STATISTICAL ANALYSIS PLAN

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

Investigational Product: Complement 5a Receptor Antagonist CCX168 (INN/USAN avacopan)
Protocol Number: CL010_168

Sponsor:
ChemoCentryx, Inc.
Mountain View, CA 94043

Version Number: 2.0
Date: 28 Oct 2019

Original Protocol: 28 November 2016
Amendment 1.0: 21 June 2017
Amendment 2.0: 15 June 2018
Amendment 3.0: 06 December 2018
Amendment 4.0: 18 January 2019

SIGNATURE PAGE

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We, the undersigned, have reviewed and approve this Statistical Analysis Plan.

Signature | Date

[redacted] | 28-OCT-2019

Project Statistician

[redacted]

[redacted] | 28-OCT-2019

Therapeutic Lead Statistician

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Study Director
ChemoCentryx, Inc.

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Medical Monitor

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[redacted] Therapeutic Lead Statistician [redacted]	
[redacted] Study Director ChemoCentryx, Inc.	29 OCT 2019
[redacted] Medical Monitor [redacted]	28 Oct 2019

VERSION HISTORY

Version	Date	Description
1.0	15May2019	Original Version
2.0	28Oct2019	Updates to the following Sections: Section 3.1.1 – To clarify glucocorticoid use for purposes of assessing the primary endpoints is specific to treatment for AAV. Section 4.1.4 – Change the threshold for significant lack of compliance of study medication administration (CCX168/placebo) to <75% Section 6.4 – To specific additional summaries of Medical History by background therapy with rituximab or cyclophosphamide will also be produced Section 6.5.1 – To specify the addition of the time period 'End of Treatment to Week 60' for the summaries of non study-supplied glucocorticoid use Sections 7.1, 7.2, 7.3 – Clarify the stratification factor values as collected in the eCRFs will be used for all stratified efficacy analyses, subgroup analyses and summaries of baseline characteristics Section 7.3.1.1 – MMRM Analysis is incorrectly specified in the example SAS code and should mimic the analysis specified in 7.3.3.1 with exception of removing baseline from the model. Section 7.3.3.1 – To specify alternate matrix structure if convergence is not achieved with Toeplitz matrix structure and updates to example SAS code. Sections 7.3.1.1, 7.3.1.2, 7.3.1.3 – To remove references to 'change from baseline' for GTI AIS and CWS analyses since calculation of these outcome measures inherently incorporate 'change from baseline' Section 7.3.4.2 – To change the exploratory analysis for time to relapse from the first time point when BVAS of 0 was achieved will be based on the Adjudicators' assessment of BVAS=0 and relapse and not the Investigators' assessment, Section 7.3.4.2 – To specify Relapse during the 52 week treatment period Section 7.3.5.1 – Add reference to section 7.3.3.1 for

		MMRM analysis Section 8.2 – To further define the number of days in the randomized treatment period Section 8.4 – Additional laboratory parameters were added to the CTCAE summaries Section 10 – Specify occurrence of relapse, as assessed by the Adjudication Committee, was performed separately for the 52 week treatment period and during the follow-up period from week 52 to week 60 Appendix 15.1.4 – Added this section to describe reference data for EQ-5D-5L Crosswalk value for countries where reference data is not available Appendices 15.3, 15.4 and 15.5 – Added to pre-specify preferred terms for Adverse events potentially associated with liver injury, WBC count decrease and glucocorticoid related toxicity.

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LIST OF ABBREVIATIONS

AAV	ANCA-associated vasculitis
AC	Adjudication Committee
AE	adverse event
AIS	Aggregate Improvement Score
ALBIA	Addressable Laser Bead ImmunoAssay
ALT	alanine aminotransferase
ANCA	anti-neutrophil cytoplasmic antibody
AR(1)	Autoregressive(1)
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemistry
BP	blood pressure
BMI	body mass index
BUN	blood urea nitrogen
BVAS	Birmingham Vasculitis Activity Score
CPK	creatine phosphokinase
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CWS	Cumulative Worsening Score
DMC	Data Monitoring Committee
EDC	Electronic Data Capture system
ECG	electrocardiogram
EQ-5D-5L	EuroQOL-5D-5L
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELISA	enzyme linked immunosorbent assay
EULAR	European League Against Rheumatism
GPA	granulomatosis with polyangiitis (Wegener's)

