
6[c]	19							
Unscheduled Deaths[b]			X	X	X	-	-	-

X = Procedure conducted; - = Not applicable; DG = Day of Presumed Gestation.

[a] Toxicokinetic study animals.

[b] See Section 4.10.2. (Unscheduled Deaths).

[c] Main study animals.

[d] The main study hamsters that delivered on DG 15 prior to scheduled euthanasia were evaluated as a scheduled euthanasia hamster (see Appendix 1, Protocol, Amended Protocol, and Deviations).

Tissue Collection and Preservation

Representative samples of the tissues identified in Table 27 were collected from all main study animals and preserved in 10% neutral buffered formalin, unless otherwise indicated.

Table 27: Tissues Collected From CCX168 Treated Maternal Hamsters in EFD Study

Tissue Collection and Preservation

Tissue	Collected	Comment
Cervix	X	Collected with uterus. All nonpregnant animals.
Esophagus	X	Infused with 10% neutral buffered formalin. Animals found dead or euthanized before scheduled termination.
Gland, mammary	X	All nonpregnant animals.
Gross lesions/masses	X	All animals.
Heart	X	Animals found dead or euthanized before scheduled termination.
Kidney	X	Animals found dead or euthanized before scheduled termination.
Liver	X	Animals found dead or euthanized before scheduled termination.
Lung	X	Infused with 10% neutral buffered formalin. Animals found dead or euthanized before scheduled termination.
Ovaries	X	All nonpregnant animals.
Spleen	X	Animals found dead or euthanized before scheduled termination.
Stomach	X	Animals found dead or euthanized before scheduled termination.
Trachea	X	Infused with 10% neutral buffered formalin. Animals found dead or euthanized before scheduled termination.
Uterus	X	Collected with cervix. All nonpregnant animals.
Vagina	X	All nonpregnant animals.

X = Procedure conducted.

No treatment related macroscopic changes were noted in maternal hamsters at necropsy.

Maternal Performance and Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

The litter averages for litter sizes, live fetuses, early and late resorptions, fetal body weights, percent post-implantation loss, and percent live male fetuses were comparable among the six dose groups and did not differ with respect to CCX168 treatment. All placentae that were examined appeared normal. Implantation was complete before the start of drug treatment.

Table 28: Summary of Maternal Performance and Cesarean Section Data in CCX168-treated Pregnant Hamsters (treatment from GD 6 to GD 12)

Female Hamsters	CCX168 Dose Groups (mg/kg/day)					
Ovarian and Uterine Contents	**Control**	**10**	**30**	**100**	**Control**	**1000**
Number pregnant/group	14	16	16	17	13	16
Copora lutea (mean)	15.3	15.2	15.4	15.2	15.3	14.8
Implantation	15.1	14.9	14.9	15.1	15.2	14.4
Preimplantation loss (%)	0.95	1.46	2.69	0.94	1.28	3.63
Early resorptions	0.7	0	0.2	0.2	0.2	0.1
Live fetuses/litter (mean)	14.4	14.5	14.6	14.8	15	14.3
Post-implantation loss (%)	7.14	3.91	2.41	2.52	0.94	0.37
Dead fetuses (mean)	0	0.4	0.1	0	0	0

Late resorptions	0	0.1	0	0.1	0	0
% Live male fetuses/litter	47.51	37.9	47.17	52.74	54.88	47.39
Live fetal body weights (g)/litter	2.65	2.5	2.65	2.6	2.6	2.6

Offspring (Malformations, Variations, etc.)

Visceral Examination
Approximately one-half of the fetuses in each litter were examined for visceral abnormalities. Each fetus was fixed in Bouin's solution and the heads were examined by free-hand sectioning.

Skeletal Examination
The remaining fetuses (approximately one-half of the fetuses in each litter) were examined for skeletal abnormalities after staining with alizarin red S. Following examination, skeletal preparations were retained in glycerin with thymol added as a preservative. Ossification sites were not counted, recorded, or summarized.

No treatment-related visceral malformations, visceral variations, or skeletal malformations were noted among examined fetuses. An increase in a skeletal variation described as supernumerary ribs was noted in all litters and 40 fetuses in the 1000 mg/kg/day group relative to 14 fetuses of 9 litters in the BID control group and 22 fetuses of 10 litters in the QD control group. This finding is considered to be a developmental delay and supernumerary ribs can resolve into the vertebral arch later in development. Although there is an apparent treatment related increase for this finding, this variation was not judged to be adverse (would not be expected to affect long-term survival).

Table 29: Summary of Fetal Variations from CCX168-treated Maternal Hamsters

Fetal Skeletal Findings	**CCX168 Dose Groups (mg/kg/day)**					
Supernumerary Rib, thoracolumbar, short-variation	**Control (QD)**	**10**	**30**	**100**	**Control (BID)**	**1000**
Number of fetuses/litters evaluated	104/13	119/16	120/16	131/17	101/13	119/16
Fetuses N (%)	22(21.2)	11(9.2)	16(13.3)	25(19.1)	14(13.9)	40(33.6)
Litters N (%)	10(76.9)	6(37.5)	10(62.5)	12(70.6)	9(69.2)	16(100)

9.22 Embryonic Fetal Development

Study title: An Embryo-Fetal Developmental Study of CCX168 by Oral (Stomach Tube) in Rabbits

Study no.:	PC0672_168
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 26, 2016 (May 29, 2016 first day of dosing)
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lot # D-15-012 and 99.5% purity

Key Study Findings

- CCX168 at doses of 0 (vehicle: Polyethylene glycol (b) (4) (b) (4) (v:v (b) (4)), 10, 30, and 200 mg/kg/day were administered via oral stomach tube in pregnant rabbits to evaluate embryofetal development. Animals were treated from gestation days (GD) 6 to 18 and sacrificed on GD 29.
- A CCX168-related increase in abortions was noted in the 200 mg/kg/day group which resulted in early euthanasia of does that aborted prior to the scheduled sacrifice on GD 29. In the 200 mg/kg/day group, five does aborted and were euthanized early from GD 21 to GD 28. Red aborted material was noted with all five does that aborted in the 200 mg/kg/day group. There were non-treatment related abortions and early euthanasia in the control, 10 mg/kg/day, and 30 mg/kg/day groups. In the control group, one doe aborted and was euthanized on GD 23. In the 10 mg/kg/day group, two does aborted early and were euthanized on GD 21 and 26, and one doe was subjected to unscheduled euthanasia on GD 19. In the 30 mg/kg/day group two does aborted and were euthanized early on GD 12 and GD 25 mg/kg/day group.
- From GD 6 to GD 18, reduced body weight gain was noted for the MD and HD treatment groups. The percent body weight changes relative to the control group were 94%, 84.9% and 79.3%, in the 10, 30 and 200 mg/kg/day dose groups, respectively, which suggests maternal toxicity was achieved at the MD and HD.
- Toxicokinetic analysis of CCX168 and CCX168-M1 revealed less than dose proportional increases in AUC and Cmax from 10 to 30 mg/kg/day. Saturation of exposure occurred at doses ≥ 30 mg/kg/day for CCX168 and CCX168-M1.
- There were no dose dependent changes in cesarean section parameters, or test article related malformations or variations up to the high dose of 200 mg/kg, which was associated with a CCX168 AUC of 4180 ng/mL and CCX168-M1 AUC of 65.1 ng*hr/mL in pregnant females on GD 18.
- The NOAEL for maternal toxicity was 10 mg/kg based on reduced body weight gain in the MD and HD groups and increased incidence of abortions at the HD.

- The NOAEL for developmental toxicity was the HD, 200 mg/kg, based on absence of treatment related fetal malformations or variations.

Methods

Doses:	0, 10, 30, and 200 mg/kg/day
Frequency of dosing:	Daily (GD 6-18)
Dose volume:	1 mL/kg/day
Route of administration:	oral stomach tube
Formulation/Vehicle:	Polyethylene glycol (b) (4) (b) (4) (v:v (b) (4))
Species/Strain:	Rabbits/New Zealand White [Crl:KBL(NZW)] (b) (4)
Number/Sex/Group:	Main Study: 20 suspected pregnant females/group TK: control: 3 females/group, CCX168 treated: 4 suspected pregnant females /group
Satellite groups:	None
Study design:	Dose selection of 10, 30 and 200 mg/kg/day were selected based on a prior GLP DRF Segment II rabbit toxicology study ((b) (4) (b) (4) study no. 20088416). In the initial phase of this study, a dose volume of 2.5 ml/kg (vehicle: Polyethylene glycol (b) (4) (v:v (b) (4))) was poorly tolerated, and an additional phase using vehicle at 1.0 mL/kg was conducted. Doses employed in that study of 10, 30 and 200 mg/kg/day were well tolerated. 200 mg/kg was the maximum feasible dose that could be employed in this additional study phase due to solubility and dose volume constraints due to toxicity associated with the vehicle at the dose volume of 2.5 mL/kg. Female rabbits were naturally bred at the Supplier, by breeder male rabbits of the same source and strain, before shipment to the Testing Facility. The day mating occurred was considered to be GD 0. The rabbits were shipped to the Testing Facility after mating to arrive on GD 1, 2, 3 or 4. The Supplier forwarded the breeding records and GD 0 body weights. CCX168 was administered once daily, from GD 6 through GD 18. On GD 19, surviving

female rabbits assigned to the toxicokinetic study were euthanized after the last blood sample collection. On GD 29, surviving rabbits assigned to the main study were euthanized, and examined for ovarian and uterine contents and gross lesions. Fetuses were weighed, sexed, and examined for external, skeletal, and visceral abnormalities.

Deviation from study protocol: No deviations were noted that were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions.

Experimental Design

Experimental Design

Group No.	Test Material	Dose Level (mg/kg/day)[b]	Concentration (mg/mL)	Dose Volume (mL/kg/day)	No. of Females	
					Main Study	Toxicokinetic Study
1	Control Article	0	0	1.0	20	3
2	CCX168	10	10	1.0	20	4[a]
3	CCX168	30	30	1.0	20	4[a]
4	CCX168	200	200	1.0	20	4[a]

[a] One additional rabbit was dosed and utilized for blood collection, to account for a possible non-pregnant doe.
[b] Dose calculations were corrected for purity, water and solvent content using the correction factor of 0.985 (1015 mg of this lot of CCX168 contains 1000 mg of the neutral compound).

Observations and Results

Mortality

The rabbits were assessed for viability at least twice daily during the study.

Early euthanasia, either due to abortion, early delivery, or other clinical signs occurred in all treatment groups. In the control group one doe aborted and was euthanized on GD 23. In the 10 mg/kg/day group, two does aborted early and were euthanized on GD 21 (red aborted tissue and material was noted) and 26, one doe was subjected to unscheduled euthanasia on GD 19, and one doe began delivering early GD 29 prior to scheduled euthanasia. In the 30 mg/kg/day group, two does aborted and were euthanized early on GD 12 and GD 25 (red aborted tissue and material was noted for both does). Abortions in the control group and 10 and 30 mg/kg/day groups within the background/spontaneous abortion range for New Zealand White rabbits.

In the 200 mg/kg/day group, five does aborted and were euthanized early from GD 21 to GD 28. Red aborted material was noted with all five does that aborted in the 200 mg/kg/day group. The increased incidence of abortion in the 200 mg/kg/group was considered CCX168 related.

Table 30: Females Rabbits That Aborted During the Study Period (CCX168 treatment from GD 6 through GD 18)

Female Rabbits	CCX168 Dose Groups (mg/kg/day)			
Abortion	**Control**	**10**	**30**	**200**
Animal Number/(Day of Euthanasia)	9110/(GD 23)	9136 (GD 21) 9132 (GD 26)	9144 (GD 12) 9152 (GD 25)	9175 (GD 21) 9176 (GD 25) 9171 (GD 26) 9172 (GD 26) 9166 (GD 28)

Clinical Signs

The rabbits were observed for general appearance once during the acclimation period and daily during the dose and postdose period. Postdose observations were recorded at 1 and 4 hours postdose.

In the 200 mg/kg/day HD group, there was a treatment related increases of clinical signs including thin body condition, ungroomed fur, and decreased fecal output relative to the control group. In addition, there was an increase in rabbits with red tissue and red liquid material, relative to the control group, which was associated with the increased number of abortions that occurred in pregnant rabbits receiving CCX168 at 200 mg/kg/day. It is noted that in general the clinical signs of thin body, red tissue, and red liquid material largely occurred after the dosing period (GD 6 - GD 18).

Table 31: Clinical Signs Noted in Pregnant Females Rabbits (treatment with CCX168 from GD 6 to GD 18)

Female Rabbits	CCX168 Dose Groups (mg/kg/day)			
Clinical Sign	**Control**	**10**	**30**	**200**
Thin body	2	3	1	5
Number of observations	13	11	1	26
Gestation Days	*19-29*	*18-26*	*18-29*	*18-29*
Ungroomed fur	2	4	2	4
Number of observations	14	11	1	18
Gestation Days	*19-29*	*13-29*	*11-12*	*13-28*
Decreased feces output	0	2	2	4
Number of observations	0	6	12	20
Gestation Days	*0*	*6-10*	*8-25*	*10-27*
Aborted tissue, red material	0	1	2	5
Number of observations	0	1	2	5
Gestation Days	*0*	*21-21*	*12-25*	*21-28*
Red liquid material	0	1	2	2
Number of observations	0	1	3	3
Gestation Days	*0*	*21-21*	12-29	*26-28*

Body Weight

Body weights were recorded on GD 0 (provided by the Supplier), on the day of arrival at the Testing Facility, and daily during the dose and postdose period.

During the dosing period (GDs 6 through 18), reduced body weight gain was noted for the MD and HD treatment groups. The percent body weight changes relative to the control group were 94%, 84.9% and 79.3%, in the 10, 30 and 200 mg/kg/day dose groups, respectively.

Table 32: Body Weight Changes in Pregnant Females Treated with CCX168 (treatment from GD 6 to GD 18)

Parameter	CCX168 mg/kg/day			
	Control	10	30	200
GD 6 (grams)	3495.14	3527.27	3494.9	3490.89
GD 18 (grams)	3603.45	3629.06	3586.90	3576.75
GD 29 (grams)	3734.43	3816.75	3750.88	3870.59
GD 6 to GD 18, Δ (grams)	108.3	101.8	92.0	85.9
% Change of GD 6 BW	3.1	2.9	2.6	2.5
% of Control	100.0	94.0	84.9	79.3
GD 18 to GD 29, Δ (grams)	239.29	289.48	255.98	379.7
% Change of GD 18 BW	6.6	8.0	7.1	10.6
% of Control	100.0	121.0	107.0	158.7

Feed Consumption

Beginning on the day after arrival, approximately 150 g of Certified Rabbit Chow® #5322 (PMI® Nutrition International) was available to each rabbit each day until the first day of dosing, at which time 180 to 185 g of the same certified food was offered to each rabbit each day. Water was available ad libitum.

Toxicokinetics

Blood samples (1 mL) were collected from all toxicokinetic animals via the medial auricular artery in the 10 mg/kg/day (LD), 30 mg/kg/day (MD), and 200 mg/kg/day (HD) groups, on GD 6 and GD 18 predose and at approximately 1, 2, 4, 8, and 24 hours postdose (see below for TK sample collection schedule). Blood samples were also collected from the control article group on GD 6 and GD 18 at approximately 2 hours postdose. Plasma samples were assayed for CCX168, CCX168-M1, and CCX168-M6 (b) (4) and the results were used for the generation of this toxicokinetic report.

TK Sample Collection Schedule

Group No.	No. of Rabbits	Sample Collection Time Points (Approximate Time Postdose) on DG 6 and 18					
		0 hour	1 hour	2 hour	4 hour	8 hour	24 hour
1	3	-	-	X	-	-	-
2	4[a]	X	X	X	X	X	X
3	4[a]	X	X	X	X	X	X
4	4[a]	X	X	X	X	X	X

X = Sample collected; - = Not applicable; DG = Day of presumed gestation
[a] One additional rabbit was utilized for blood collection, to account for a non-pregnant doe.

The increase in exposure (AUC) from 10 to 30 mg/kg/day was less than dose proportional on GD 6. Saturation of exposure occurred at doses ≥ 30 mg/kg/day. There was a decrease in exposure from 30 to 200 mg/kg/day on GD 6. The increase in exposure from 30 to 200 mg/kg/day on GD 18 was negligible. Accumulation of CCX168 was noted from GD 6 to GD 18. The increase in Cmax was less than dose proportional from 10 to 30 mg/kg/day on GD 18. There was a decrease in Cmax from 30 to 200 mg/kg/day on GD 6 and on GD 18.

Table 33: Summary of CCX168 Toxicokinetic Parameters in Pregnant Female Rabbits (treatment from GD 6 to GD 18)

Interval	Dose Group	Dose Level (mg/kg/day)	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)
DG 6	2	10	480	1480
	3	30	478	1990
	4	200	253	1750
DG 18	2	10	442	2350
	3	30	729	3990
	4	200	509	4180

The increase in exposure (AUC) from 10 to 30 mg/kg/day was less than dose proportional for CCX168-M1 on GD 6. Saturation of exposure occurred at doses ≥ 30 mg/kg/day. There was a decrease in exposure from 30 to 200 mg/kg/day on GD 6. The increase in exposure from 30 to 200 mg/kg/day on GD 18 was negligible. Accumulation of CCX168-M1 was noted from GD 6 to GD 18. The increase in Cmax was less than dose proportional from 10 to 30 mg/kg/day on GD 18. There was a decrease in Cmax from 30 to 200 mg/kg/day on GD 6 and on GD 12.

Table 34: Summary of CCX168-M1 Toxicokinetic Parameters in Pregnant Female Rabbits (treatment from GD 6 to GD 18)

Interval	Dose Group	CCX168 Dose Level (mg/kg/day)	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)
DG 6	2	10	50.2	314
	3	30	69.4	573
	4	200	27.1	361
DG 18	2	10	35.7	364
	3	30	73.9	730
	4	200	65.1	780

Dosing Solution Analysis

The dosing suspensions of CCX168 prepared in polyethylene glycol (b) (4) (b) (4)) (v:v (b) (4)) were analyzed and found to be homogeneous under the conditions of this study. The first preparation of the dosing suspensions of 10, 30 and 200 mg/mL were analyzed and found to be within -2.3%, +3.0% and +8.0% of the target concentrations, respectively. The homogeneity values obtained for the first preparations were 2.3%, 1.8% and 2.6% RSD for the 10, 30 and 200 mg/mL formulations, respectively.

All homogeneity and concentration analysis results met the protocol specified acceptance criteria.

Necropsy

On GD 19, female rabbits assigned to the toxicokinetic groups were euthanized by IV administration of a 'euthanasia solution', after the last blood sample collection. Pregnancy status was recorded, and the carcasses were discarded without further evaluation.

On GD 29, surviving rabbits assigned to the main study groups were euthanized by IV administration of a 'euthanasia solution', and examined for ovarian and uterine contents and gross lesions.

A gross necropsy of the thoracic, abdominal and pelvic viscera was performed for all rabbits assigned to the main study.

Terminal Procedures

Group No.	No. of Rabbits	Scheduled Euthanasia Day	Necropsy Procedures				Histology	Histopathology
			Ovarian/ Uterine Examination	Necropsy	Tissue Collection	Organ Weights		
1[a]	3	DG 19	Pregnancy Status	-	-	-	-	-
2[a]	4						-	-
3[a]	4						-	-
4[a]	4						-	-
Unscheduled Deaths[a,b]			Pregnancy Status	X	-	-	-	-
1[c]	20	DG 29	X	X	X[d]	-	-	-
2[c]	20						-	-
3[c]	20						-	-
4[c]	20						-	-
Unscheduled Deaths[c]			X	X	X[d]	-	-	-

X = Procedure conducted; - = Not applicable.; DG = Day of presumed gestation
[a] Rabbits assigned to the toxicokinetic study.
[b] See Section 4.10.2. (Unscheduled Deaths).
[c] Main study animals.
[d] See Section 4.10.5. (Tissue Collection and Preservation) for tissue that were retained.

Tissue Collection and Preservation

Representative samples of the tissues listed in Table 35 were collected from all main study rabbits and preserved in 10% neutral buffered formalin, unless otherwise indicated. As noted, all other tissues were discarded. Tissues were not collected for rabbits assigned to the toxicokinetic study.

Table 35: Tissues Collected from CCX168 Treated Maternal Rabbits in EFD Study

Tissue	Collected	Comment
Cervix	X	Collected with uterus. All nonpregnant rabbits.
Esophagus	X	Infused with 10% neutral buffered formalin. Rabbits euthanized before scheduled termination.
Gross lesions/masses	X	All rabbits.
Heart	X	Rabbits euthanized before scheduled termination.
Kidney	X	Rabbits euthanized before scheduled termination.
Liver	X	Rabbits euthanized before scheduled termination.
Lung	X	Infused with 10% neutral buffered formalin. Rabbits euthanized before scheduled termination.
Ovaries	X	All nonpregnant rabbits.
Spleen	X	Rabbits euthanized before scheduled termination.
Stomach	X	Rabbits euthanized before scheduled termination.
Trachea	X	Infused with 10% neutral buffered formalin. Rabbits euthanized before scheduled termination.
Uterus	X	Collected with cervix. All nonpregnant rabbits.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

The reproductive tract was dissected from the abdominal cavity. The uterus was opened, and the contents were examined. The fetuses were removed from the uterus and placed in individual containers for the fetal examinations.

The ovaries and uterus were examined for number and distribution of corpora lutea, implantation sites, placentae (size, color, and shape), live and dead fetuses and early and late resorptions.

There were 19 (95%) pregnancies in each main study group (20 females/group). Abortions were noted in 1, 2, 2 and 5 does in the 0, 10, 30 and 200 mg/kg/day dose groups, respectively. Ovarian and uterine contents observations were based on 17, 16, 18 and 14 pregnant rabbits in the 0, 10, 30, and 200 mg/kg/day groups respectively, reflecting the instances of abortion or early deliveries. Generally, litter averages for corpora lutea, implantations, preimplantation loss, early resorptions, live fetuses, post implantation loss, dead fetuses, late resorptions, and percent male fetuses were comparable across all groups. Fetal body weights were not affected by treatment.

Table 36: Summary of Maternal Performance, Uterine Contents, and Fetal Data in CCX168 Treated Rabbits (treatment from GD 6 to GD 18)

Female Hamsters	**CCX168 Dose Groups (mg/kg/day)**			
Maternal Performance	**Control N=20**	**10 N=20**	**30 N=20**	**200 N=20**
Pregnant/Mated	19/20 (95%)	19/20 (95%)	19/20 (95%)	19/20 (95%)
Dams with live fetuses	17	16	18	14
Dams with all dead or resorbed	2	3	1	5
Dam aborted	1	2	2	5
Uterine Contents	**N=17**	**N=16**	**N=18**	**N=14**
Copora lutea (mean)	11.4	12.0	11.3	12.3
Implantations	11.1	11.4	10.3	11.2
Preimplantation loss (%)	2.68	8.36	7.94	8.51
Early resorptions	1.0	1.0	0.4	0.6
Live fetuses/litter (mean)	9.8	9.2	9.4	10.3
Post-implantation loss (%)	12.17	16.53	9.28	8.84
Dead fetuses (mean)	0	0	0	0.1
Late resorptions	0.3	1.2	0.5	0.3
% Live male fetuses/litter	49.31	48.65	49.76	48.32
Live fetal body weights (g)/litter	2.65	2.5	2.65	2.6
Fetal Data	**Control**	**10**	**30**	**200**
Mean fetal body weight, g (male)	38.9	38.4	39.0	38.4

Mean fetal body weight, g (female)	38.2	36.8	36.7	39.9
Mean fetal body weight (M and F combined), g	38.6	37.8	37.7	38.7

Offspring (Malformations, Variations, etc.)

Fetuses were examined for external, visceral, and skeletal abnormalities (*i.e.* malformation or variations). Individual fetal body weights were recorded. During the visceral examination, the sex of each fetuses was determined to the extent possible.

No treatment related malformations or variations were noted.

9.23 Prenatal and Postnatal Development

Study title: An Oral (Gavage) Prenatal/Postnatal Developmental Toxicity Study of CCX168 in Hamsters, Including a Postnatal Behavioral/Functional Evaluation

Study no.:	PC0673_168
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 20, 2017 (July 31, 2017 initiation of dosing)
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lot # D-15-012; Purity 99.1%

Key Study Findings

- In a pre- and postnatal development (PPND) study, mated F0 female hamster received CCX168 at doses of 0 (vehicle- PEG (b) (4)), 10, 30, or 100 mg/kg once daily or 0 (vehicle- PEG (b) (4)) and 500 mg/kg twice daily (1000 mg/kg) from Gestation Day (GD) 6 to Lactation Day/Postnatal Day (LD/PND) 20.
- No treatment-related changes of body weight gain were noted in F0 dams during the gestation period (GD 6 to GD 14) or lactation period (LD1 to LD21).
- F0 dams showed no treatment related effects on reproductive parameters. There were no treatment related effects on the gestation length, the number of implantation sites, the number of live births, or on viability of F1 offspring.
- There were no treatment related effects on body weight gains of F1 offspring from birth to weaning (LD 1 to LD 21)
- For F1 generation pups, growth, physical (motor evaluation) and neurological development (passive avoidance) were unaffected with doses up to 1000 mg/kg

in F0 females. Mating and fertility indices were unaffected in F1 adults with doses up to 1000 mg/kg in F0 females. Post-implantation loss and numbers of viable embryos were similar across F1 groups.

- The NOAEL for F0 maternal toxicity and for F1 pup development was the high dose of 500 mg/kg BID (1000 mg/kg/day).

Methods

Doses:	0 (vehicle), 10, 30, or 100 mg/kg/day on daily or vehicle and 500 mg/kg/dose twice daily (1000 mg/kg/day)
Frequency of dosing:	Daily from GD 6 to PND 20 (or GD 20 for hamsters that did not deliver a litter)
Dose volume:	Dose Groups 0, 10, 30, 100 mg/kg/day: 5 mL/kg Dose group 0 and 500 mg/kg BID: 2.5 mL/kg/dose
Route of administration:	Oral gavage
Formulation/Vehicle:	Polyethyleneglycol (b) (4) (b) (4) (v:v (b) ( )).
Species/Strain:	Mated female Crl:LVG(SYR) Golden Syrian hamsters (b) (4)
Number/Sex/Group:	F_0 main study 22 pregnant hamsters/group F_0 TK 5/control group and 6/CCX168-treatment groups
Satellite groups:	None
Study design:	Female hamsters were mated with breeder untreated male hamsters of the same source and strain. The cohabitation period consisted of up to 5 days. Female hamster with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug observed in situ were considered to be at GD 0 and assigned to individual housing. Mated F_0 female hamsters received CCX168 by oral gavage at doses of 0 (vehicle), 10, 30, or 100 mg/kg/day or vehicle and 500 mg/kg/dose twice daily (1000 mg/kg/day) from Gestation Day (GD) 6 to Lactation Day/Postnatal Day (LD/PND) 20 (or GD 20 for hamsters that did not deliver a litter). F_1 generation pups were not directly given the test article and/or the control article formulations, were possibly exposed to the test article and/or the control article formulations article during maternal gestation (in utero exposure) or via maternal milk during the lactation period. "Litters will not be culled during the lactation period because random selection of pups for culling could result in potential biases in pup viabilities and body weight gains during this period." For the F_1 generation, at weaning on Postpartum Day 21, 22 male and 22 female

pups per group, resulting in a total of 264 F_1 generation hamsters (132 per sex) were chosen for continued evaluation. Within each dose group, hamsters were assigned to cohabitation (i.e., pairing) on Postpartum Days 95, 96, 97, 98 or 99, one male per one female, based on computer-generated random units, with the exclusion of sibling pairings. The cohabitation period consisted of up to 14 days for each pairing after being observed to be compatible. Females observed with spermatozoa in a smear of the vaginal contents and/or a copulatory plug observed in situ were considered to be at GD 0 and assigned to individual housing. Females not mated within the first 7 days of cohabitation were assigned alternate males that had mated (within the cohabitation period) and remained in cohabitation for up to 7 additional days. Females not mated after completion of the 14-day cohabitation period were assigned to individual housing and euthanized 3 days after the end of the cohabitation period. On GD 12, surviving F1 generation female hamsters were euthanized and subjected to ovarian and uterine examinations and were examined for gross lesions. On Postpartum Days 116, 117, 118, 119 or 120, surviving F1 generation male hamsters were euthanized and examined for gross lesions.

Basis of Dose Selection: The dose levels were selected based on prior repeat-dose toxicology and toxicokinetic evaluation in this species. The mid-high dose (100 mg/kg/day) and the high dose (1000 mg/kg/day) were anticipated to produce maximal systemic exposure to the test article. Additionally, the dose of 1000 mg/kg/day represented the limit dose (ICH M3(R2) and S5(R3) Guidances) for evaluation in reproductive toxicology studies. The NOAEL for developmental toxicity was 1000 mg/kg/day (500 mg/kg BID).

No deviations were noted that were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions.

Deviation from study protocol:

Experimental Design: Once Daily (QD) Dosing Groups

Experimental Design - QD (Once Daily)

Group No.	Test Material	Dose Level (mg/kg/day)[a]	Concentration (mg/mL)	Dose Volume (mL/kg/day)	No. of Hamsters	
					Main Study	Toxicokinetic
1	Control	0	0	5	22	5
2	CCX168	10	2	5	22	6
3	CCX168	30	6	5	22	6
4	CCX168	100	20	5	22	6

[a] Hamsters were dosed once daily at approximately the same time as the first daily dose for animals in Groups 5 and 6.

Experimental Design: Twice Daily (BID) Dosing Groups

Experimental Design - BID (Twice Daily)

Group No.	Test Material[a]	Dose Level (mg/kg/dose)	Dose Level (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg/dose)[b]	No. of Hamsters	
						Main Study	Toxicokinetic
5	Control	0	0	0	2.5	22	5
6	CCX168	500	1000	200	2.5	22	6

[a] Hamsters were dosed twice per day (approximately 8 hours apart).

[b] Total dose volume/day = 5 mL/kg; Vehicle: Polyethyleneglycol (b) (4) (b) (4) (v:v (b) (4)).

Observations and Results

F_0 Dams

Survival: The hamsters were assessed for viability at least twice daily during the study.

No treatment-related deaths occurred in the F_0 adult animals.

Clinical signs: The hamsters were observed for general appearance twice during the acclimation period, on GD 0 and daily during the dose and postdose period (including the day of scheduled euthanasia). During the QD Phase, postdose observations were recorded at approximately 2 hours postdose. During the BID Phase, postdose observations were recorded at approximately 2 hours postdose (relative to the 1st daily dose) and at the end of the normal working day (after the 2nd daily dose). Maternal observations were recorded daily during the postpartum period

No treatment related clinical signs were noted in F_0 dams during the gestation or lactation period.

Body weight: Body weights were recorded twice during the acclimation period, on GD 0 and daily during the dose and postdose period.

Increases in body weight gains were noted in drug-treated F0 dams during the gestation period (GD 6 to GD 14). Due to the small magnitudes and lack of a clear dose response, the body weight gains were not considered treatment related during the gestation period in F0 dams.

There were no treatment-related changes of BW gain during the lactation period. It is noted that all groups including vehicle-controls were observed with body weight losses during this period.

Table 37: Body Weight Changes in CCX168-Treated F0 Pregnant Female Hamsters During Gestation

F0 Body Weights	CCX168 mg/kg/day QD groups				CCX168 mg/kg/day BID Groups	
Gestation Phase (g)	Vehicle	10	30	100	Vehicle	1000
GD 6	145.9	145.4	143.6	148	143.8	143.9
GD 14	183.1	185.6	183.8	192.5	192.2	197.2
GD 6 to 14, Δ	37.2	40.2	40.2	44.5	48.4	53.3

% Δ of GD 6 BW	25.5	27.6	28.0	30.1	33.7	37.0
% of Control	100	108.1	108.1	119.6	100	110.1

Body weight losses were noted during the lactation phase in all groups of F0 hamsters including vehicle-control groups. During the treatment phase of the lactation phase (LD 1 to LD 20), body weight changes (body weight loss) across all CCX168 dose groups were comparable (Table 38).

Table 38: Body Weight Changes in CCX168 Treated F0 Maternal Female Hamsters During Lactation

F0 Body Weights	CCX168 mg/kg/day QD groups				CCX168 mg/kg/day BID Groups	
Lactation Phase (g)	Vehicle	10	30	100	Vehicle	1000
LD 1	146.4	146.8	144.1	151.1	152.5	155.3
LD 4	146	144.8	142.6	150.7	150.9	156.9
LD 7	144.3	141.6	139.1	146.5	148	153.1
LD 14	138.8	134.1	132.9	140.7	143.3	145
LD 20	134.1	129.3	126.8	135.1	138.7	139.8
LD 21	134.8	130.4	127.1	136.9	139.4	141.1
LD 1 to 20, Δ	-12.3	-17.5	-17.3	-16	-13.8	-15.5
% Δ of LD 1 BW	-8.4	-11.9	-12.0	-10.6	-9.0	-10.0
% of Control	100.0	142.3	140.7	130.1	100.0	112.3

Feed consumption:

Food consumption values were recorded on DGs 6, 9, 12, 15, 18 and 21 (if necessary) and on LDs 1, 4, 7, 10 and 12.

No treatment related effects on food consumption were noted during the gestation or lactation phases for F0 hamsters.

Litter Observations and Uterine content:

Natural delivery observations (duration of gestation, litter size, and pup viability at birth) were recorded. F0 female hamsters were sacrificed on LD21. The reproductive tract was dissected from the abdominal cavity for all main study hamsters. The number and distribution of implantation sites were recorded.

There were no treatment related effects on the number of dams that delivered litters, the duration of gestation, numbers of dams with stillborn pups, viability index, lactation index (average number of live pups on Day 21 postpartum per number of live pups on Day 4 postpartum). The results for selected parameters are shown in Table 39

Table 39: Summary of Litter Observations, Uterine Content, and Pup Viability

F0 Dams	CCX168 mg/kg/day QD groups				CCX168 BID groups	
Litter Observations	**Vehicle**	**10**	**30**	**100**	**Vehicle**	**1000**
Tested	22	22	22	22	22	22
Pregnant	21	21	21	22	21	22
Delivered	21	21	21	22	21	22
Implantations	321	315	337	341	329	346
Dams with Stillborn pups	1	1	2	0	0	2
Viability index[a] (LD 1-4)	75.6%	80.7%	77.2%	81.7%	70.9%	77.4%
Lactation index[b] (LD 4-21)	93.6%	97.5%	97.2%	94%	94.6%	96.9%

[a] Number of live pups on LD 4 postpartum/number of liveborn pups on Day 1 postpartum.

[b] Number of live pups on LD 21 (weaning) postpartum/number of live pups on Day 4 postpartum.

Necropsy observation:

TK F_0 animals were euthanized on LD 16 and were not subject to necropsy.

Main study F_0 dams were euthanized on LD 21 by carbon dioxide asphyxiation. During necropsy, each F_0 generation female hamster was examined for any notable abnormalities or lesions, followed by a gross examination of the thoracic, abdominal and pelvic viscera. Histopathological examinations were not conducted on F_0 hamsters.

Representative samples of the tissues identified in Table 40 were collected from all main study hamsters and preserved in 10% neutral buffered formalin, unless otherwise indicated. All other tissues were discarded.

Tissue Collection

Ovarian and uterine contents were examined, tissues were collected and preserved, and organ weights were measured.

Table 40: Tissues collected from F_0 Hamsters

Tissue	Weighed	Collected
Cervix	X	X
Esophagus	-	X
Gland, mammary	-	X
Gross lesions/masses	-	X
Lung	-	X
Oviduct	X	X
Ovaries	X	X
Trachea	-	X
Uterus	X	X
Vagina	-	X

There were no treatment related gross findings in F_0 hamsters.

Toxicokinetics: On LD 16, female hamsters assigned to the toxicokinetic study along with pups not selected for blood collected were euthanized after the last blood sample collection for the dam and discarded without further evaluation. Pups selected for blood collection were euthanized and blood samples were collected and discarded without further evaluation.

Exposure, as assessed by CCX168 and CCX168-M1 Cmax and AUC0-24, increased with increasing CCX168 dose level from 10 to 100 mg/kg/day. The increases in Cmax and AUC0-24 values were greater than dose proportional from 10 to 30 mg/kg/day and were less than dose proportional from 30 to 100 mg/kg/day. Exposure to CCX168 decreased from 100 mg/kg/day to 1000 mg/kg/day. There was a slight increase in CCX168-M1 from 100 mg/kg/day to 1000 mg/kg/day. The metabolite to parent ratio ranged from 0.0355 to 0.0788 for Cmax and from 0.0650 to 0.105 for AUC0-24. The pup:maternal ratios indicated that CCX168 and CCX168-M1 were present in pups after dosing of maternal hamsters with CCX168 once or twice daily.

Table 41: Summary of the CCX168 Toxicokinetic Parameters on Lactation Day 15 Hamster Plasma

Dose Level (mg/kg/day)	$C_{max\ 0\text{-}24}$ (ng/mL)	$T_{max\ 0\text{-}24}$ (h)	$AUC_{0\text{-}8}$ (ng·h/mL)	$AUC_{0\text{-}10}$ (ng·h/mL)	$AUC_{0\text{-}24}$ (ng·h/mL)
10	783	2.00	2940	NA	4910
30	3950	1.00	14500	NA	25300
100	4210	1.00	22700	NA	43800
1000	2400	1.00	NA	15800	30900

Table 42: Summary of the CCX168-M1 Toxicokinetic Parameters on Lactation Day 15 Hamster Plasma

Dose Level (mg/kg/day)	$C_{max\ 0\text{-}24}$ (ng/mL)	$T_{max\ 0\text{-}24}$ (h)	$AUC_{0\text{-}8}$ (ng·h/mL)	$AUC_{0\text{-}10}$ (ng·h/mL)	$AUC_{0\text{-}24}$ (ng·h/mL)
10	41.3	2.00	232	NA	423
30	140	4.00	848	NA	1650
100	202	2.00	1370	NA	2960
1000	190	10.0	NA	1520	3260

Dosing Solution Analysis	Duplicate (1 mL) sets of top, middle, and bottom samples for the sampling time points were collected. Concentration results were considered acceptable if mean sample concentration results were within or equal to ± 10% of nominal concentration. Each individual sample concentration result was considered acceptable if it was within or equal to ± 15% of nominal concentration. For homogeneity, the criteria for acceptability were a relative standard deviation (RSD) of concentrations of ≤ 5% for each group. All homogeneity and concentration analysis results met the protocol specified acceptance criteria.
Other:	

F_1 Generation: Litters were not be culled during the lactation period because random selection of pups for culling could result in potential biases in pup viabilities and body weight gains during this period. At weaning on Postpartum Day 21, 22 male and 22 female pups per group, resulting in a total of 264 F_1 generation hamsters (132 per sex) were chosen for continued evaluation.

Survival: Litters were observed for dead pups twice daily pre- and post-weaning. The pups in each litter were counted once daily.

No treatment related effects on F1 pup survival were observed from LD 1 (birth) to LD 4 or LD 4 to LD 21 (weaning). Survival was unaffected during the postweaning period and up to Postpartrum Day 116-120 in males and GD12 in females.

Clinical signs: Clinical observations were recorded daily in the preweaning period. Male hamsters were observed for general appearance once weekly during the postweaning period and on the day of scheduled euthanasia. Female hamsters were observed for general appearance once weekly during the postweaning period and on GDs 0, 3, 7, 10, 11 and 12.

No treatment related clinical signs were noted in F1 generation pups

Body weight: Body weights were recorded on Postpartum Days 1 (birth), 4, 7, 14 and 21. Body weights for the male hamsters were recorded once weekly during the postweaning period and on the day of scheduled euthanasia. Body weights for the female hamsters were recorded once weekly during the postweaning period and on GDs 0, 3, 7, 10, 11 and 12.

There were no treatment related changes in body weights or body weight gains in male F1 hamsters during the weaning and post-weaning periods. There were no treatment related changes in body weights during the weaning, post-weaning, pre-cohabitation, or gestation periods in female F1 hamsters.

Feed consumption: Food consumption values for the male hamsters were recorded once weekly until cohabitation. Food consumption values for the female hamsters were recorded once weekly until cohabitation and on GDs 0, 3, 7, 10, 11 and/or 12

There were no treatment related changes in food consumption during the post-weaning, pre-cohabitation, or gestation periods in male or female F1 hamsters.