GTI	Glucocorticoid Toxicity Index
HEENT	head, eyes, ears, nose, throat
IRT	interactive response technology
ITT	Intent-to-Treat
IV	intravenous(ly)
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
mg	milligram
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MCP-1	monocyte chemoattractant protein-1
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effects model for repeated measures
MPA	microscopic polyangiitis
MPO	myeloperoxidase
MRI	Magnetic Resonance Imaging
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	Per Protocol
PR3	proteinase-3
PRES	posterior reversible leukoencephalopathy syndrome
SAP	statistical analysis plan
SAE	serious adverse event
SD	standard deviation
SEM	standard error of the mean
SF-36 v2	Short Form-36 version 2
TB	tuberculosis
TEAE	treatment emergent adverse event

TESAE	treatment emergent serious adverse events
UACR	urinary albumin:creatinine ratio
VAS	visual analogue scale
VDI	Vasculitis Damage Index
WHO	World Health Organization

1 INTRODUCTION

The purpose of this document is to provide a description of the statistical methods and procedures to be implemented for the analysis of data from ChemoCentryx, Inc. Protocol CL010_168. This document is based on protocol amendment 4.0 (18JAN2019) and CRF version 7.7 (09OCT2019). If circumstances arise during the study such that more appropriate analytic procedures become available, the statistical analysis plan (SAP) may be revised. The statistical definitions and analytical methods described in this SAP supersede that in the protocol. Any revisions to the primary endpoint analyses and significant revisions to the secondary endpoint analyses will be made prior to the database freeze for the data in the double-blind treatment period through Week 52. Reasons for such revisions will be described in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is to evaluate the efficacy of CCX168 (avacopan) to induce and sustain remission in subjects with active anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), when used in combination with cyclophosphamide followed by azathioprine, or in combination with rituximab. Disease remission is defined as achieving a Birmingham Vasculitis Activity Score (BVAS) of zero (0) and not taking glucocorticoids for treatment of AAV within 4 weeks prior to Week 26. Sustained remission is defined as remission at Week 26 without relapse to Week 52 (BVAS of 0 and not taking glucocorticoids for treatment of AAV within 4 weeks prior to Week 52). A relapse between Week 26 and 52 would disqualify a subject from having a sustained remission.

2.1.2 Secondary Objectives

1. Evaluation of the glucocorticoid-induced toxicity in the CCX168 plus rituximab or cyclophosphamide/azathioprine group, compared to prednisone plus rituximab or cyclophosphamide/azathioprine, based on the Glucocorticoid Toxicity Index (GTI);
2. Evaluation of rapidity of response in the CCX168 plus rituximab or cyclophosphamide/azathioprine group, compared to prednisone plus rituximab or cyclophosphamide/azathioprine, based on remission (BVAS of 0) at Week 4. (BVAS remission at Week 4 is defined as BVAS = 0, regardless of receipt of glucocorticoids);
3. Evaluation of the safety of CCX168 plus rituximab or cyclophosphamide/azathioprine, compared to prednisone plus rituximab or cyclophosphamide/azathioprine based on the incidence of serious and non-serious adverse events, adverse events of interest, and changes in vital signs, clinical laboratory tests, and electrocardiograms (ECGs) in these subjects;