Physical development:

In females, sexual maturation was evaluated once daily beginning on Day 7 postpartum until the criterion was achieved. In males, sexual maturation was evaluated once daily beginning on Day 35 postpartum until the criterion (preputial separation) was achieved

There was no treatment related effect on sexual maturation in male or female F1 hamsters.

Table 43: Timing of Sexual Maturation for F1 Male and Female Hamsters

F1 Hamsters	CCX168 mg/kg/day QD groups				CCX168 BID groups	
Sexual Maturation Day	**Vehicle**	**10**	**30**	**100**	**Vehicle**	**1000**
Males Preputial separation [a]	39	39.8	41.0	41.6	39.7	41.3
Females [b]	94.3	94.5	94.4	96.1	93.3	95.3

[a] Average day postpartum that the prepuce was observed to be separated.

[b] Average day postpartum that at least 50% of the pups had the developmental measure present.

Passive Avoidance and Motor Activity Evaluations:

Beginning at Day 24 postpartum ± 1 day, one male hamster and one female hamster from each litter, where possible, were tested in sets of up to 4 for passive avoidance.

There were no treatment related effects in the values for learning, short-term retention, long-term retention, or response inhibition in the F1 generation male and female hamsters, as evaluated by performance in a passive avoidance paradigm.

Motor activity was evaluated on Day 80 (± 2 days) postpartum.

There were no treatment related effects in the values for the motor activity evaluation in the F1 generation male and female hamsters.

Estrous cycling and Reproduction:

Estrous cycles were evaluated by examining the vaginal discharge and/or by samples obtained by vaginal lavage from F1 females for 14 consecutive days before initiation of cohabitation and then until spermatozoa were observed in a smear of the vaginal contents and/or a copulatory plug was observed in situ during the cohabitation period.

On GD 12, surviving F1 generation female hamsters were euthanized and examined for gross lesions. The reproductive tract from the F1 generation female hamsters was dissected from the

abdominal cavity. The uterus was opened, and the contents were examined. The embryos were removed from the uterus. The ovaries and uterus were examined for number and distribution of corpora lutea, implantation sites, placentae (size, color, and shape), and live and dead embryos.

No treatment-related changes in estrous cycling, number of days in cohabitation, number of hamsters that mated, fertility index (number of pregnancies per number of hamsters that mated) were noted in the F1 generation. The litter averages for corpora lutea, implantations, preimplantation loss, viable and nonviable embryos, and postimplantation loss were comparable across all groups. All placentae appeared normal.

Toxicokinetics: Blood samples (0.06 mL-0.6 mL) were collected from up to 3 pups/sex/litter via vena cava following euthanasia at approximately 2 hours after the first dose for Groups 0, 10, 30, 100 mg/kg/day and approximately 10 hours after the first dose of the day for Groups 0 and 1000 mg/kg/day on Day 15 postpartum and placed into K_2EDTA tubes.

CCX168 and CCX168-M1 were present in nursing pups after maternal hamsters were administered CCX168 once or twice daily on LD 15. The ratios of CCX168 and CCX168-M1 in pups relative to maternal hamsters are shown in Table 44.

Table 44: Summary of the Mean Pup:Maternal Ratios of CCX168 and CCX168-M1 on Lactation Day 15

Dose Level (mg/kg/day)	CCX168 Ratio	CCX168-M1 Ratio
10	0.00888	0.00815
30	0.0237	0.0431
100	0.0733	0.132
1000	0.373	0.382

Necropsy and Histopathology: Surviving F1 generation female hamsters were euthanized on GD 12 and examined for gross lesions. On Days 116 to 120 postpartum, surviving F1 generation male hamsters were euthanized and examined for gross lesions.

During necropsy, each F1 generation male hamster was examined for any notable abnormalities or lesions, followed by a gross examination of the thoracic, abdominal and pelvic viscera. The organs and tissues in Table X were collected and weighed or examined microscopically as noted in the table.

Table 45: Tissue Collected from F1 Male and Female Hamsters

Tissue	Weighed	Collected	Microscopically Evaluated
Bone marrow, femur	-	X	X
Bone marrow, smear	-	X	X
Cervix	X	X	-
Epididymis	X	X	-
Gland, mammary	-	X	-
Gland, prostate	X	X	-
Gland, seminal vesicle	X	X	-
Gross lesions/masses	-	X	X
Lymph node, mandibular	-	X	X
Lymph node, mesenteric	-	X	X
Oviduct	X	X	-
Ovaries	X	X	-
Spleen	X	X	X
Testis	X	X	-
Thymus	X	X	X
Uterus	X	X	-
Vagina	-	X	-

No treatment related gross changes, organ weight changes, or microscopic changes were noted upon examination following necropsy.

Histopathological examinations were performed on 10/hamsters/sex for the control groups (QD and BID) and the 100 and 1000 mg/kg/day groups.

No CCX168-related microscopic findings were noted in male or female F1 offspring from F0 maternal hamsters treated with CCX168 at 100 or 1000 mg/kg/day.

10 Special Toxicology Studies

Phototoxicity

Effects of CCX168 in a Neutral Red Uptake Phototoxicity Assay in BALB/c 3T3 Mouse Fibroblasts (Study Report No. PC0663_168)

Methods: CCX168 absorbed UV light at 290 nm with a molar extinction coefficient of 2989 L mol^{-1} cm^{-1}. The phototoxic potential of CCX168 was measured in the BALB/c 3T3 mouse fibroblast assay. CCX168 was assessed at concentrations ranging from 0.18 to 10.0 µg/mL. Cells were exposed to 5 J/cm^2 of UVA and 22 mJ/cm^2 of UVB from a xenon arc solar simulator equipped with a Schott WG 320 filter. Cytotoxicity was assessed in the presence and absence of UVA.

Results: CCX168 did not demonstrate phototoxic potential in this assay at the limit of solubility used in this assay. CCX168 was negative in a Neutral Red Uptake Phototoxicity Assay in BALB/c 3T3 Mouse Fibroblasts. This assay has a high rate of false positive, so the negative assay indicated that there was or no minimal concern for potential phototoxicity.

11 Integrated Summary and Safety Evaluation

Avacopan (CCX168) is a small molecule antagonist of complement component 5a receptor (C5aR), that is being developed as an oral treatment for adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. This review evaluates the nonclinical pharmacology and toxicology program to support the safety of avacopan for marketing approval.

Primary Pharmacology
Specific leukocytes, including neutrophils and monocytes, express C5aR, which mediates chemotaxic activity and activation of these cells by the anaphylotoxin, C5a. Pharmacology studies demonstrated that CCX168 is a antagonist of complement component 5a receptor (C5aR). C5aR amino acid sequence alignment identified a key tryptophan residue located within the 5th transmembrane region (TM-5) for human, cynomolgus monkeys, and hamster, while other species have variable amino acid residues at this location.

In Vitro Pharmacology
In an in vitro competitive ligand binding assay, CCX168 was evaluated for its ability to displace ^{125}I-human C5a from the C5a receptor on human U937 cells. In this assay CCX168 displaced ^{125}I-human C5a from the C5a receptor with an average IC_{50} of 0.45 nM.

Calcium mobilization assays were conducted in human neutrophils and U937 cells. CCX168 was added to the cells and hC5a was added either 25 seconds (neutrophils) or 1-2 minutes later (U937 cells). In the calcium mobilization assay in U937 cells, the A2 value (a 2- shift in the dose-response curve) was 0.1 nM. CCX168 inhibited C5aR-mediated calcium mobilization with an IC_{50} value of 0.2 nM for human neutrophils and 0.4 nM for human monocytes. No calcium mobilization was detected in neutrophils or

monocytes in the time window (1-2 minutes) between the addition of CCX168 and prior to the addition of C5a.

In nonclinical and clinical studies, CCX168-M1, a methyl hydroxylation metabolite, was found to be the major metabolite of CCX168. In clinical studies with ANCA patients CCX168-M1 was found to constitute approximately 30-50% of the total systemic exposure at steady state. In vitro assays demonstrated that the M1 metabolite possessed pharmacologic activity similar to CCX168. Pretreatment with the M1 metabolite (C0335273) was demonstrated to have activity against human C5aR in multiple chemotaxis assays using either the human U937 cell line or human peripheral blood leukocytes (in whole blood) when stimulated with h5Ca, resulting in A2 values of 0.3 nM and 3 nM, respectively. In addition, CCX168-M1 demonstrated inhibition of upregulation of the neutrophil surface CD11b adhesion molecule in response to stimulation with hC5a. Therefore, metabolite CCX168-M1 could contribute to potential systemic pharmacodynamic activity of avacopan.

In chemotaxis assays using peripheral blood leukocytes (human, cynomolgus, hamster, rabbit) or thioglycollate-elicited peritoneal lavage leukocytes, a mixture of neutrophils and macrophages (rat and mouse), pretreatment with CCX168 inhibited C5a-mediated chemotaxis of leukocytes in human, cynomolgus monkey, and hamster whole blood at A2 of 1.7, 18, 14 nM respectively. Similarly, CCX168-M1 inhibited C5a-mediated chemotaxis of leukocytes with comparable activity to CCX168 in human, cynomolgus monkey, and hamster whole blood at A2 values of 3 nM, 2.6 nM, and 10 nM, respectively. Therefore, the cynomolgus monkey and hamster were considered pharmacologically relevant species. Based on the lack of affinity of CCX168 and CCX168-M1 for the rat, mouse, and rabbit C5aRs (A2 > 1,000 nM) these nonclinical species were not considered pharmacologically relevant species.

In Vivo Pharmacology
In a C5a-induced neutropenia challenge study in cynomolgus monkeys, pretreatment with CCX168 reduced hC5a-induced neutropenia. Cynomolgus monkeys were first pretreated with CCX168 at 3 mg/kg or 30 mg/kg. Subsequently the monkeys were administered C5a at doses ranging from 2, 10, or 50 µg/kg to induce neutropenia. In a previous proof of concept neutropenia challenge study, 10 µg/kg hC5a was shown to induce neutropenia challenge adhesion causing neutrophils to adhere to blood vessel walls, thereby reducing the neutrophil concentration in blood. Pretreatment with CCX168 at 3 mg/kg and 30 mg/kg resulted in 50% and 100% inhibition of C5a-induced neutropenia, respectively.

Because of that lack of affinity of CCX168 for the mouse and rat C5a receptor, mice and rats were considered not pharmacologically relevant species for CCX168. Therefore, a human C5a receptor knock in (hC5aR KI) transgenic mouse strain was generated, where the murine C5aR gene was replaced by the human C5aR gene. In an in vitro proof of concept assay, neutrophils from these hC5aR knock-in mice were activated by C5a in a functional assay conducted in whole blood. Pretreatment with CCX168 at 38 nM in blood inhibited this effect by 10-fold (A10 value of 38 nM). In a murine ANCA

disease model, ten-week-old female hC5aR KI mice were injected in the tail vein with 50 mg/kg anti-myeloperoxidase (MPO) antibody, mimicking autoantibodies against neutrophil cytoplasm-expressed proteins, which cause lysis of neutrophils, releasing granule components which kill nearby endothelial cells, thereby activating the alternative complement pathway. In turn, more neutrophils are recruited, and they are primed for respiratory burst. The mice were dosed orally with CCX168 at doses of 0.1, 1 or 37.5 mg/kg once daily or vehicle control once daily, or 5 mg/kg CCX168 twice daily for 7 days. Mice were euthanized on day 7. Blood and urine samples were collected, and the kidneys were harvested and then analyzed for glomerular necrosis and crescent formation. Administration of CCX168 at 5 mg/kg BID and 37.5 mg/kg QD resulted in significant reduction in the incidence of glomerular crescent formation and necrosis, relative to vehicle treated mice. Analysis of blood and urine samples indicated CCX168 treatment resulted in dose-dependent decreases in urinary leukocytes and erythrocytes. Treatment-related reduction in total urinary protein was also noted, although the relationship to the dose was not clear

CCX168 was tested ex vivo for the ability to inhibit C5a-mediated CD11b upregulation of leukocytes using hC5aR KI mice. hC5aR-KI mice were treated with CCX168 at doses from 0.1 up to 5 mg/kg, or vehicle. Blood was collected 1-hour post CCX168 treatment and recombinant hC5a was added to whole blood to stimulate neutrophils. The samples were analyzed by flow cytometry for upregulation of CD11b. A dose response for a CCX168-dependent shift in the EC_{50} of hC5a-mediated CD11b upregulation on neutrophils relative to vehicle treated mice was noted. A CCX168 plasma concentration of 4.75 nM was required to shift the EC_{50} value 2-fold and a plasma concentration of 38 nM was required to shift the EC_{50} value 10-fold. These data were suggestive that treatment with CCX168 reduced the potency of exogenous hC5a to upregulate the adhesion molecule CD11b on blood neutrophils in hC5aR mice.

From the totality of the Sponsor's in vitro and in vivo pharmacology studies, it was concluded that CCX168 and its metabolite, CCX168-M1, were potent antagonists of the human C5a receptor. CCX168 and CCX168-M1 did not appear to have agonist activity at C5aR on neutrophils or monocytes.

Secondary Pharmacology
The off-target selectivity of CCX168 was evaluated at 10 µM against a panel of 55 receptors and membrane associated proteins and the glucocorticoid receptor. CCX168 at 10 µM did not achieve 50% inhibition against any receptors or membrane associated protein in the screening panel. There was greater than 1000-fold selectivity for hC5aR relative to off-target activities identified in this study.

The M1 metabolite was tested for off-target activity at 10 µM against a panel of 17 chemotactic receptors and a panel of 56 unrelated receptors and membrane-associate proteins. The M1 metabolite exhibited weak activity at the human CB1 receptor (53% inhibition), sodium channel (site 2) (65% inhibition), and the GABAA receptor (51% inhibition) at 10 µM.

CCX168 was evaluated in a human glucocorticoid radioligand binding assay using Human Hela 53 cells with 3 nM [^{3}H] Dexamethasone. No significant effects were noted at the screening concentration of 10 µM.

Safety Pharmacology
CCX168 was evaluated in a standard battery of safety pharmacology studies. In vitro, CCX168 did not inhibit hERG channel current in HEK293 cells, stably expressing hERG, at concentrations up to 6.9 µM. CCX168-M1 inhibited hERG channel currents by 38% at 3 µM. CCX168-M1 at concentrations of 10 and 15.8 µM resulted in a similar degree of inhibition. In a cardiovascular safety pharmacology studies in telemetered male cynomolgus monkeys (single oral doses of 0, 5, 15, 50 mg/kg CCX168), systolic, diastolic, and arterial blood pressure values were decreased by approximately 7 - 10% at the 50 mg/kg dose level relative to controls during the time period from 15 mins – 225 mins after dosing. No treatment related effects were observed on QTc interval. In a respiratory safety pharmacology in rats (single oral doses 0, 3.5, 19, 73 mg/kg CCX168), no treatment related effects were observed at any dose tested. No treatment related findings were observed in CNS or renal safety pharmacology studies in rats at doses up to 100 mg/kg. In totality, single high doses of avacopan did not have any significant adverse effects on the cardiovascular, CNS, respiratory, and renal parameters that were evaluated.

Pharmacokinetics
Absorption
Oral bioavailability of CCX168 ranged from 55-104% in SD rats when dosed at 30 and 100 mg/kg.

When SD rats were administered oral doses of CCX168 of 100 or 300 mg/kg once daily (QD), and at 50, 100 or 300 mg/kg twice daily (BID) for 7 days, exposures (AUC0-24) and Cmax of CCX168 and CCX168-M1 were higher at 100 mg/kg than 300 mg/kg QD and BID. These data suggest saturation of exposure occurred at ≥ 100 mg/kg QD or BID.

Distribution
CCX168 and CCX168-M1 were highly protein bound (>99%) in plasma from SD rats, hamsters, cynomolgus monkey, and humans and >96.7% bound in plasma from CD-1 mice, rabbits, and dogs.

Metabolism
CCX168 was extensively metabolized in liver microsomes from human and nonclinical species. There were no metabolites unique to humans. CCX168-M1 was the major metabolite in human, monkey, rabbit, and rat (17.7%, 10.6%, 17.1%, and 20.4%, respectively) in liver microsome incubations. The unchanged parent compound accounted for the largest proportion of all metabolites detected. Characterization of the human metabolic pathways of CCX168 suggested that CYP3A4/5 was the primary isozyme involved in the in vitro metabolism of CCX168 and M1.

Excretion
In cynomolgus monkey, metabolism, rather than direct renal and biliary elimination of the intact drug, was the dominant route of CCX168 elimination. The primary route of elimination of the metabolites was through biliary excretion into feces.

General Toxicology
Several GLP-compliant pivotal repeat-dose toxicology studies were conducted with CCX168 for up to 13-weeks in hamster, 26-weeks in rats, and 44 weeks in monkey. The hamster and monkey were determined to be pharmacologically relevant species. The rat was not a pharmacologically relevant species, although metabolism of CCX168 was similar to that observed in humans. The hamster and monkey could assess on- and off-target toxicity while the rat could only assess off-target toxicity.

In the 13-week oral toxicity study in hamster, animals received 0 (vehicle), 10, 30, 100 and 1000 (500 BID) mg/kg/day CCX168. It is noted that the hamster is a pharmacologically relevant species for CCX168. No CCX168-related adverse findings were identified during the dosing or recovery period. Administration of CCX168 at doses up to 1000 mg/kg/day for 13-weeks was well tolerated. CCX168 exposure was saturated at doses ≥ 100 mg/kg/day. Based upon the observed saturation, the NOAEL was 100 mg/kg/day, the lowest dose where the saturation was first observed and the highest drug exposure was achieved. Exposure values for CCX168 at the 100 mg/kg/day were Cmax = 4,410 ng/mL, and AUC0-24 = 39,900 ng*hr/mL for combined sexes on day 91 of dose administration.

In the pivotal 6-month chronic oral toxicity study in rats, animals received 0 (vehicle), 5, 15, 100 and 200 (100 mg/kg BID) mg/kg/day CCX168. There were no treatment-related toxicities at any of the doses tested. It is noted that the rat is not a pharmacologically relevant species for CCX168. CCX168 exposure was saturated at doses ≥ 100 mg/kg/day. Based upon the observed saturation, the NOAEL was 100 mg/kg/day, the lowest dose where the saturation was first observed and the highest drug exposure was achieved.

In the pivotal 44-week chronic toxicity study in monkeys, monkeys received either 0 (vehicle control article), 5, 15 mg/kg QD, or 30 (15 BID) mg/kg/day of CCX168 over the first 25 weeks of the study (Groups 1-5). At the beginning of the study, CCX168 and the vehicle were administered by nasogastric intubation (Weeks 1-5). Starting at Week 6, the route of administration was switched to oral gavage (Weeks 6-44). After week 25, to increase CCX168 exposure, the doses were increased to 0 (vehicle control article), 7.25, 22.5 mg/kg QD, or 22.5 mg/kg BID (45 mg/kg/day) of CCX168 for Groups 1-5, respectively, from Weeks 26-44. No CCX168-related mortalities occurred during the treatment or recovery period. No CCX168 treatment related findings were observed. The NOAEL was considered as the high dose (30 mg/kg/day (Weeks 1- 25) and 45 mg/kg/day (Weeks 26-44)).

Genetic Toxicology
Avacopan was negative for genotoxicity in a standard battery of genetic toxicology

tests (in vitro Ames bacterial reverse mutation test, in vitro mouse lymphoma assay, and in vivo rat micronucleus assay). Metabolite CCX168-M1 was judged negative for mutagenicity in the Ames test for bacterial gene mutation based on confirmation that CCX168-M1 was formed upon incubation of CCX168 with S9.

Carcinogenicity
No treatment-related tumors were identified in 2-year oral studies with SD rats and hamsters that were conducted to assess the carcinogenic potential of CCX168.

Reproductive and Developmental Toxicology
Fertility and Early Embryonic Development
In a hamster fertility study, male and female hamsters were treated before being paired for mating (28 days for males and 15 days for females), throughout mating, and once daily up through gestation day 12 in females and up to dosing day 50 to 53 in males with oral doses of 0, 10, 30, and 100 mg/kg once daily (QD) or 0 and 500 mg/kg BID (0 and 1000 mg/kg/day, respectively). Treatment with CCX168 was well-tolerated in male and female hamsters. There were no deaths in the test article-treated groups. CCX168 did not affect fertility or reproductive performance (mating and fertility indices) in male or female rats. The paternal and maternal NOAELs for general and reproductive toxicity of CCX168 was 1000 mg/kg/day.

Embryo-Fetal Development
In a hamster EFD study, time-mated female hamsters were treated with oral doses of 0 (vehicle), 10, 30, and 100 mg/kg/day and 0 and 500 mg/kg BID (0 and 1000 mg/kg/day) CCX168 administered during the period of organogenesis from GD 6-12. There were no treatment-related effects on maternal performance or on maternal body weight gains. No treatment-related fetal malformations were noted, however, an increase in a skeletal variation described as supernumerary ribs was noted in all litters (40 fetuses) in the 1000 mg/kg/day group. This finding is considered a developmental delay and supernumerary ribs can resolve into the vertebral arch later in development. Toxicokinetic analysis identified saturation of exposure occurred at ≥ 100 mg/kg/day. The NOAEL for maternal and developmental toxicity was 1000 mg/kg/day.

In a rabbit EFD study, time-mated female rabbits were treated with oral doses of 0 (vehicle), 10, 30, and 200 mg/kg/day CCX168 administered during the period of organogenesis from GD 6-18 and were sacrificed on GD 29. An increase in the number of abortions was noted in the 200 mg/kg/day group. Decreases in body weight gain were seen in the 30 and 200 mg/kg/day groups. No treatment-related changes in cesarean section parameters or fetal malformations or variations were identified. Toxicokinetic analysis identified saturation of exposure occurred at ≥ 30 mg/kg/day. The NOAEL for maternal toxicity was the low dose of 10 mg/kg/day and the NOAEL for developmental toxicity was the high dose of 200 mg/kg/day.

Prenatal and Postnatal Development
In a hamster PPND study, mated female hamsters (F0 generation) were treated with oral doses of 0 (vehicle), 10, 30, and 100 mg/kg/day and 0 and 500 mg/kg BID CCX168

from GD 6 to LD 20. F0 dams showed no treatment related effects on reproductive or uterine parameters. There were no treatment related effects on the gestation length, the number of implantation sites, the number of live births, or on viability of F1 offspring. CCX168 and CCX168-M1 were present in the plasma of nursing F1 pups on LD 15. No treatment related effects on body weights of F1 offspring from birth to weaning (LD 1 to LD 21) were seen. There was no effect of CCX168-treatment of the F0 mothers on the postweaning growth, physical, and neurological development of F1 offspring as assessed by measurements of body weight gain, achievements of developmental milestones, motor evaluation, and performance in a passive avoidance test. There was no effect of CCX168-treatment of the F0 mothers on fertility in the F1 offspring. There was no effect of CCX168-treatment in the F0 mothers on numbers of corpora lutea, implantations, pre-and post-implantation losses, and viable embryos in pregnant F1 females. The NOAEL for F0 maternal toxicity and for F1 pup development was the high dose of 500 mg/kg BID (1000 mg/kg/day).

Phototoxicity
While CCX168 absorbed UV light at 290 nm with a molar extinction coefficient of 2989 L mol^{-1} cm^{-1}. CCX168 was negative in a Neutral Red Uptake Phototoxicity Assay in BALB/c 3T3 Mouse Fibroblasts. This assay has a high rate of false positive, so the negative assay indicated that there was minimal concern for potential phototoxicity.

Table 46: Summary of Plasma AUC for Avacopan (CCX168) and Major Metabolite (CCX168-M1) at Dose Level of 30 mg BID in Human Clinical Subjects at Week 52 Based on Phase 3 Study CL010_168

Avacopan (30 mg BID) Exposure at Week 52 in ANCA patients	AUC0-12 (ng*hr/mL)	AUC0-24 (2X AUC0-12) (ng*hr/mL)
Avacopan (CCX168)	3466	6932
Major Metabolite (CCX168-M1)	1283	2566

Table 47: Animal to Human Exposure Margins for Avacopan (CCX168) and Major Metabolite (CCX168-M1) Based on AUC for the Proposed Clinical Dose of 30 mg BID for pivotal toxicology and reproductive toxicology studies

Pivotal Toxicology Studies with CCX168				Nonclinical $AUC_{0\text{-}24}$ ng*hr/mL	Animal to Human Exposure Margin (Clinical Daily dose 30 mg BID) [a,b]
Study No.	NOAEL (mg/kg/day)	ROA	CCX168 or M1		
13-Week Hamster (PC0677_168)	100	Oral	CCX168	39,900	5.8
			M1	2480	0.97
26-Week rat	100	Oral	CCX168	73,150	10.5

(PC0655_168)			M1	2,460	0.96
44-Week Monkey (PC0654_168)	45	Oral	CCX168	29,300	4.2
			M1	9590	3.7

Reproductive and Developmental Toxicity Studies with CCX168				Nonclinical AUC ng*hr/mL	Animal to Human Exposure Margin (Clinical Daily dose 30 mg BID) [a,b]
Study No.	**NOAEL (mg/kg/day)**	**ROA**	**CCX168 or M1**		
FEED hamster (PC0670-168)	Maternal and Paternal 1000 (HD)	Oral	CCX168	47,339	6.8
			M1	7,795	3.0
EFD hamster (PC0671_168)	Maternal and Developmental 1000 (HD)	Oral	CCX168	36,400	5.3
			M1	1,680	0.7
EFD rabbit (PC0672_168)	Maternal: 10 (LD)	Oral	CCX168	2350	0.34
			M1	364	0.14
	Developmental: 200 (HD)	Oral	CCX168	4180	0.60
			M1	780	0.3
PPND hamster (PC0673_168)	Maternal and Developmental 1000 (HD)	Oral	CCX168	30,900	4.5
			M1	3,260	1.3

[a] Steady state human CCX681 AUC_{0-24}: 6932 ng*hr/mL
[b] Steady state human CCX681-M1 AUC_{0-24}: 2566 ng*hr/mL

Table 48: Exposure Margins for Clinical Dose of 30 mg BID CCX168 and CCX168-M1 based on the 2-Year Carcinogenicity Study in Rats and Hamsters

2-Year Carcinogenicity Study in Rats	CCX168 (mg/kg/day)	CCX168		CCX168-M1	
		AUC_{0-24} (ng*hr/mL)	**Exposure Margin**	**AUC_{0-24} (ng*hr/mL)**	**Exposure Margin**
Males	10	11,500	1.66	445	0.17
	30	25,600	3.7	1140	0.44
	100	17,400	2.51	1440	0.56

Females	10	13,600	1.96	3670	1.43
	30	33,400	4.8	1830	0.71
	100	21,400	3.09	1970	0.77
2-Year Carcinogenicity Study in Hamster	**CCX168 (mg/kg/day)**	**CCX168**		**CCX168-M1**	
		AUC_{0-24} (ng*hr/mL)	**Exposure Margin**	**AUC_{0-24} (ng*hr/mL)**	**Exposure Margin**
Males	10	5,560	0.8	363	0.1
	30	21,600	3.1	1,550	0.6
	100	42,000	6.1	2,850	1.1
Females	10	4,290	0.6	282	0.1
	30	24,500	3.5	1,750	0.7
	100	35,600	5.1	2,500	1.0

Recommendation: From the nonclinical perspective, the application is recommended for approval. An evaluation of the product labeling will be conducted in a separate review. There are no outstanding issues. No further nonclinical studies are required.

12 Appendix/Attachments

12.1 The Appendices are listed below. The Appendix was loaded into DARRTS as a separate document.

Appendix	Application	Reviewer	Date in DARRTS	Notes
1	IND 120784	Dr. Matthew Whittaker	7-15-2014	30 Day Safety Review 13-week rat and 20-week monkey study review
2	IND 120784	Dr. Matthew Whittaker	11-09-2017	Review of 6-month toxicology study with rats and genetic toxicology studies
3	IND 120784	Dr. Dong Zhao	11-14-2017	Review of 13-week hamster toxicology study
4	IND 120784	Dr. Karen Davis-Bruno	11-09-2017	ECAC meeting minutes

5	IND 120784	Dr. Matthew Whittaker	08-22-2019 (Comments were conveyed on 08-13-2019)	Early termination criteria for 104-week carcinogenicity study with rats
6	NDA 214487	Dr. Karen Davis-Bruno	2-25-2021	ECAC meeting minutes
7	IND 120784	Dr. Timothy W. Robison	3-1-2021	Pharmacology and TK/ADME

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

IJEOMA K UZOMA
03/08/2021 09:39:59 AM

TIMOTHY W ROBISON
03/08/2021 09:50:11 AM
I concur

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	NDA 214487
Drug Name:	(b) (4) (CCX168)
Indication(s):	Treatment of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis.
Studies	Two Year Oral Gavage Carcinogenicity Study in Rats and Hamster.
Applicant:	Sponsor: Chemocentryx Inc 850 Maude Ave, Mountain View, California 94043, USA. Test facility for rat study: (b) (4)
Documents Reviewed:	Electronic submission, dated: December 2, 2020 via SN0016 Electronic data submitted on December 2, 2020 via SN0016
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -VI
Statistical Reviewer:	Malick Mbodj, Ph.D.
Secondary Reviewer:	Hepei Chen
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Pharmacology-Toxicology for Immunology & Inflammation
Reviewing Pharmacologist:	Ijeoma K. Uzoma, PhD
Project Manager:	Susie B. Choi PharmD
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in hamsters. These studies were intended to assess the carcinogenic potential of CCX168 in rats and hamsters when administered orally by gavage at appropriate drug levels for about 104 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Uzoma.

In this review, the phrase "dose response relationship" (trend) refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Rat Study

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups, one water control group and one vehicle control group. Two hundred and eighty five Sprague Dawley rats of each sex were assigned to three treated groups, one water control group and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 57 animals, as indicated in Table 1. The dose levels for treated groups were 10, 30, and 100 mg/kg/day for both males and females. In this review, these dose groups were referred to as the low, intermediate (medium), and high dose group, respectively. The vehicle control group was exposed to Vehicle Item only (polyethylene glycol (b) (4) [(b) (4) v:v]) administered orally by gavage for about 104 weeks in the same manner as the treated groups. water control group was exposed to Purified water. Due to early termination threshold of 20 surviving rats in the control groups, early final scheduled necropsies were conducted (based on FDA recommendations) to 97 weeks for males and 92 weeks for females of the dosing phase.

Table 1: Experimental Design in Rat Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Control I (vehicle)	1	0	0	57	57
Control II (water)	2	0	0	57	57
Low	3	10	10	57	57
Intermediate (medium)	4	30	30	57	57
High	5	100	100	57	57

Early final scheduled necropsies were conducted to 97 weeks for males and 92 weeks for females

During the study period all animals were observed for general health/mortality and moribundity twice daily (at the beginning and end of each working day.), abnormal findings were recorded throughout the study. Cage side observations were conducted for each carcinogenicity animal once daily during the dosing phase, except on days when detailed observations were conducted. Detailed observations were conducted for each carcinogenicity animal at least once prior to dosing on Day 1, and weekly thereafter throughout the dosing phase. Detailed examinations for palpable masses were done weekly, the time of onset, location, size, appearance, and progression of each grossly visible or palpable mass, observed in carcinogenicity rats, was recorded weekly, particular attention being paid to the animals during and for the four hours after dosing. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively will be euthanized. Observations will include, but will not be limited to, evaluation for reaction to treatment. Histopathological examinations were performed on all animals found dead or killed moribund or sacrificed at the end of the experiment. Body

weights were recorded once during the predose phase, before dosing on Day 1 of the dosing phase, weekly thereafter to Week 16, once every 4 weeks thereafter during the dosing phase, and for each carcinogenic animal of that sex/group during the week of sacrifice.

2.1. Sponsor's analyses

2.1.1. Survival analysis

In the sponsor's analysis, the tests for survival comparisons were performed with a two-sided risk for increasing and decreasing mortality with dose. Tests were performed for dose response (vehicle control and dosed groups only), and for each dosed group against vehicle control group using Kaplan-Meier product-limit estimates, along with log-rank and Wilcoxon tests. These were performed using the LIFETEST procedure in SAS. The time to death or sacrifice (in weeks) was the dependent variable. Treatment group was included as the strata

Any animal with accidental injury that causes its death, or its unscheduled sacrifice was censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day. Results of all pair-wise comparisons are reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

Sponsor's findings:

Sponsor's analysis showed the numbers of rats surviving to their terminal necropsy were 26, 20, 21, 21, and 27 in the vehicle control, water control group, low, intermediate, and high dose groups, in male rats, respectively, and 20, 29, 28, 26, and 26 in vehicle control, water control group, low, intermediate, and high dose groups, in female rats, respectively. The sponsor's report concluded that there was no statistically significant difference in mortality across the vehicle control group and the treated groups in either sex of rats. The pairwise comparisons showed no statistically significant increase or decrease in mortality between the treated groups, and the vehicle control group in either sex of rats.

2.1.2. Tumor data analysis

In the sponsor's analysis, tests to compare tumor incidence were performed, with a one-sided risk for increasing incidence with dose. Tests were performed for dose response (vehicle control and dosed groups only) and for each dosed group against the vehicle control group. Occult or non-palpable tumors were analyzed by the IARC asymptotic fixed interval-based prevalence test (Peto et al., 1980). For males, the cutoff points for the interval-based test were Weeks 0 to 52, 53 to 78, 79 to 92, 93 to before terminal sacrifice, and the terminal sacrifice. For females, the cutoff points were Weeks 0 to 52, 53 to 78, 79 to before terminal sacrifice, and the terminal sacrifice. Actual dose levels were used as the scores. Fatal and non-fatal tumors were analyzed together, with separate stratum for each. Tumors of uncertain context were included in the analysis as non-fatal. The test was implemented using PROC MULTTEST in the SAS system (SAS, 2008). In the case of sparse tables (<10 total tumor bearing animals in the groups analyzed for the trend or pairwise test), the exact form of the test was used. Otherwise, the asymptotic version of the test was used. Observable or palpable (superficial as in mammary or skin) tumors were analyzed using the methods previously described for analyzing survival, using the time to death or time of detection of the tumor (in weeks) as a surrogate for the tumor onset time. For each given tumor type, statistical analysis was performed if the incidence in at least one dosed group was increased by at least two occurrences over the vehicle control group.

Site or tumor combinations were statistically analyzed if the incidence in at least one dosed group was increased by at least two occurrences over the vehicle control group. Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded in the data and were not assigned based on the day/week of necropsy.

Adjustment for the multiplicity:

Unadjusted P-values were assessed based on rare or common tumor type, in line with the current FDA guidelines (Food and Drug Administration Draft Guidance for Industry, 2001). The incidence rate for defining whether a tumor type is rare or common is based on site-specific background historical data. The Study Pathologist determined whether a tumor type was rare or common.

Sponsor's findings:

The sponsor's analysis showed at 5% level a statistically significant dose response relationship in benign dermal fibroma in skin/subcutis of male (p-value =0.0424 using Log-Rank test), the combined benign-tumor, basal cell, benign and malignant tumor, basal cell, malignant in skin/subcutis of female (p-value =0.0139 using Log-Rank test and = 0.0150 using Wisconxon test). However, following the multiple testing adjustment method described above, these p-values were not considered to be statistically significant since these tumors were considered as common. Also, the pairwise comparisons showed in the skin/subcutis of male rats , a statistically significant increases at 5% level, for the incidences of malignant fibrosarcoma in the low dose group (p-value =0.0390 using Log-Rank test and = 0.0352 using Wisconxon test) and the combined benign tumor, hair follicle, benign and malignant Tumor, basal cell, malignant in the intermediate dose group (p-value = 0.0150 using Wisconxon test), when compare to the vehicle control group. However, since these tumors were considered as common then, these p-values were not considered to be statistically significant following the multiple testing adjustment method described above

Following the multiple testing adjustment method described in the FDA draft guidance for industry, 2001, the sponsor's analysis concluded that there were no tumor types with a statistically significant dose response relationship in tumor incidences with increased CCX168 dose. The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in CCX168 treated groups, when compare to the vehicle control group in either male or female rats.

2.2 Reviewer's analyses

To verify sponsor's analysis and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed the survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on December 2, 2020 via SN0016.

2.2.1 Survival analysis

In the reviewer's analysis, intercurrent mortality data were analyzed using the Kaplan-Meier product limit method. The Kaplan-Meier's curves were presented graphically for male and female rats separately. The dose response relationship and homogeneity of survival distributions were tested for the treatment groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the

appendix for male and female rats, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 26, 20, 21, 21, and 27 in the vehicle control, water control group, low, intermediate (medium), and high dose groups, in male rats, respectively, and 20, 29, 28, 26, and 26 in vehicle control, water control group, low, intermediate(medium), and high dose groups, in female rats, respectively. This reviewer's analysis showed no statistically significant increase or decrease in mortality across the vehicle control group and the three treated groups in either sex of rats. The pairwise comparisons showed no statistically significant increase or decrease in mortality between the treated groups, and the vehicle control group in either sex of rats.

2.2.2. Tumor data analysis

In the reviewer's analysis, the tumor data were analyzed for dose response relationship across vehicle control group and the treated groups, as well as the pairwise comparisons of vehicle control group with each of the treated groups using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method, an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice with development of the tumor type being tested gets a score of s_h =1. An animal that dies at Week w_h without development of the given tumor type before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}} \right)^k$ <1. The adjusted group size is defined as Σs_h . As an interpretation, an animal with score s_h =1 can be considered as a whole animal, while an animal with score s_h <1 can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal develops the given tumor being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise comparison) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104-week standard rat and mouse studies, a value of k=3 is suggested in the literature [Gebregziabher and Hoel (2009), Moon et al. (2003), Portier, et al. (1986)]. Hence, this reviewer used k=3 for the analysis of the data. Based on the intent to treat (ITT) principle Wmax was considered as 105 for both male and female rats.

For the calculation of p-values, if there were less than 10 tumor bearing animals across all treatment groups for a given tumor type, the exact tests based on the discrete permutation distribution were used, with dose levels (0, 0, 10, 30, and 100 for both male and female rats) as scores, and asymptotic tests were used for tumor types with higher incidences. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male rats and female rats, respectively.

Multiple testing adjustments:

Following the FDA draft guidance for the carcinogenicity study design and data analysis (2001), for the two-year rat study this reviewer used significance levels of 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

A tumor is defined as a rare tumor if the published spontaneous rate or the spontaneous rate of the vehicle control of the tumor is less than 1%, and a common tumor is defined as one with tumor rate greater than or equal to 1%.

Reviewer's findings:

Table 2: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons **Treated Groups and Control Group in Rats**

Sex	Organ Name	Tumor Name	0 mg Veh. Cont (N=57) P - Trend	0 mg Water (N=57) P - VC vs. W	10 mg Low (N=57) P - VC vs. L	30 mg Med(N=57) P - VC vs. M	100 mg High (N=57) P - VC vs. H
Male	Adrenal	B-Adenoma, cortex	0/57 (35) 0.0404@	1/57 (34) 0.4928	1/57 (33) 0.4853	0/57 (36) NC	3/57 (38) 0.1356
	Pituitary	B-Adenoma, Pars Distalis/ M-Carcinoma, Pars Distalis	17/56 (40) 0.3853	28/57 (43) 0.0322@	14/57 (36) 0.7097	23/57 (43) 0.2174	19/57 (42) 0.4893

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
@: not Statistically significant at 0.025 for rare tumor in dose response relationship.

Following the multiple testing adjustment method described above, this reviewer's analysis showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased CCX168dose. The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in CCX168 treated groups, when compare to the vehicle control group in either male or female rats.

3. Hamster Study

Two separate experiments were conducted, one in male hamsters and one in female hamsters. In each of these two experiments three treated groups, one water control group and one vehicle control group. Three hundred and twenty five HsdHan: AURA (Syrian Golden) hamsters of each sex were assigned to three treated groups, one water control group and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 65 animals, as indicated in Table 3. The dose levels for treated groups were 10, 30, and 100 mg/kg/day for both males and females. In this review, these dose groups were referred to as the low, intermediate (medium), and high dose group, respectively. The vehicle control group was exposed to Vehicle Item only (polyethylene glycol (b) (4) [(b) (4) v:v]) administered orally by gavage for about 104 weeks in the same manner as the treated groups. water control group was exposed to Purified water. Due to early termination threshold of 20 surviving hamsters in the control groups, early final scheduled necropsies were conducted (based on FDA recommendations). Females were terminated during or after Week 92 due to mortality in the water control group and males were terminated during or after Week 98 due to mortality in the vehicle control group.