4. Assessment of health-related quality-of-life changes based on the Medical Outcomes Survey Short Form-36 version 2 (SF-36 v2) and EuroQOL-5D-5L (EQ-5D-5L) with CCX168 plus rituximab or cyclophosphamide/azathioprine, compared to prednisone plus rituximab or cyclophosphamide/azathioprine;
5. Assessment of changes in parameters of renal disease including estimated glomerular filtration rate (eGFR), albuminuria, and urinary excretion of monocyte chemoattractant protein-1 (MCP-1) in subjects with active renal disease at baseline with CCX168 plus rituximab or cyclophosphamide/azathioprine, compared to prednisone plus rituximab or cyclophosphamide/azathioprine;
6. Assessment of changes in cumulative organ damage based on the Vasculitis Damage Index (VDI) with CCX168 plus rituximab or cyclophosphamide/azathioprine, compared to prednisone plus rituximab or cyclophosphamide/azathioprine;
7. Assessment of changes in markers of pharmacodynamics in plasma and urine with CCX168 plus rituximab or cyclophosphamide/azathioprine, compared to prednisone plus rituximab or cyclophosphamide/azathioprine;
8. Evaluation of the pharmacokinetic profile of CCX168 in subjects with AAV.

2.2 Study Design

2.2.1 Overview

This is a Phase 3, randomized, double-blind, double-dummy, active-controlled, multicenter international clinical trial. Approximately 300 subjects with AAV who fulfill all the eligibility criteria will be enrolled into the study from study sites in North America, Europe, Australia, New Zealand, and Japan.

All subjects have scheduled visits during the screening period, on Day 1 and at Weeks 1, 2, 3, 4, 7, 10, 13, 16, 20, 23, 26, 29, 32, 35, 39, 42, 45, 48, 52 (last treatment visit with blinded study drug), and 60 (follow up). The study schema is provided below. For additional details regarding the study design, please refer to the protocol.

2.2.2 Randomization and Blinding

Subjects will be randomized in a 1:1 ratio to the following study treatments:

Group A: CCX168-matching placebo plus cyclophosphamide/azathioprine or rituximab plus a full starting dose of prednisone (Placebo + Standard of Care) or

Group B: CCX168 plus cyclophosphamide/azathioprine or rituximab plus prednisone-matching placebo (Avacopan + Standard of Care).

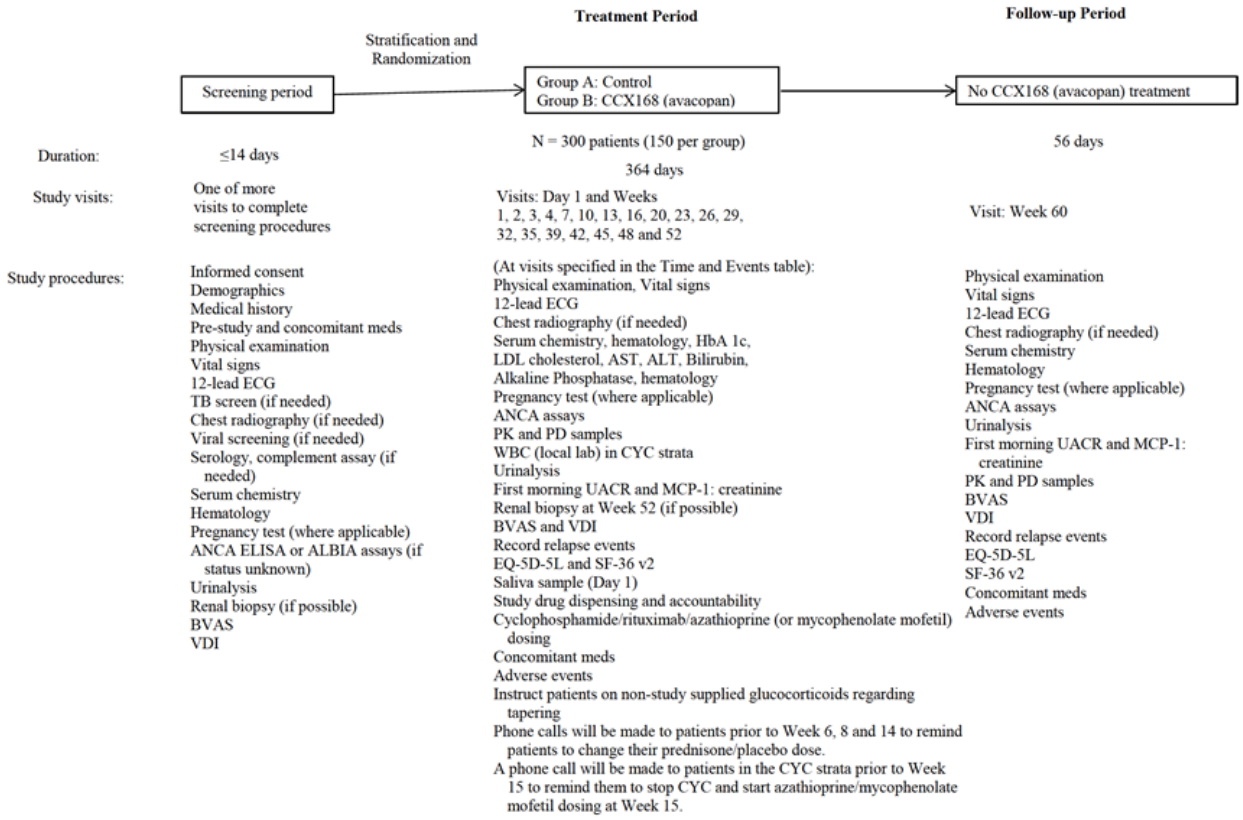
The treatment period is 52 weeks (364 days), followed by an 8-week (56 days) follow-up.