Table 3: Experimental Design in Hamster Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Control I (vehicle)	1	0	0	65	65
Control II (water)	2	0	0	65	65
Low	3	10	10	65	65
Intermediate (Medium)	4	30	30	65	65
High	5	100	100	65	65

Early final scheduled necropsies were conducted during or after Week 98 for males and during or after Week 92 for females

Animals were checked twice daily (a.m. and p.m.) for mortality, abnormalities, and signs of pain or distress., abnormal findings were recorded throughout the study. Cage side observations were conducted for each carcinogenicity animal once daily Days 1 through 7 of the dosing phase. Detailed observations were conducted for each carcinogenicity animal at least once during the pre-dose phase, prior to dosing on Day 1, and weekly thereafter throughout the dosing phase. Observations will include, but will not be limited to, evaluation for reaction to treatment. The time of onset, location, size, appearance, and progression of each grossly visible or palpable mass, observed in carcinogenicity hamsters, was recorded at the same intervals as detailed observations, particular attention being paid to the animals during and for the first hour after dosing. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively will be euthanized. Histopathological examinations were performed on all animals found dead, killed moribund, or sacrificed at the end of the experiment. Body weights were recorded once during the pre-dose phase, before dosing on Day 1, weekly thereafter (based on Day 1) to Week 16 during the dosing phase, and every 4 weeks thereafter.

3.1. Sponsor's analyses

3.1.1 Survival analysis

The sponsor used similar methodologies to analyze the hamster survival data as those used to analyze the rat survival data.

Sponsor’s findings:

Sponsor’s analysis showed the numbers of hamsters surviving to their terminal necropsy were 20, 41, 26, 26, and 26, in vehicle control, water control, low, intermediate (medium), and high dose groups in male hamsters, respectively, and 22, 20, 26, 18, and 20, in female hamsters, respectively. The sponsor’s report concluded that there was no statistically significant difference in mortality across the vehicle control group and the treated groups in either sex of hamsters. The pairwise comparisons showed no statistically significant increase or decrease in mortality between the treated groups, and the vehicle control group in either sex of hamsters.

For males, the vehicle control group had a higher mortality than the water control group, with P = 0.0002 and P = 0.0002 for the Log-Rank and Wilcoxon tests, respectively.

3.1.2 Tumor data analysis

The sponsor used similar methodologies to analyze the hamster tumor data as those used to analyze the rat tumor data.

The analysis of tumors was based on the following fixed time intervals: Weeks 0 to 52, 53 to 78, 79 to 92, 93 to before the terminal sacrifice, and the terminal sacrifice for males and Weeks 0 to 52, 53 to 78, 79 to before the terminal sacrifice, and the terminal sacrifice for females.

Multiple testing adjustment:

For multiplicity adjustment testing, the sponsor used similar test levels of significance as those used for rat study to adjust for multiple testing.

Sponsor's findings:

following the multiple testing adjustment method described above, the sponsor analysis showed statistically significant increasing dose response relationships across the vehicle control and the treated groups, for the incidence of malignant pleomorphic lymphoma (P=0.0158) in females since this tumor type was consider as rare; however, the incidence of this tumor was similar or higher in water control females compared with CCX168-treated animals so this was thought to be a chance event and not attributable to the test article.

Statistically significant differences noted in water controls compared with vehicle controls for adrenal cortical adenomas in males (P=0.0054) and parathyroid adenomas in females (P=0.0427) were also thought to be chance events.

3.2 Reviewer's analyses

Similar to the rat study, this reviewer independently performed the survival and tumor data analyses of the mouse study. For the analysis of the survival data and the tumor data of the mouse study, this reviewer used similar methodologies that were used for the analyses of the survival and tumor data of the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1 Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for male and female hamsters, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for male and female hamsters, respectively. Results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 5A and 5B in the appendix for male and female hamsters, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of hamsters surviving to their terminal necropsy were 20, 41, 26, 26, and 26, in vehicle control, water control, low, intermediate (medium), and high dose groups in male hamsters, respectively, and 22, 20, 26, 18, and 20, in female hamsters, respectively. This reviewer's analysis showed no statistically significant increase or decrease in mortality across the vehicle control group and the three treated groups in either sex of hamsters. The pairwise comparisons showed no statistically significant increase or decrease in mortality between the treated groups, and the vehicle control group in either sex of hamsters.

Also, this reviewer's analysis showed a statistically significant decrease in mortality in the water control group, when compared the vehicle control group in male Hamster (p=0.0002)

3.2.2 Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and the pairwise comparisons of vehicle control and treated groups are given in Table 6A and 6B in the appendix for male and female hamsters, respectively.

Multiple testing adjustment:

For multiplicity adjustment testing, this reviewer used similar test levels of significance as those used for

rat study to adjust for multiple testing, (FDA 2001 draft guidance for the carcinogenicity study design and data analysis).

Reviewer's findings:

Table 4: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons **Treated Groups and Control Group in Hamster.**

Sex	Organ Name	Tumor Name	0 mg Veh. Cont (N=65) P - Trend	0 mg Water (N=65) P - VC vs. W	10 mg Low (N=65) P - VC vs. L	30 mg Med(N=65) P - VC vs. M	100 mg High (N=65) P - VC vs. H
Male	Adrenal	B-Cortical Adenoma	5/65 (37) 0.5392	21/65 (51) 0.0042*	13/65 (41) 0.0498@	7/65 (40) 0.4350	8/65 (39) 0.3079
	Stomach	B-Squamous Cell Papilloma	0/65 (35) 0.0164*	3/64 (46) 0.1779	1/65 (36) 0.5070	1/65 (39) 0.5270	4/65 (38) 0.0678
Female	Adrenal	B-Benign Pheochromocytoma	3/65 (35) 0.0227@	3/65 (33) 0.6347	0/65 (34) 1.0000	2/65 (33) 0.8031	6/65 (35) 0.2386
	Hemolympho-Reticular System	M-Malignant Lymphoma-Pleomorphic	0/65 (34) 0.0172*	3/65 (33) 0.1139	0/65 (34) NC	1/65 (33) 0.4925	3/65 (33) 0.1139
	Parathyroid	B-Adenoma	9/62 (35) 0.4391	18/59 (37) 0.0382@	16/62 (38) 0.1096	17/61 (38) 0.0729	12/60 (34) 0.2735
	Uterus	B-Adenoma	1/65 (34) 0.0406@	0/65 (31) 1.0000	1/65 (34) 0.7537	1/65 (33) 0.7463	4/65 (33) 0.1686
	Vagina	B-Squamous Cell Papilloma	0/65 (34) 0.0610	2/65 (32) 0.2312	3/65 (34) 0.1194	2/65 (33) 0.2388	4/65 (32) 0.0499*
		B-Squamous Cell Papilloma/ M-Squamous Cell Carcinoma	0/65 (34) 0.0972	2/65 (32) 0.2312	4/65 (35) 0.0606	2/65 (33) 0.2388	4/65 (32) 0.0499*

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
*: Statistically significant at 0.005 and 0.025 level for common and rare tumor or 0.01 and 0.05 level for common and rare tumors for tests of dose response relationship and pairwise comparison, respectively.
@: not Statistically significant at 0.005 and 0.025 level for common and rare tumor or 0.01 and 0.05 level for common and rare tumors for tests of dose response relationship and pairwise comparison, respectively

Following the multiple testing adjustment method described above, this reviewer's analyses showed a statistically significant increasing dose response relationships across the vehicle control and the treated groups for the incidence of benign squamous cell papilloma in the stomach, in male hamsters and the incidence of malignant lymphoma-Pleomorphic in the hemolymphoreticular system, in female hamsters (p-values = 0.0164, and =0.0172, respectively). The pairwise comparisons showed statistically significant increases in the high dose group for the incidences of benign squamous cell papilloma and the combined benign squamous cell papilloma and malignant Squamous Cell Carcinoma, in the vagina in female hamsters (p-values = 0.0499, and =0.0499, respectively).

Also, this reviewer's analyses showed Statistically significant in water controls group for the incidences of adrenal cortical adenomas, when compared to the vehicle control group in male hamsters (P=0.0042)

4. Summary

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in hamster. These studies were intended to assess the carcinogenic potential of CCX168 in rats and

hamsters when administered orally by gavage at appropriate drug levels for about 104 weeks.

Rat Study:

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups, one water control group and one vehicle control group. Two hundred and eighty five Sprague Dawley rats of each sex were assigned to three treated groups, one water control group and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 57 animals, as indicated in Table 1. The dose levels for treated groups were 10, 30, and 100 mg/kg/day for both males and females. In this review, these dose groups were referred to as the low, intermediate (medium), and high dose group, respectively. The vehicle control group was exposed to Vehicle Item only (polyethylene glycol (b) (4) [(b) (4) v:v]) administered orally by gavage for about 104 weeks in the same manner as the treated groups. water control group was exposed to Purified water. Due to early termination threshold of 20 surviving rats in the control groups, early final scheduled necropsies were conducted (based on FDA recommendations) to 97 weeks for males and 92 weeks for females of the dosing phase.

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 26, 20, 21, 21, and 27 in the vehicle control, water control group, low, intermediate (medium), and high dose groups, in male rats, respectively, and 20, 29, 28, 26, and 26 in vehicle control, water control group, low, intermediate (medium), and high dose groups, in female rats, respectively. This reviewer's analysis showed no statistically significant increase or decrease in mortality across the vehicle control group and the three treated groups in either sex of rats. The pairwise comparisons showed no statistically significant increase or decrease in mortality between the treated groups, and the vehicle control group in either sex of rats.

For tumor data, this reviewer's analysis showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased CCX168dose. The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in CCX168 treated groups, when compare to the vehicle control group in either male or female rats.

Hamster Study:

Two separate experiments were conducted, one in male hamsters and one in female hamsters. In each of these two experiments three treated groups, one water control group and one vehicle control group. Three hundred and twenty five HsdHan: AURA (Syrian Golden) hamsters of each sex were assigned to three treated groups, one water control group and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 65 animals, as indicated in Table 3. The dose levels for treated groups were 10, 30, and 100 mg/kg/day for both males and females. In this review, these dose groups were referred to as the low, intermediate (medium), and high dose group, respectively. The vehicle control group was exposed to Vehicle Item only (polyethylene glycol (b) (4) (b) (4) [(b) (4) v:v]) administered orally by gavage for about 104 weeks in the same manner as the treated groups. water control group was exposed to Purified water. Due to early termination threshold of 20 surviving hamsters in the control groups, early final scheduled necropsies were conducted (based on FDA recommendations). Females were terminated during or after Week 92 due to mortality in the water control group and males were terminated during or after Week 98 due to mortality in the vehicle control group.

This reviewer's analysis showed the numbers of hamsters surviving to their terminal necropsy were 20, 41, 26, 26, and 26, in vehicle control, water control, low, intermediate (medium),, and high dose groups in male hamsters, respectively, and 22, 20, 26, 18, and 20, in female hamsters, respectively. This reviewer's analysis

showed no statistically significant increase or decrease in mortality across the vehicle control group and the three treated groups in either sex of hamsters. The pairwise comparisons showed no statistically significant increase or decrease in mortality between the treated groups, and the vehicle control group in either sex of hamsters.

Also, this reviewer's analysis showed a statistically significant decrease in mortality in the water control group when compared the vehicle control group in male Hamster (p=0.0002)

For tumor data, following the multiple testing adjustment method described above, this reviewer's analyses showed a statistically significant increasing dose response relationships across the vehicle control and the treated groups for the incidence of benign squamous cell papilloma in the stomach, in male hamsters and the incidence of malignant lymphoma-Pleomorphic in the hemolymphoreticular system, in female hamsters (p-values = 0.0164, and =0.0172, respectively). The pairwise comparisons showed statistically significant increases in the high dose group for the incidences of benign squamous cell papilloma and the combined benign squamous cell papilloma and malignant Squamous Cell Carcinoma, in the vagina in female hamsters (p-values = 0.0499, and =0.0499, respectively).

Also, this reviewer's analyses showed Statistically significant in water controls group for the incidences of adrenal cortical adenomas, when compared to the vehicle control group in male hamsters (P=0.0042)

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Mathematical Statistician

Concur: Karl Lin, Ph.D. Team Leader, DBVI
Hepei Chen, secondary reviewer
cc:
Archival NDA 214487- CCX168
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5. Appendix

Table1A: Intercurrent Mortality Rate

Male Rats

	0mg|kg|day Veh. Cont		0mg|kg|day Water Cont.		10 mg|kg|day Low		30 mg|kg|day Med		100 mg|kg|day High	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	3	5.26	1	1.75	5	8.77	1	1.75	2	3.51
53 - 78	11	24.56	15	28.07	11	28.07	10	19.30	5	12.28
79 - 92	12	45.61	15	54.39	9	43.86	18	50.88	11	31.58
93 - 98	4	52.63	5	63.16	8	57.89	6	61.40	9	47.37
ADD	1	54.39	1	64.91	3	63.16	1	63.16	3	52.63
Ter. Sac.	26	45.61	20	35.09	21	36.84	21	36.84	27	47.37
Total	57	100.00	57	100.00	57	100.00	57	100.00	57	100.00

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded
ADD: accidental death

Table1B: Intercurrent Mortality Rate

Female Rats

	0mg|kg|day Veh. Cont		0mg|kg|day Water Cont.		10 mg|kg|day Low		30 mg|kg|day Med		100 mg|kg|day High	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	5	8.77	1	1.75	2	3.51	2	3.51	3	5.26
53 - 78	11	28.07	14	26.32	16	31.58	11	22.81	16	33.33
79 - 93	17	57.89	13	49.12	9	47.37	16	50.88	10	50.88
ADD	4	64.91	.	.	2	47.37	2	50.88	2	50.88
Ter. Sac.	20	35.09	29	50.88	28	49.12	26	45.61	26	45.61
Total	57	100.00	57	100.00	57	100.00	57	100.00	57	100.00

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded

Table 2A: Intercurrent Mortality Comparison for
Male Rats

Test Statistics	**P-value for Vehicle Cont. Low, Med, high**	**P-value for Vehicle Cont. vs Water**	**P-value for Vehicle Cont. vs Low**	**P-value for Vehicle Cont. vs Med**	**P-value for Vehicle Cont. vs High**
Dose-Response (Likelihood Ratio)	0.2080	0.3294	0.4890	0.6045	0.4564
Homogeneity (Log-Rank)	0.4453	0.3238	0.4843	0.5997	0.4513

Table 2B: Intercurrent Mortality Comparison for
Female Rats

Test Statistics	**P-value for Vehicle Cont. Low, Med, high**	**P-value for Vehicle Cont. vs Water**	**P-value for Vehicle Cont. vs Low**	**P-value for Vehicle Cont. vs Med**	**P-value for Vehicle Cont. vs High**
Dose-Response (Likelihood Ratio)	0.7823	0.1231	0.2507	0.2367	0.4535
Homogeneity (Log-Rank)	0.5927	0.1169	0.2442	0.2293	0.4464

Table3A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Male Rats Poly-3 Test

Organ Name	Tumor Name	0 mg Veh. Cont (N=57) P - Trend	0 mg Water (N=57) P - VC vs. W	10 mg Low(N=57) P - VC vs. L	30 mg Med (N=57) P - VC vs. M	100 mg High (N=57) P - VC vs. H
Abdominal Cavity	M-Hemangiosarcoma	0/57 (35) 0.5214	0/57 (34) NC	0/57 (32) NC	1/57 (36) 0.5070	0/57 (37) NC
	M-Mesothelioma, Malignant	0/57 (35) 0.2643	0/57 (34) NC	0/57 (32) NC	0/57 (36) NC	1/57 (37) 0.5139
Adrenal	B-Adenoma, Cortex	0/57 (35) 0.0404	1/57 (34) 0.4928	1/57 (33) 0.4853	0/57 (36) NC	3/57 (38) 0.1356
	B-Phaeochromocytoma, Benign	5/57 (37) 0.3381	2/57 (35) 0.9378	3/57 (33) 0.8299	7/57 (38) 0.3966	6/57 (39) 0.5382
	M-Carcinoma, Cortex	0/57 (35) NC	1/57 (34) 0.4928	0/57 (32) NC	0/57 (36) NC	0/57 (37) NC
	M-Phaeochromocytoma, Malignant	2/57 (35) 0.6049	1/57 (34) 0.8751	0/57 (32) 1.0000	0/57 (36) 1.0000	1/57 (37) 0.8903
	Phaeochromocytoma, Benign/ Pheochromocytoma Malignant	7/57 (37) 0.5031	3/57 (35) 0.9484	3/57 (33) 0.9374	7/57 (38) 0.6372	6/57 (39) 0.7620
Brain	B-Tumour, Granular Cell, Benign	2/57 (36) 0.8987	0/57 (34) 1.0000	1/57 (33) 0.8637	2/57 (36) 0.6929	0/57 (37) 1.0000
	M-Glioma, Mixed, Malignant	1/57 (35) 0.6482	2/57 (35) 0.5000	2/57 (34) 0.4890	0/57 (36) 1.0000	1/57 (37) 0.7672
	M-Tumour, Granular Cell, Malignant	0/57 (35) NC	1/57 (34) 0.4928	0/57 (32) NC	0/57 (36) NC	0/57 (37) NC
Connective Tissue	B-Fibroma	0/57 (35) 0.5214	1/57 (34) 0.4928	0/57 (32) NC	1/57 (36) 0.5070	0/57 (37) NC
	B-Haemangioma	0/57 (35) 0.2643	0/57 (34) NC	0/57 (32) NC	0/57 (36) NC	1/57 (37) 0.5139
	M-Fibrosarcoma	0/57 (35) 0.0712	0/57 (34) NC	0/57 (32) NC	0/57 (36) NC	2/57 (38) 0.2675
	M-Osteosarcoma	0/57 (35) 0.7518	0/57 (34) NC	1/57 (33) 0.4853	0/57 (36) NC	0/57 (37) NC
Femur + Marrow	B-Osteoma	0/57 (35) 0.5214	0/57 (34) NC	0/57 (32) NC	1/57 (36) 0.5070	0/57 (37) NC
	M-Osteosarcoma	0/57 (35) 0.2643	0/57 (34) NC	0/57 (32) NC	0/57 (36) NC	1/57 (37) 0.5139
Heart	B-Schwannoma, Endocardial	0/57 (35) 0.5214	0/57 (34) NC	0/57 (32) NC	1/57 (36) 0.5070	0/57 (37) NC
Hemolympho-Reticular System	M-Histiocytic Sarcoma	0/57 (35) 0.8438	0/57 (34) NC	3/57 (34) 0.1142	1/57 (36) 0.5070	0/57 (37) NC

Male Rats Poly-3 Test

Organ Name	Tumor Name	0 mg Veh. Cont (N=57) P - Trend	0 mg Water (N=57) P - VC vs. W	10 mg Low(N=57) P - VC vs. L	30 mg Med (N=57) P - VC vs. M	100 mg High (N=57) P - VC vs. H
	M-Lymphocytic Leukaemia	0/57 (35) 0.6415	0/57 (34) NC	1/57 (33) 0.4853	1/57 (36) 0.5070	0/57 (37) NC
	M-Sarcoma, Nos	1/57 (35) 1.0000	0/57 (34) 1.0000	0/57 (32) 1.0000	0/57 (36) 1.0000	0/57 (37) 1.0000
Jejunum	M-Adenocarcinoma	0/54 (34) 0.2687	0/53 (32) NC	0/52 (31) NC	0/52 (33) NC	1/54 (36) 0.5143
Kidney	B-Adenoma	0/57 (35) 0.2643	1/57 (34) 0.4928	0/57 (32) NC	0/57 (36) NC	1/57 (37) 0.5139
Liver	B-Adenoma, Hepatocyte	0/57 (35) 0.8227	0/57 (34) NC	2/57 (33) 0.2318	0/57 (36) NC	0/57 (37) NC
	M-Carcinoma, Hepatocyte	0/57 (35) 0.5214	0/57 (34) NC	0/57 (32) NC	1/57 (36) 0.5070	0/57 (37) NC
	Adenoma, Hepatocyte/ Carcinoma, Hepatocyte	0/57 (35) 0.7526	0/57 (34) NC	2/57 (33) 0.2318	1/57 (36) 0.5070	0/57 (37) NC
	M-Histiocytic Sarcoma	0/57 (35) 0.5214	0/57 (34) NC	0/57 (32) NC	1/57 (36) 0.5070	0/57 (37) NC
Lymph Node, Mesenteric	B-Haemangioma	2/57 (36) 0.3948	1/57 (34) 0.8696	1/56 (33) 0.8637	0/57 (36) 1.0000	2/56 (38) 0.7130
	M-Haemangiosarcoma	0/57 (35) 0.2643	0/57 (34) NC	0/56 (32) NC	0/57 (36) NC	1/56 (37) 0.5139
Mammary Gland	B-Adenoma	2/44 (29) 0.8976	0/43 (25) 1.0000	0/42 (23) 1.0000	1/46 (29) 0.8816	0/41 (26) 1.0000
	B-Fibroadenoma	1/44 (28) 0.9321	1/43 (26) 0.7358	1/42 (23) 0.7035	0/46 (29) 1.0000	0/41 (26) 1.0000
	M-Adenocarcinoma	0/44 (28) 0.7358	0/43 (25) NC	1/42 (23) 0.4510	0/46 (29) NC	0/41 (26) NC
Pancreas	B-Adenoma, Acinar Cell	2/57 (35) 0.5307	1/56 (34) 0.8751	2/56 (32) 0.6584	1/57 (36) 0.8855	2/57 (37) 0.7137
	B-Adenoma, Islet Cell	3/57 (36) 0.7450	3/56 (35) 0.6496	3/56 (33) 0.6205	4/57 (37) 0.5156	2/57 (38) 0.8376
	M-Carcinoma, Islet Cell	1/57 (36) 0.9362	0/56 (34) 1.0000	1/56 (32) 0.7234	0/57 (36) 1.0000	0/57 (37) 1.0000
	Adenoma, Islet Cell/ Carcinoma, Islet Cell	4/57 (36) 0.8610	3/56 (35) 0.7738	4/56 (33) 0.5944	4/57 (37) 0.6604	2/57 (38) 0.9122
Parathyroid	B-Adenoma	2/52 (32) 0.2888	1/57 (34) 0.8916	0/54 (31) 1.0000	0/56 (36) 1.0000	2/54 (36) 0.7366
Pituitary	B-Adenoma, Pars Distalis	17/56 (40) 0.4372	27/57 (43) 0.0512	13/57 (36) 0.7891	22/57 (42) 0.2502	18/57 (42) 0.5756

Male Rats Poly-3 Test

Organ Name	Tumor Name	0 mg Veh. Cont (N=57) P - Trend	0 mg Water (N=57) P - VC vs. W	10 mg Low(N=57) P - VC vs. L	30 mg Med (N=57) P - VC vs. M	100 mg High (N=57) P - VC vs. H
	B-Adenoma, Pars Intermedia	1/56 (35) 0.9397	0/57 (34) 1.0000	1/57 (33) 0.7388	0/57 (36) 1.0000	0/57 (37) 1.0000
	M-Carcinoma, Pars Distalis	0/56 (34) 0.3209	1/57 (34) 0.5000	1/57 (33) 0.4925	1/57 (36) 0.5143	1/57 (37) 0.5211
	B-Adenoma, Pars Distalis/ M-Carcinoma, Pars Distalis	17/56 (40) 0.3853	28/57 (43) 0.0322	14/57 (36) 0.7097	23/57 (43) 0.2174	19/57 (42) 0.4893
Preputial/ Clitoral Gland	M-Carcinoma, Squamous Cell	0/54 (33) 0.2741	0/53 (31) NC	0/53 (31) NC	0/55 (34) NC	1/57 (37) 0.5286
Prostate	M-Adenocarcinoma	0/57 (35) 0.5214	0/57 (34) NC	0/57 (32) NC	1/57 (36) 0.5070	0/57 (37) NC
	M-Carcinosarcoma	0/57 (35) 0.5214	0/57 (34) NC	0/57 (32) NC	1/57 (36) 0.5070	0/57 (37) NC
Skin/Subcutis	B-Dermal Fibroma	2/57 (36) 0.0648	5/57 (36) 0.2145	0/57 (32) 1.0000	1/57 (37) 0.8852	4/57 (38) 0.3635
	B-Fibroma	3/57 (36) 0.7810	2/57 (34) 0.8034	4/57 (33) 0.4503	2/57 (36) 0.8215	2/57 (37) 0.8298
	B-Keratoacanthoma	2/57 (36) 0.5021	2/57 (35) 0.6822	2/57 (33) 0.6593	0/57 (36) 1.0000	2/57 (38) 0.7130
	B-Lipoma	0/57 (35) 0.5214	0/57 (34) NC	0/57 (32) NC	1/57 (36) 0.5070	0/57 (37) NC
	B-Papilloma, Squamous Cell	0/57 (35) NC	1/57 (34) 0.4928	0/57 (32) NC	0/57 (36) NC	0/57 (37) NC
	B-Tumour, Hair Follicle, Benign	2/57 (36) 0.4025	4/57 (35) 0.3233	2/57 (33) 0.6593	5/57 (38) 0.2380	3/57 (38) 0.5260
	M-Carcinoma, Sebaceous Cell	0/57 (35) 0.7518	0/57 (34) NC	1/57 (33) 0.4853	0/57 (36) NC	0/57 (37) NC
	M-Carcinoma, Squamous Cell	0/57 (35) 0.5248	0/57 (34) NC	0/57 (32) NC	1/57 (37) 0.5139	0/57 (37) NC
	M-Fibrosarcoma	1/57 (36) 0.9559	1/57 (35) 0.7465	5/57 (35) 0.0929	3/57 (38) 0.3281	0/57 (37) 1.0000
	M-Haemangiosarcoma	1/57 (35) 1.0000	0/57 (34) 1.0000	0/57 (32) 1.0000	0/57 (36) 1.0000	0/57 (37) 1.0000
	M-Histiocytic Sarcoma	0/57 (35) 0.2643	0/57 (34) NC	0/57 (32) NC	0/57 (36) NC	1/57 (37) 0.5139
	M-Sarcoma Nos	0/57 (35) 0.5214	0/57 (34) NC	0/57 (32) NC	1/57 (36) 0.5070	0/57 (37) NC
	M-Schwannoma, Malignant	0/57 (35) 0.7518	0/57 (34) NC	1/57 (33) 0.4853	0/57 (36) NC	0/57 (37) NC

Male Rats Poly-3 Test

Organ Name	Tumor Name	0 mg Veh. Cont (N=57) P - Trend	0 mg Water (N=57) P - VC vs. W	10 mg Low(N=57) P - VC vs. L	30 mg Med (N=57) P - VC vs. M	100 mg High (N=57) P - VC vs. H
	M-Tumour, Basal Cell, Malignant	0/57 (35) 0.5214	0/57 (34) NC	0/57 (32) NC	1/57 (36) 0.5070	0/57 (37) NC
Spleen	M-Sarcoma Nos	1/57 (35) 1.0000	0/57 (34) 1.0000	0/57 (32) 1.0000	0/57 (36) 1.0000	0/57 (37) 1.0000
Tail	B-Keratoacanthoma	0/57 (35) 0.7518	1/57 (34) 0.4928	1/57 (33) 0.4853	0/57 (36) NC	0/57 (37) NC
Testis	B-Adenoma, Leydig Cell	2/57 (35) 0.6969	0/57 (34) 1.0000	1/57 (33) 0.8694	0/57 (36) 1.0000	1/57 (37) 0.8903
	B-Adenoma, Rete Testis	0/57 (35) 0.5214	0/57 (34) NC	0/57 (32) NC	1/57 (36) 0.5070	0/57 (37) NC
	B-Seminoma, Benign	0/57 (35) NC	1/57 (34) 0.4928	0/57 (32) NC	0/57 (36) NC	0/57 (37) NC
	M-Carcinoma, Leydig Cell	1/57 (35) 1.0000	0/57 (34) 1.0000	0/57 (32) 1.0000	0/57 (36) 1.0000	0/57 (37) 1.0000
	B-Adenoma, Leydig Cell / M-Carcinoma, Leydig Cell	2/57 (35) 0.6969	0/57 (34) 1.0000	1/57 (33) 0.8694	0/57 (36) 1.0000	1/57 (37) 0.8903
Thyroid	B-Adenoma, C-Cell	7/55 (36) 0.1187	6/57 (36) 0.7293	9/57 (34) 0.3391	9/57 (40) 0.4835	13/57 (40) 0.1516
	B-Adenoma, Follicular Cell	0/55 (34) 0.7571	0/57 (34) NC	1/57 (33) 0.4925	0/57 (36) NC	0/57 (37) NC
	M-Carcinoma, C-Cell	1/55 (34) 0.1988	1/57 (34) 0.7537	0/57 (32) 1.0000	1/57 (36) 0.7677	2/57 (38) 0.5422
	B-Adenoma, C-Cell/ M-Carcinoma, C-Cell	8/55 (36) 0.0650	7/57 (36) 0.7186	9/57 (34) 0.4458	10/57 (40) 0.4954	15/57 (40) 0.1152
Urinary Bladder	B-Fibroma	0/57 (35) 0.5180	0/57 (34) NC	0/56 (32) NC	1/57 (36) 0.5070	0/56 (36) NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable

Table3B: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Female Rats Poly-3 Test

Organ Name	Tumor Name	0 mg Cont (N=57) P - Trend	0 mg Water(N=57) P - VC vs. W	10 mg Low(N=57) P - VC vs. L	30 mg Med (N=57) P - VC vs. M	100 mg High (N=57) P - VC vs. H
Adrenal	B-Adenoma, Cortex	1/57 (27) 0.0664	0/57 (33) 1.0000	0/57 (30) 1.0000	1/57 (31) 0.7877	3/57 (30) 0.3469
	M-Carcinoma, Cortex	0/57 (27) 0.5128	0/57 (33) NC	0/57 (30) NC	1/57 (31) 0.5345	0/57 (29) NC
	B-Adenoma, Cortex/ M-Carcinoma, Cortex	1/57 (27) 0.0736	0/57 (33) 1.0000	0/57 (30) 1.0000	2/57 (32) 0.5645	3/57 (30) 0.3469
	B-Phaeochromocytoma, Benign	0/57 (27) 0.3069	0/57 (33) NC	1/57 (30) 0.5263	1/57 (31) 0.5345	1/57 (29) 0.5179
	M-Phaeochromocytoma, Malignant	0/57 (27) 0.5931	1/57 (33) 0.5500	0/57 (30) NC	3/57 (32) 0.1526	0/57 (29) NC
	Pheochromocytoma Benign/ Pheochromocytoma Malignant	0/57 (27) 0.4378	1/57 (33) 0.5500	1/57 (30) 0.5263	4/57 (32) 0.0790	1/57 (29) 0.5179
Brain	B-Tumour, Granular Cell, Benign	0/57 (27) 0.2479	0/57 (33) NC	0/57 (30) NC	0/57 (31) NC	1/57 (29) 0.5179
	M-Glioma, Mixed, Malignant	1/57 (28) 0.8431	1/57 (33) 0.7934	1/57 (30) 0.7713	1/57 (32) 0.7864	0/57 (29) 1.0000
Heart	B-Schwannoma, Endocardial	0/57 (27) NC	1/57 (33) 0.5500	0/57 (30) NC	0/57 (31) NC	0/57 (29) NC
Hemolympho-Reticular System	M-Histiocytic Sarcoma	1/57 (27) 1.0000	2/57 (34) 0.5871	0/57 (30) 1.0000	0/57 (31) 1.0000	0/57 (29) 1.0000
	M-Malignant Lymphoma-Pleomorphic	1/57 (28) 0.9462	0/57 (33) 1.0000	1/57 (31) 0.7791	0/57 (31) 1.0000	0/57 (29) 1.0000
Kidney	B-Adenoma	0/57 (27) 0.2542	0/57 (33) NC	0/57 (30) NC	0/57 (31) NC	1/57 (30) 0.5263
Liver	B-Adenoma, Hepatocyte	1/57 (27) 0.9483	1/57 (33) 0.8017	1/57 (30) 0.7801	0/57 (31) 1.0000	0/57 (29) 1.0000
Lung	M-Carcinoma, Bronchiolo-Alveolar	1/57 (27) 1.0000	0/57 (33) 1.0000	0/57 (30) 1.0000	0/57 (31) 1.0000	0/57 (29) 1.0000
Mammary Gland	B-Adenoma	15/56 (35) 0.9658	15/57 (39) 0.7329	14/57 (36) 0.7194	6/56 (33) 0.9937	7/56 (31) 0.9785
	B-Fibroadenoma	26/56 (40) 0.8162	25/57 (43) 0.8070	23/57 (41) 0.8524	24/56 (41) 0.7957	20/56 (38) 0.9101
	M-Adenocarcinoma	11/56 (34) 0.0545	10/57 (38) 0.7945	8/57 (35) 0.8755	9/56 (35) 0.8085	16/56 (37) 0.2424
	M-Carcinosarcoma	0/56 (27) 0.5086	1/57 (33) 0.5500	0/57 (30) NC	1/56 (31) 0.5345	0/56 (28) NC

Female Rats Poly-3 Test

Organ Name	Tumor Name	0 mg Cont (N=57) P - Trend	0 mg Water(N=57) P - VC vs. W	10 mg Low(N=57) P - VC vs. L	30 mg Med (N=57) P - VC vs. M	100 mg High (N=57) P - VC vs. H
	M-Sarcoma Arising in Fibroadenoma	0/56 (27) 0.5086	0/57 (33) NC	0/57 (30) NC	1/56 (31) 0.5345	0/56 (28) NC
Ovary	B-Adenoma, Tubulostromal	0/57 (27) NC	1/57 (33) 0.5500	0/57 (30) NC	0/57 (31) NC	0/57 (29) NC
	M-Tumor, Granulosa Cell, Malignant	0/57 (27) 0.1923	0/57 (33) NC	0/57 (30) NC	1/57 (31) 0.5345	1/57 (29) 0.5179
Pancreas	B-Adenoma, Acinar Cell	0/57 (27) 0.5044	0/56 (32) NC	0/57 (30) NC	2/57 (31) 0.2813	0/57 (29) NC
	B-Adenoma, Islet Cell	1/57 (27) 0.3354	2/56 (33) 0.5760	2/57 (30) 0.5402	0/57 (31) 1.0000	2/57 (29) 0.5273
Parathyroid	B-Adenoma	0/53 (25) 0.2041	0/54 (31) NC	0/52 (27) NC	1/56 (31) 0.5536	1/54 (28) 0.5283
Pituitary	B-Adenoma, Pars Distalis	31/56 (41) 0.5903	30/57 (46) 0.9022	28/57 (42) 0.8731	36/57 (46) 0.4838	29/56 (41) 0.7724
	B-Adenoma, Pars Intermedia	1/56 (27) 1.0000	0/57 (33) 1.0000	0/57 (30) 1.0000	0/57 (31) 1.0000	0/56 (28) 1.0000
	M-Carcinoma, Pars Distalis	4/56 (29) 0.7454	3/57 (34) 0.8476	5/57 (32) 0.5647	4/57 (33) 0.7177	3/56 (31) 0.8148
	B-Adenoma, Pars Distalis/ M-Carcinoma, Pars Distalis	35/56 (43) 0.7352	33/57 (47) 0.9312	33/57 (44) 0.8367	40/57 (49) 0.5931	32/56 (43) 0.8507
Skin/Subcutis	B-Dermal Fibroma	0/57 (27) 0.6415	1/57 (33) 0.5500	1/57 (30) 0.5263	1/57 (31) 0.5345	0/57 (29) NC
	B-Fibroma	0/57 (27) 0.3125	2/57 (34) 0.3066	1/57 (31) 0.5345	1/57 (31) 0.5345	1/57 (30) 0.5263
	B-Lipoma	0/57 (27) 0.2479	1/57 (33) 0.5500	0/57 (30) NC	0/57 (31) NC	1/57 (29) 0.5179
	B-Papilloma, Squamous Cell	0/57 (27) NC	1/57 (34) 0.5574	0/57 (30) NC	0/57 (31) NC	0/57 (29) NC
	B-Tumour, Basal Cell, Benign	0/57 (27) 0.2479	0/57 (33) NC	0/57 (30) NC	0/57 (31) NC	1/57 (29) 0.5179
	M-Fibrosarcoma	1/57 (27) 0.4002	0/57 (33) 1.0000	0/57 (30) 1.0000	1/57 (31) 0.7877	1/57 (29) 0.7721
	M-Sarcoma Nos	0/57 (27) NC	1/57 (33) 0.5500	0/57 (30) NC	0/57 (31) NC	0/57 (29) NC
	M-Tumour, Basal Cell, Malignant	0/57 (27) 0.2479	0/57 (33) NC	0/57 (30) NC	0/57 (31) NC	1/57 (29) 0.5179
Thymus	B-Thymoma, Benign	0/55 (26) 0.3140	0/51 (29) NC	1/55 (29) 0.5273	0/55 (29) NC	1/53 (27) 0.5094

Female Rats Poly-3 Test

Organ Name	Tumor Name	0 mg Cont (N=57) P - Trend	0 mg Water(N=57) P - VC vs. W	10 mg Low(N=57) P - VC vs. L	30 mg Med (N=57) P - VC vs. M	100 mg High (N=57) P - VC vs. H
Thyroid	B-Adenoma, C-Cell	5/56 (29) 0.8098	5/57 (34) 0.7329	8/57 (33) 0.3602	10/57 (35) 0.2221	4/57 (30) 0.7814
	B-Adenoma, Follicular Cell	0/56 (27) 0.2479	0/57 (33) NC	0/57 (30) NC	0/57 (31) NC	1/57 (29) 0.5179
	M-Carcinoma, C-Cell	0/56 (27) 0.3205	0/57 (33) NC	1/57 (30) 0.5263	0/57 (31) NC	1/57 (29) 0.5179
	B-Adenoma, C-Cell/ M-Carcinoma, C-Cell	5/56 (29) 0.7483	5/57 (34) 0.7329	9/57 (34) 0.2846	10/57 (35) 0.2221	5/57 (31) 0.6778
Uterus	B-Polyp, Endometrial Stromal	4/57 (28) 0.8779	5/57 (34) 0.6259	5/57 (32) 0.5876	7/57 (33) 0.3595	2/57 (30) 0.9178
	M-Histiocytic Sarcoma	1/57 (27) 1.0000	0/57 (33) 1.0000	0/57 (30) 1.0000	0/57 (31) 1.0000	0/57 (29) 1.0000
	M-Sarcoma, Endometrial Stromal	0/57 (27) 0.2542	0/57 (33) NC	0/57 (30) NC	0/57 (31) NC	1/57 (30) 0.5263
	Polyp, Endometrial Stromal/ Sarcoma, Endometrial Stromal	4/57 (28) 0.7752	5/57 (34) 0.6259	5/57 (32) 0.5876	7/57 (33) 0.3595	3/57 (31) 0.8283
	M-Schwannoma, Malignant	0/57 (27) 0.2479	1/57 (33) 0.5500	0/57 (30) NC	0/57 (31) NC	1/57 (29) 0.5179
Zymbal Gland	M-Carcinoma, Squamous Cell	1/57 (28) 1.0000	0/57 (33) 1.0000	0/57 (30) 1.0000	0/57 (31) 1.0000	0/57 (29) 1.0000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Figure 1A: Kaplan-Meier Survival Curves for
Male Rats