Randomization will be stratified by the following factors:

- One of the following treatment regimens:
  a. IV rituximab
  b. IV cyclophosphamide followed by oral azathioprine
  c. Oral cyclophosphamide followed by oral azathioprine

- Positive test for proteinase-3 (PR3) vs. myeloperoxidase (MPO) ANCA at diagnosis
- Newly-diagnosed vs. relapsing disease (AAV)

STUDY SCHEMA



Randomization will be performed centrally via an interactive response technology (IRT) system and minimization algorithm, using the stratification factors. In order to protect the blinding, the randomization schedule will not be accessible to study personnel who have contact with study centers or who are involved in data management and analysis prior to database freeze.

2.2.3 Up to 14-Day Screening Period

The screening period will be kept as short as possible in order not to delay initiation of treatment and must not exceed 14 days. Screening evaluations will be performed to determine subject eligibility for study. Eligible subects must be ANCA-positive (having tested positive for antibodies to PR3 or MPO by ELISA or ALBIA, either at the time of enrollment or in the past), and must have at least one "major" item, or at least 3 minor items, or at least the two renal items of proteinuria and hematuria in the BVAS. Care must be taken to ensure that the renal items are due to vasculitis activity and not other factors such as menses or cyclophosphamide-related cystitis. If a subject has "other" items, not specified in the BVAS, these need to be discussed with the Medical Monitor before enrollment.

After all screening procedures have been completed, and the subject satisfies all eligibility criteria, the study schedule will be discussed with the subject and the schedule will be provided to the subject to ensure compliance with the study visits.

2.2.4 52-Week Double-blind Treatment Period

Eligible subjects will visit the study center on Day 1, after an overnight fast of at least 9 hours, for physical examination and vital signs, serum chemistry tests (including HbA1c and LDL cholesterol), hematology tests, serum pregnancy test (in women of childbearing potential), urinalysis (including hematuria, urinary albumin:creatinine ratio [UACR], and MCP-1:creatinine ratio assessment), eGFR, ANCA measurement (anti-PR3 and anti-MPO ELISA), SF-36 v2 and EQ-5D-5L assessment, Glucocorticoid Toxicity Index (GTI) baseline assessment, baseline pharmacokinetic (PK) and pharmacodynamic (PD) blood sample collection, saliva sample collection, stratification and randomization. Medication will be administered (IV) and dispensed (for oral medications). The subjects will take the first dose of CCX168 or placebo, and prednisone or placebo while at the study center. The selection of IV cyclophosphamide, oral cyclophosphamide, or IV rituximab is at the discretion of the Investigator. For study centers where enrollment of adolescents (12 to 17 years old) is approved, CCX168 or placebo dosing will initially be given based on body weight at screening and the dose will be adjusted based on CCX168 plasma levels on Day 1 (refer to the Section 3.3 of the protocol for more details).