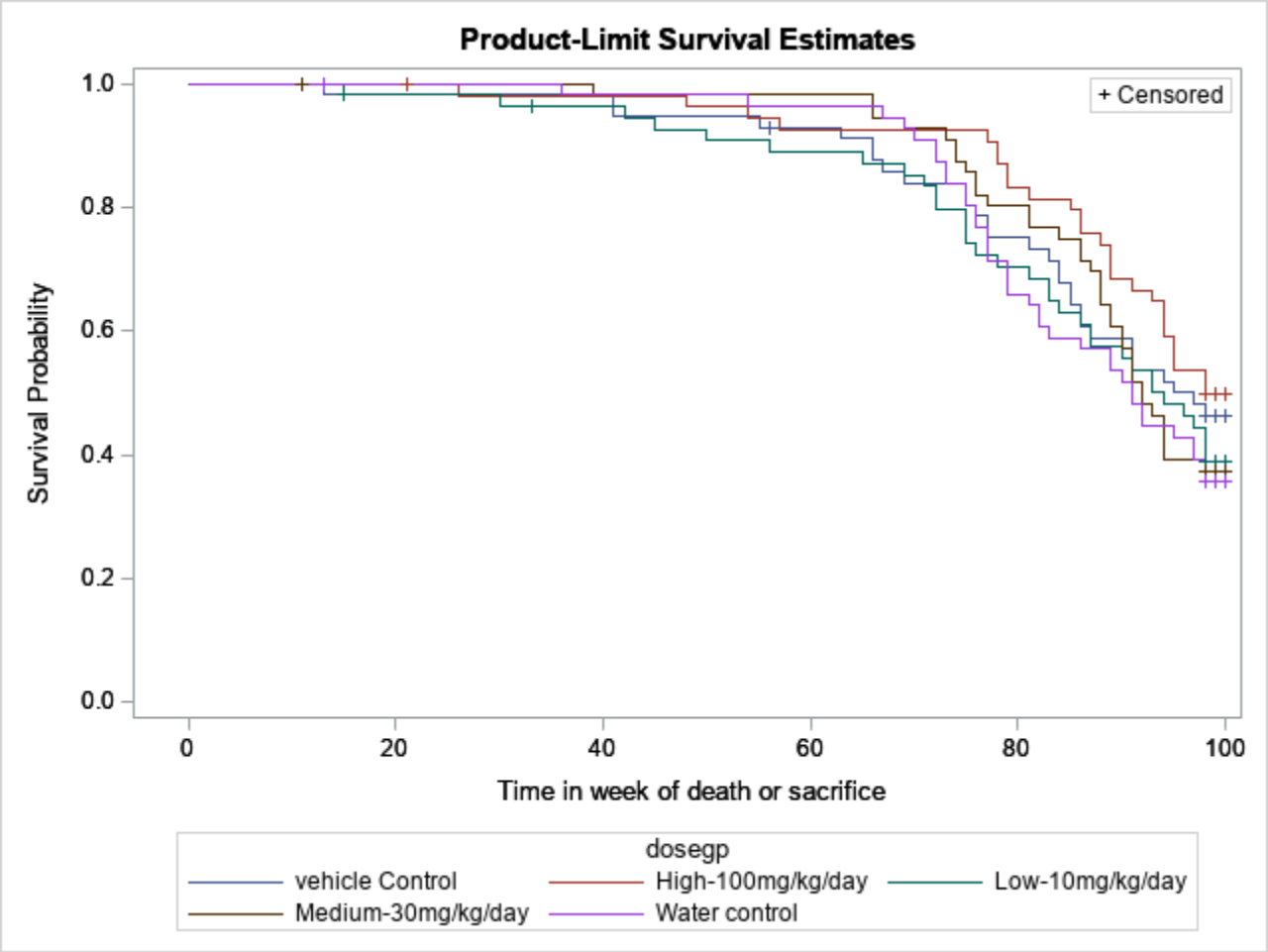


Figure 1B: Kaplan-Meier Survival Curves **for Female Rats**

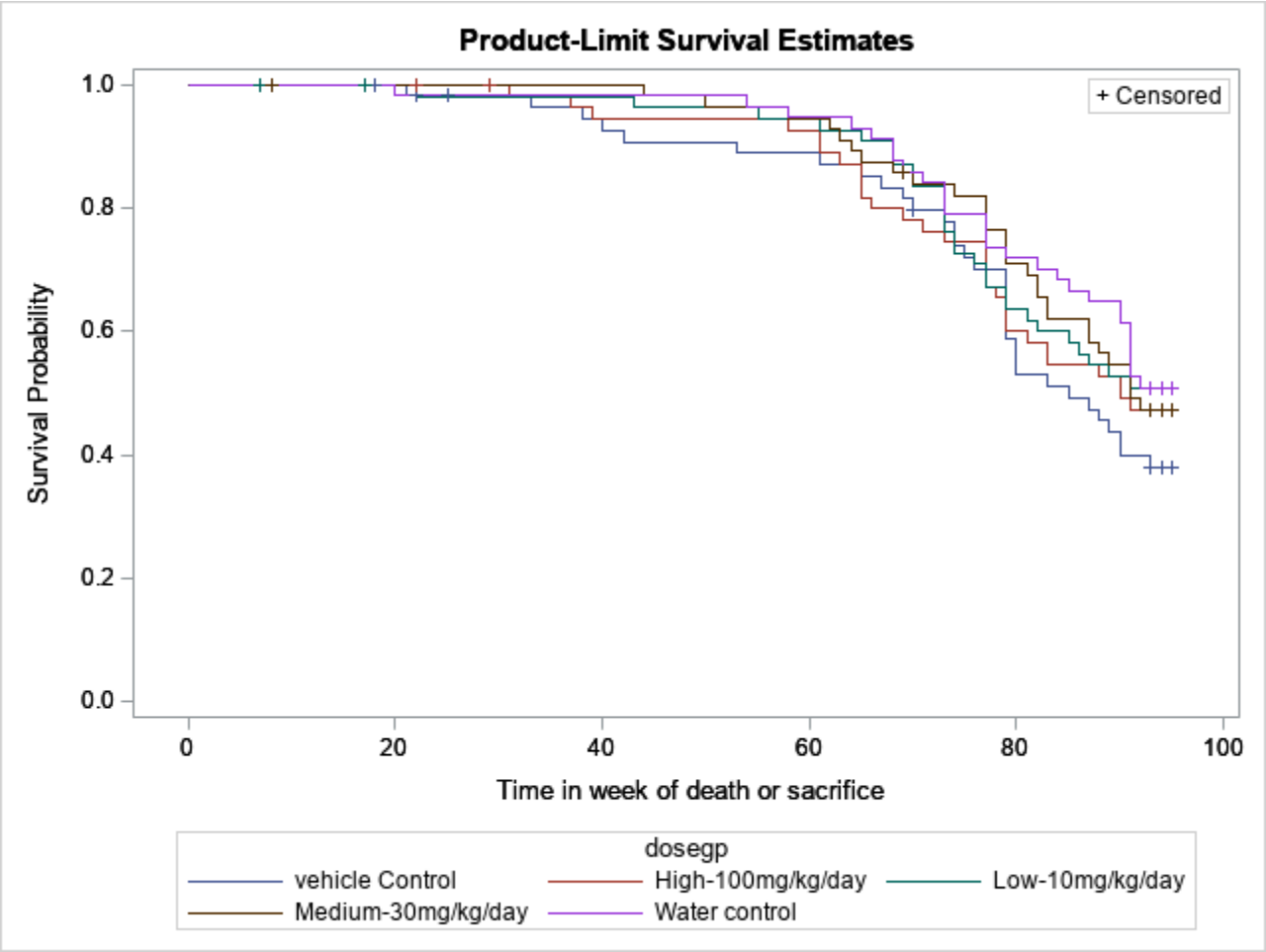


Table4A: Intercurrent Mortality Rate
Male Hamsters

	0mg|kg|day Veh. Cont		0mg|kg|day Water Cont.		10 mg|kg|day Low		30 mg|kg|day Med		100 mg|kg|day High	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	10	15.38	1	1.54	8	12.31	8	12.31	12	18.46
53 - 78	15	38.46	10	16.92	15	35.38	10	27.69	5	26.15
79 - 92	10	53.85	7	27.69	13	55.38	10	43.08	12	44.62
93 - 98	10	69.23	6	36.92	3	60.00	10	58.46	9	58.46
ADD	.	.	.	.	.	.	1	60.00	1	60.00
Ter. Sac.	20	30.77	41	63.08	26	40.00	26	40.00	26	40.00
Total	65	100.00	65	100.00	65	100.00	65	100.00	65	100.00

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded
ADD: accidental death

Table4B: Intercurrent Mortality Rate
Female Hamsters

	0mg|kg|day Veh. Cont		0mg|kg|day Water Cont.		10 mg|kg|day Low		30 mg|kg|day Med		100 mg|kg|day High	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	3	4.62	5	7.69	5	7.69	5	7.69	5	7.69
53 - 78	17	30.77	18	35.38	12	26.15	16	32.31	20	38.46
79 - 92	23	66.15	22	69.23	22	60.00	26	72.31	20	69.23
Ter. Sac.	22	33.85	20	30.77	26	40.00	18	27.69	20	30.77
Total	65	100.00	65	100.00	65	100.00	65	100.00	65	100.00

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded

Table 5A: Intercurrent Mortality Comparison for
Male Hamsters

Test Statistics	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Water	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High
Dose-Response (Likelihood Ratio)	0.4001	0.0002*	0.4798	0.2259	0.2836
Homogeneity (Log-Rank)	0.6094	0.0002*	0.4752	0.2186	0.2763

* = statistically significant at the 0.05 significance level

Table 5B: Intercurrent Mortality Comparison for
Female Hamsters

Test Statistics	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Water	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High
Dose-Response (Likelihood Ratio)	0.3160	0.4999	0.6424	0.4145	0.4622
Homogeneity (Log-Rank)	0.5234	0.4900	0.6368	0.4048	0.4541

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise Comparisons

Male Hamster Poly-3 Test

Organ Name	Tumor Name	0 mg Veh. Cont (N=65) P - Trend	0 mg Water (N=65) P - VC vs. W	10 mg Low(N=65) P - VC vs. L	30 mg Med (N=65) P - VC vs. M	100 mg High (N=65) P - VC vs. H
Adrenal	B-Benign phaeochromocytoma	1/65 (36) 0.1613	5/65 (49) 0.1889	3/65 (37) 0.3177	3/65 (39) 0.3384	4/65 (38) 0.1961
	B-Cortical adenoma	5/65 (37) 0.5392	21/65 (51) 0.0042*	13/65 (41) 0.0498	7/65 (40) 0.4350	8/65 (39) 0.3079
	B-Subcapsular cell adenoma	17/65 (41) 0.8472	31/65 (55) 0.1078	18/65 (42) 0.5374	10/65 (41) 0.9704	13/65 (41) 0.8742
	M-Cortical carcinoma	5/65 (37) 0.8578	2/65 (47) 0.9736	3/65 (37) 0.8694	3/65 (40) 0.8924	2/65 (38) 0.9503
	B-Cortical adenoma/ M-Cortical carcinoma	10/65 (38) 0.8031	23/65 (52) 0.0634	15/65 (41) 0.2305	10/65 (41) 0.6758	9/65 (39) 0.7235
	M-Malignant phaeochromocytoma	1/65 (36) 1.0000	0/65 (46) 1.0000	0/65 (36) 1.0000	0/65 (39) 1.0000	0/65 (37) 1.0000
	Benign phaeochromocytoma/ Malignant phaeochromocytoma	2/65 (36) 0.2458	5/65 (49) 0.3628	3/65 (37) 0.5132	3/65 (39) 0.5385	4/65 (38) 0.3635
Caecum	M-Sarcoma nos	1/64 (36) 1.0000	0/65 (46) 1.0000	0/65 (36) 1.0000	0/64 (38) 1.0000	0/65 (37) 1.0000
Connective Tissue	B-Dermal fibroma	0/65 (35) NC	1/65 (46) 0.5679	0/65 (36) NC	0/65 (39) NC	0/65 (37) NC
	M-Fibrosarcoma, pleomorphic	1/65 (36) 1.0000	1/65 (47) 0.8149	0/65 (36) 1.0000	0/65 (39) 1.0000	0/65 (37) 1.0000
	M-Haemangiosarcoma	0/65 (35) 0.5170	0/65 (46) NC	0/65 (36) NC	1/65 (39) 0.5270	0/65 (37) NC
	M-Sarcoma nos	0/65 (35) 0.5170	0/65 (46) NC	0/65 (36) NC	1/65 (39) 0.5270	0/65 (37) NC
Gall Bladder	B-Adenoma	0/65 (35) 0.2603	0/64 (46) NC	0/63 (35) NC	0/64 (38) NC	1/62 (38) 0.5205
Hemolympho-reticular System	M-Malignant lymphoma nos	0/65 (35) NC	1/65 (47) 0.5732	0/65 (36) NC	0/65 (39) NC	0/65 (37) NC
	M-Malignant lymphoma-lymphocytic	1/65 (36) 1.0000	0/65 (46) 1.0000	0/65 (36) 1.0000	0/65 (39) 1.0000	0/65 (37) 1.0000
	M-Malignant lymphoma-plasmacytic	0/65 (35) 0.5170	0/65 (46) NC	0/65 (36) NC	1/65 (39) 0.5270	0/65 (37) NC
	M-Malignant lymphoma-pleomorphic	0/65 (35) 0.7635	0/65 (46) NC	1/65 (37) 0.5139	0/65 (39) NC	0/65 (37) NC
Kidney	B-Adenoma	0/65 (35) 0.5170	0/65 (46) NC	0/65 (36) NC	1/65 (39) 0.5270	0/65 (37) NC

Male Hamster Poly-3 Test

Organ Name	Tumor Name	0 mg Veh. Cont (N=65) P - Trend	0 mg Water (N=65) P - VC vs. W	10 mg Low(N=65) P - VC vs. L	30 mg Med (N=65) P - VC vs. M	100 mg High (N=65) P - VC vs. H
Liver	B-Haemangioma	0/65 (35) 0.7635	0/65 (46) NC	1/65 (37) 0.5139	0/65 (39) NC	0/65 (37) NC
	B-Hepatocellular adenoma	1/65 (36) 0.8394	0/65 (46) 1.0000	1/65 (37) 0.7603	1/65 (39) 0.7730	0/65 (37) 1.0000
	M-Cholangiocarcinoma	0/65 (35) 0.2568	1/65 (46) 0.5679	0/65 (36) NC	0/65 (39) NC	1/65 (38) 0.5205
Lymph Node, Mesenteric	B-Haemangioma	0/54 (31) 0.5154	0/59 (44) NC	0/58 (32) NC	1/55 (32) 0.5079	0/57 (35) NC
Muscle, Other	M-Haemangiosarcoma	1/65 (36) 1.0000	0/65 (46) 1.0000	0/65 (36) 1.0000	0/65 (39) 1.0000	0/65 (37) 1.0000
	M-Osteosarcoma	0/65 (35) NC	1/65 (46) 0.5679	0/65 (36) NC	0/65 (39) NC	0/65 (37) NC
Oral Mucosa	M-Sarcoma - NOS	0/65 (35) 0.2568	0/65 (46) NC	0/65 (36) NC	0/65 (39) NC	1/65 (38) 0.5205
Pancreas	B-Islet cell adenoma	0/65 (35) 0.2568	1/65 (46) 0.5679	0/65 (36) NC	0/65 (39) NC	1/65 (38) 0.5205
	M-Islet cell carcinoma	0/65 (35) NC	1/65 (46) 0.5679	0/65 (36) NC	0/65 (39) NC	0/65 (37) NC
Parathyroid	B-Adenoma	2/64 (35) 0.3285	1/58 (41) 0.9069	0/62 (35) 1.0000	3/59 (37) 0.5268	2/60 (36) 0.7036
Preputial/ Clitoral Gland	B-Adenoma	0/48 (26) 0.2264	0/56 (41) NC	0/50 (30) NC	0/42 (26) NC	1/40 (24) 0.4800
Prostate	M-Fibrosarcoma	0/65 (35) NC	1/65 (46) 0.5679	0/65 (36) NC	0/65 (39) NC	0/65 (37) NC
Skin/Subcutis	B-Benign hair follicle tumor	0/65 (35) NC	1/65 (46) 0.5679	0/65 (36) NC	0/65 (39) NC	0/65 (37) NC
	B-Benign melanoma	0/65 (35) 0.7635	0/65 (46) NC	1/65 (37) 0.5139	0/65 (39) NC	0/65 (37) NC
	B-Dermal fibroma	1/65 (36) 1.0000	2/65 (47) 0.6000	0/65 (36) 1.0000	0/65 (39) 1.0000	0/65 (37) 1.0000
	B-Plasmacytoma	0/65 (35) NC	1/65 (46) 0.5679	0/65 (36) NC	0/65 (39) NC	0/65 (37) NC
	B-Squamous cell papilloma	1/65 (36) 1.0000	0/65 (46) 1.0000	0/65 (36) 1.0000	0/65 (39) 1.0000	0/65 (37) 1.0000
	M-Haemangiosarcoma	0/65 (35) 0.7619	0/65 (46) NC	1/65 (36) 0.5070	0/65 (39) NC	0/65 (37) NC
	M-Malignant basal cell tumor	1/65 (36) 0.4463	0/65 (46) 1.0000	0/65 (36) 1.0000	0/65 (39) 1.0000	1/65 (38) 0.7668

Male Hamster Poly-3 Test

Organ Name	Tumor Name	0 mg Veh. Cont (N=65) P - Trend	0 mg Water (N=65) P - VC vs. W	10 mg Low(N=65) P - VC vs. L	30 mg Med (N=65) P - VC vs. M	100 mg High (N=65) P - VC vs. H
	M-Malignant schwannoma	0/65 (35) NC	1/65 (46) 0.5679	0/65 (36) NC	0/65 (39) NC	0/65 (37) NC
	M-Sarcoma NOS	2/65 (37) 1.0000	1/65 (46) 0.9154	0/65 (36) 1.0000	0/65 (39) 1.0000	0/65 (37) 1.0000
	M-Squamous cell carcinoma	0/65 (35) 0.5170	0/65 (46) NC	0/65 (36) NC	1/65 (39) 0.5270	0/65 (37) NC
Spleen	B-Haemangioma	0/64 (35) 0.5170	1/65 (46) 0.5679	0/65 (36) NC	1/65 (39) 0.5270	0/65 (37) NC
Stomach	B-Squamous cell papilloma	0/65 (35) 0.0164*	3/64 (46) 0.1779	1/65 (36) 0.5070	1/65 (39) 0.5270	4/65 (38) 0.0678
Tail	B-Hemangioma	1/65 (36) 1.0000	0/65 (46) 1.0000	0/65 (36) 1.0000	0/65 (39) 1.0000	0/65 (37) 1.0000
Thymus	B-Benign thymoma	1/54 (28) 1.0000	0/46 (34) 1.0000	0/49 (27) 1.0000	0/46 (28) 1.0000	0/50 (28) 1.0000
Thyroid	B-C-cell adenoma	0/65 (35) 0.2552	1/63 (46) 0.5679	0/63 (35) NC	0/63 (38) NC	1/62 (37) 0.5139
	B-Follicular cell adenoma	0/65 (35) 0.5172	0/63 (46) NC	0/63 (35) NC	1/63 (38) 0.5205	0/62 (37) NC
	M-C-cell carcinoma	0/65 (35) 0.2028	0/63 (46) NC	0/63 (35) NC	1/63 (38) 0.5205	1/62 (38) 0.5205
	B-C-cell adenoma/ M-C-cell carcinoma	0/65 (35) 0.0692	1/63 (46) 0.5679	0/63 (35) NC	1/63 (38) 0.5205	2/62 (38) 0.2675

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
*: Statistically significant at 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and The pairwise comparisons

Female Hamsters Poly-3 Test

Organ Name	Tumor Name	0 mg Veh. Cont (N=65) P - Trend	0 mg Water (N=65) P - VC vs. W	10 mg Low(N=65) P - VC vs. L	30 mg Med (N=65) P - VC vs. M	100 mg High (N=65) P - VC vs. H
Abdominal Cavity	M-Malignant mesothelioma	0/65 (34) 0.7405	0/65 (31) NC	1/65 (34) 0.5000	0/65 (32) NC	0/65 (31) NC
Adrenal	B-Benign phaeochromocytoma	3/65 (35) 0.0227	3/65 (33) 0.6347	0/65 (34) 1.0000	2/65 (33) 0.8031	6/65 (35) 0.2386
	B-Cortical adenoma	10/65 (38) 0.6275	11/65 (36) 0.4415	9/65 (37) 0.6780	10/65 (36) 0.5473	8/65 (35) 0.7297
	B-Subcapsular cell adenoma	9/65 (38) 0.1706	7/65 (35) 0.7455	8/65 (37) 0.6870	5/65 (34) 0.8968	11/65 (36) 0.3433
	M-Cortical carcinoma	1/65 (34) 0.4438	3/65 (33) 0.2954	3/65 (34) 0.3068	3/65 (33) 0.2954	2/65 (32) 0.4769
	B-Cortical adenoma/ M-Cortical carcinoma	11/65 (38) 0.6081	14/65 (38) 0.3129	12/65 (38) 0.5000	12/65 (37) 0.4693	10/65 (36) 0.6435
	M-Malignant phaeochromocytoma	3/65 (35) 0.7687	1/65 (32) 0.9317	1/65 (34) 0.9394	1/65 (33) 0.9357	1/65 (32) 0.9317
Connective Tissue	M-Fibrosarcoma, pleomorphic	0/65 (34) 0.4848	0/65 (31) NC	0/65 (34) NC	1/65 (33) 0.4925	0/65 (31) NC
	M-Haemangiosarcoma	0/65 (34) 0.2424	0/65 (31) NC	0/65 (34) NC	0/65 (32) NC	1/65 (32) 0.4848
	M-Osteosarcoma	1/65 (34) 1.0000	0/65 (31) 1.0000	0/65 (34) 1.0000	0/65 (32) 1.0000	0/65 (31) 1.0000
	M-Sarcoma nos	1/65 (34) 1.0000	1/65 (32) 0.7385	0/65 (34) 1.0000	0/65 (32) 1.0000	0/65 (31) 1.0000
Foot	M-Haemangiosarcoma	1/65 (35) 1.0000	0/65 (31) 1.0000	0/65 (34) 1.0000	0/65 (32) 1.0000	0/65 (31) 1.0000
Hemolympho-reticular System	M-Granulocytic leukaemia	0/65 (34) 0.2424	0/65 (31) NC	0/65 (34) NC	0/65 (32) NC	1/65 (32) 0.4848
	M-Histiocytic sarcoma	1/65 (34) 1.0000	1/65 (32) 0.7385	0/65 (34) 1.0000	0/65 (32) 1.0000	0/65 (31) 1.0000
	M-Malignant lymphoma-immunoblastic	1/65 (34) 1.0000	0/65 (31) 1.0000	0/65 (34) 1.0000	0/65 (32) 1.0000	0/65 (31) 1.0000
	M-Malignant lymphoma-lymphocytic	0/65 (34) NC	1/65 (32) 0.4848	0/65 (34) NC	0/65 (32) NC	0/65 (31) NC
	M-Malignant lymphoma-plasmacytic	0/65 (34) NC	1/65 (32) 0.4848	0/65 (34) NC	0/65 (32) NC	0/65 (31) NC
	M-Malignant lymphoma-pleomorphic	0/65 (34) 0.0172*	3/65 (33) 0.1139	0/65 (34) NC	1/65 (33) 0.4925	3/65 (33) 0.1139

Female Hamsters Poly-3 Test

Organ Name	Tumor Name	0 mg Veh. Cont (N=65) P - Trend	0 mg Water (N=65) P - VC vs. W	10 mg Low(N=65) P - VC vs. L	30 mg Med (N=65) P - VC vs. M	100 mg High (N=65) P - VC vs. H
Leg	M-Sarcoma nos	1/65 (35) 1.0000	0/65 (31) 1.0000	0/65 (34) 1.0000	0/65 (32) 1.0000	0/65 (31) 1.0000
Liver	B-Cholangioma	0/65 (34) NC	1/65 (32) 0.4848	0/65 (34) NC	0/65 (32) NC	0/65 (31) NC
	B-Haemangioma	0/65 (34) 0.4809	0/65 (31) NC	0/65 (34) NC	1/65 (32) 0.4848	0/65 (31) NC
	B-Hepatocellular adenoma	4/65 (35) 1.0000	2/65 (33) 0.8873	0/65 (34) 1.0000	0/65 (32) 1.0000	0/65 (31) 1.0000
	M-Haemangiosarcoma	1/65 (34) 1.0000	3/65 (33) 0.2954	0/65 (34) 1.0000	0/65 (32) 1.0000	0/65 (31) 1.0000
Muscle, Other	M-Sarcoma nos	0/65 (34) 0.2424	0/65 (31) NC	0/65 (34) NC	0/65 (32) NC	1/65 (32) 0.4848
Oral Cavity	M-Schwannoma	0/65 (34) 0.4848	0/65 (31) NC	0/65 (34) NC	1/65 (33) 0.4925	0/65 (31) NC
Oral Mucosa	M-Fibrosarcoma	0/65 (34) 0.7405	0/65 (31) NC	1/65 (34) 0.5000	0/65 (32) NC	0/65 (31) NC
Ovary	B-Benign granulosa cell tum*	2/64 (34) 0.2842	2/64 (32) 0.6700	0/64 (33) 1.0000	1/64 (32) 0.8692	2/65 (32) 0.6700
	B-Benign luteoma	0/64 (33) 0.7442	0/64 (31) NC	1/64 (33) 0.5000	0/64 (32) NC	0/65 (31) NC
	B-Benign mixed sex cord str*	0/64 (33) 0.7442	0/64 (31) NC	1/64 (33) 0.5000	0/64 (32) NC	0/65 (31) NC
	M-Thecoma	2/64 (34) 1.0000	0/64 (31) 1.0000	0/64 (33) 1.0000	0/64 (32) 1.0000	0/65 (31) 1.0000
Oviduct	B-Adenoma	0/65 (34) 0.7405	0/65 (31) NC	1/65 (34) 0.5000	0/65 (32) NC	0/65 (31) NC
Pancreas	B-Islet cell adenoma	1/65 (34) 1.0000	1/65 (32) 0.7385	0/64 (34) 1.0000	0/65 (32) 1.0000	0/65 (31) 1.0000
	M-Islet cell carcinoma	0/65 (34) NC	1/65 (32) 0.4848	0/64 (34) NC	0/65 (32) NC	0/65 (31) NC
Parathyroid	B-Adenoma	9/62 (35) 0.4391	18/59 (37) 0.0382	16/62 (38) 0.1096	17/61 (38) 0.0729	12/60 (34) 0.2735
Pituitary	B-Adenoma	8/63 (36) 0.2153	12/64 (37) 0.2376	8/65 (37) 0.6348	6/64 (34) 0.7808	10/63 (35) 0.3663
	M-Carcinoma	1/63 (33) 0.9360	0/64 (31) 1.0000	1/65 (34) 0.7612	0/64 (32) 1.0000	0/63 (30) 1.0000
	B-Adenoma/ M-Carcinoma	8/63 (36) 0.2550	12/64 (37) 0.2376	9/65 (37) 0.5259	6/64 (34) 0.7808	10/63 (35) 0.3663

Female Hamsters Poly-3 Test

Organ Name	Tumor Name	0 mg Veh. Cont (N=65) P - Trend	0 mg Water (N=65) P - VC vs. W	10 mg Low(N=65) P - VC vs. L	30 mg Med (N=65) P - VC vs. M	100 mg High (N=65) P - VC vs. H
Preputial/ Clitoral Gland	B-Squamous cell papilloma	0/37 (19) 0.4714	0/34 (16) NC	0/37 (18) NC	1/35 (16) 0.4571	0/37 (17) NC
Rectum	B-Adenoma	0/65 (34) 0.1711	0/65 (31) NC	0/65 (34) NC	1/64 (32) 0.4848	1/65 (31) 0.4769
Skin/Subcutis	B-Benign melanoma	1/65 (34) 1.0000	0/65 (31) 1.0000	0/65 (34) 1.0000	0/65 (32) 1.0000	0/65 (31) 1.0000
	B-Dermal fibroma	1/65 (34) 1.0000	0/65 (31) 1.0000	0/65 (34) 1.0000	0/65 (32) 1.0000	0/65 (31) 1.0000
	B-Haemangioma	0/65 (34) 0.2424	0/65 (31) NC	0/65 (34) NC	0/65 (32) NC	1/65 (32) 0.4848
	B-Plasmacytoma	0/65 (34) 0.7405	0/65 (31) NC	1/65 (34) 0.5000	0/65 (32) NC	0/65 (31) NC
	M-Histiocytic sarcoma	0/65 (34) 0.6177	0/65 (31) NC	1/65 (34) 0.5000	2/65 (33) 0.2388	0/65 (31) NC
	M-Malignant basal cell tumo*	0/65 (34) 0.2424	0/65 (31) NC	0/65 (34) NC	0/65 (32) NC	1/65 (32) 0.4848
	M-Sarcoma NOS	1/65 (34) 1.0000	0/65 (31) 1.0000	0/65 (34) 1.0000	0/65 (32) 1.0000	0/65 (31) 1.0000
Spleen	B-Haemangioma	0/65 (34) 0.7984	0/65 (31) NC	2/65 (34) 0.2463	0/65 (32) NC	0/65 (31) NC
	M-Haemangiosarcoma	0/65 (34) NC	2/65 (32) 0.2312	0/65 (34) NC	0/65 (32) NC	0/65 (31) NC
Sternum + Marrow	M-Osteosarcoma	0/65 (34) 0.4809	0/65 (31) NC	0/65 (34) NC	1/64 (32) 0.4848	0/65 (31) NC
Stomach	B-Squamous cell papilloma	1/65 (34) 0.3655	1/65 (32) 0.7385	0/65 (34) 1.0000	1/65 (32) 0.7385	1/65 (31) 0.7303
Thymus	M-Malignant thymoma	1/50 (27) 1.0000	0/53 (25) 1.0000	0/45 (21) 1.0000	0/48 (23) 1.0000	0/53 (25) 1.0000
Thyroid	B-C-cell adenoma	3/65 (35) 0.8629	3/64 (32) 0.6194	8/64 (37) 0.1124	5/64 (34) 0.3382	2/63 (31) 0.7821
	B-Follicular cell adenoma	2/65 (34) 0.5648	1/64 (31) 0.8630	0/64 (33) 1.0000	0/64 (31) 1.0000	1/63 (31) 0.8630
	M-C-cell carcinoma	0/65 (34) 0.2734	0/64 (31) NC	1/64 (34) 0.5000	1/64 (32) 0.4848	1/63 (31) 0.4769
	B-C-cell adenoma / M-C-cell carcinoma	3/65 (35) 0.7842	3/64 (32) 0.6194	9/64 (38) 0.0758	6/64 (35) 0.2386	3/63 (32) 0.6194
	M-Follicular cell carcinoma	1/65 (34) 1.0000	0/64 (31) 1.0000	0/64 (33) 1.0000	0/64 (31) 1.0000	0/63 (30) 1.0000

Female Hamsters Poly-3 Test

Organ Name	Tumor Name	0 mg Veh. Cont (N=65) P - Trend	0 mg Water (N=65) P - VC vs. W	10 mg Low(N=65) P - VC vs. L	30 mg Med (N=65) P - VC vs. M	100 mg High (N=65) P - VC vs. H
	B-Follicular cell adenoma/ M-Follicular cell carcinoma	3/65 (35) 0.6844	1/64 (31) 0.9274	0/64 (33) 1.0000	0/64 (31) 1.0000	1/63 (31) 0.9274
Uterus	B-Adenoma	1/65 (34) 0.0406	0/65 (31) 1.0000	1/65 (34) 0.7537	1/65 (33) 0.7463	4/65 (33) 0.1686
	B-Leiomyoma	3/65 (35) 0.7700	6/65 (33) 0.2093	5/65 (35) 0.3548	3/65 (34) 0.6494	2/65 (32) 0.7929
	B-Polyp, endometrial stromal	2/65 (34) 0.5497	3/65 (33) 0.4856	3/65 (35) 0.5140	2/65 (33) 0.6819	2/65 (32) 0.6700
	M-Adenocarcinoma	5/65 (36) 0.6615	6/65 (34) 0.4583	9/65 (38) 0.2189	5/65 (34) 0.5949	5/65 (34) 0.5949
	M-Haemangiosarcoma	0/65 (34) 0.2366	0/65 (31) NC	0/65 (34) NC	0/65 (32) NC	1/65 (31) 0.4769
	M-Leiomyosarcoma	0/65 (34) 0.7984	1/65 (32) 0.4848	2/65 (34) 0.2463	0/65 (32) NC	0/65 (31) NC
Vagina	B-Squamous cell papilloma	0/65 (34) 0.0610	2/65 (32) 0.2312	3/65 (34) 0.1194	2/65 (33) 0.2388	4/65 (32) 0.0499*
	M-Squamous cell carcinoma	0/65 (34) 0.7405	0/65 (31) NC	1/65 (34) 0.5000	0/65 (32) NC	0/65 (31) NC
	B-Squamous cell papilloma/ M-Squamous cell carcinoma	0/65 (34) 0.0972	2/65 (32) 0.2312	4/65 (35) 0.0606	2/65 (33) 0.2388	4/65 (32) 0.0499*

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ= total number of animals observed;
NC = Not calculable;
*: Statistically significant at 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

Figure 2A: Kaplan-Meier Survival Curves for

Male Hamsters

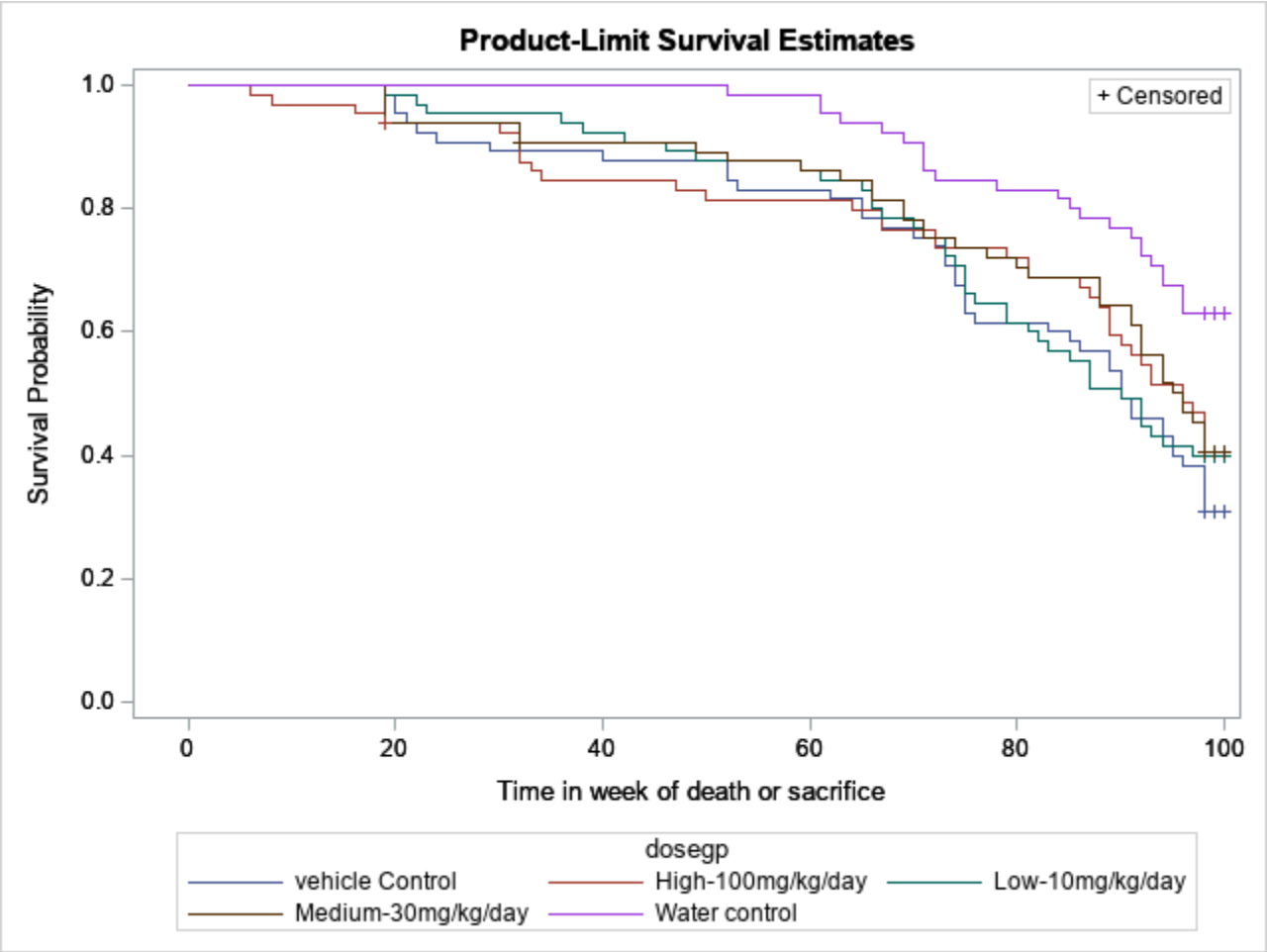
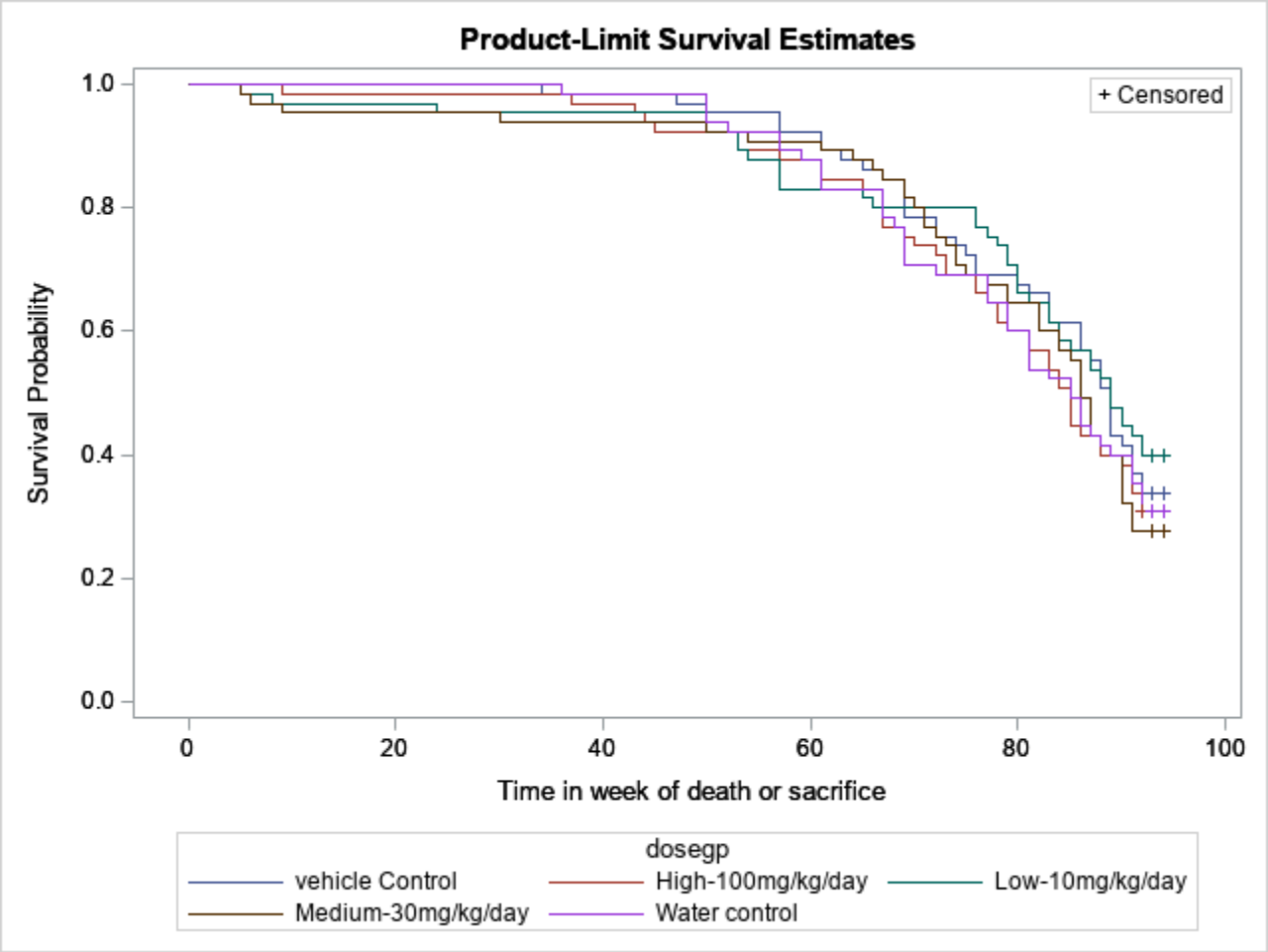


Figure 2B: Kaplan-Meier Survival Curves for
Female Hamsters



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