Twice daily dosing of CCX168 or placebo will continue for 364 days. At post-Day 1 study visits, study medication will be administered according to the protocol schedule, and blood and urine samples will be collected for safety and efficacy and PK/PD measurements. BVAS assessments will be made at Screening and Weeks 4, 10, 16, 26, 39, 52, and 60. VDI assessments will be made at Screening and Weeks 26, 52, and 60. SF-36 v2 and EQ-5D-5L will be completed on Day 1 and Weeks 4, 10, 16, 26, 39, 52, and 60. GTI assessments will be done on Day 1 and at Weeks 13 and 26. Renal biopsy for histology at Week 52 is optional. Physical examinations, vital sign assessments, and ECG measurements will be performed throughout the study. Concomitant medication and adverse event assessments will be made at every study visit.

2.2.5 8-Week Follow-up Period at Study End

After completion of the 52-week double-blind treatment period, subjects will be followed up for an additional 8 weeks during which the blinding will be maintained. Subjects will be discharged from the study when all the Study Week 60 visit procedures have been completed. Each subject's condition will be evaluated by the Investigator at the end of the clinical trial (Week 60) and appropriate standard of care medical treatment will be provided to all subjects as needed.

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

3.1.1 Primary Efficacy Endpoints

1. The proportion of subjects achieving disease remission at Week 26.

   Disease remission at Week 26 is defined as:

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

2. The proportion of subjects achieving sustained disease remission at Week 52.

   Sustained remission at Week 52 is defined as:

   - Disease remission at Week 26 defined as a BVAS score of 0 as determined by the AC
   - No disease relapse between Week 26 and Week 52 as determined by the AC AND
   - 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 proportion of subjects achieving sustained disease remission at Week 52 will be based on assessment by the blinded AC that disease remission has been achieved at Week 26, that disease remission has been achieved at Week 52, and that no relapse has occurred between Week 26 and Week 52. Relapse is defined in section 3.1.2.

Glucocorticoid use for purposes of assessing the primary endpoints are based on absence of glucocorticoid use, both study supplied and non-study supplied, for treatment of AAV for the 4 weeks prior to the BVAS assessment at Week 26 and Week 52. Note that subjects are 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 will be classified as responders for purposes of assessment of the primary endpoints if all other requirements for response are met.

3.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

1. Glucocorticoid-induced toxicity as measured at specified timepoints over the first 26 weeks in the glucocorticoid toxicity index (GTI). GTI assessments are performed on Day 1 and at Weeks 13 and 26. Both the Cumulative Worsening Score (CWS) and the Aggregate Improvement Score (AIS) will be analyzed (see section 7.3.1).
2. Early remission defined as a BVAS of 0 at Week 4, regardless of whether the subjects received glucocorticoids during this period of time. Early remission at Week 4 will be based on assessment by the blinded AC that disease remission has been achieved at Week 4 based on BVAS=0 at Week 4.
3. Change from baseline over 52 weeks in health-related quality-of-life as measured by the domains and component scores of the SF-36 v2 and EQ-5D-5L visual analogue scale (VAS) and index. SF-36 v2 and EQ-5D-5L are completed on Day 1 and Weeks 4, 10, 16, 26, 39, and 52.
4. Proportion of subjects and time to experiencing a relapse after achieving remission at Week 26, as assessed by the blinded AC.

   Relapse is assessed by the AC and is defined as active disease, after previously achieving remission at Week 26 in the study, that involves (1) one or more major items in the BVAS, (2) three or more minor items in the BVAS, or (3) one or two minor items in the BVAS recorded at two consecutive study visits. See Section 3.1.1 for a description of determination of disease remission at Week 26.
5. In subjects with renal disease at baseline (based on the BVAS renal component; see section 4.1.5), the change in absolute eGFR from baseline over 52 weeks including the following timepoints: Weeks 1, 2, 3, 4, 7, 10, 13, 16, 20, 26, 32, 39, 45, and 52.
6. In subjects with renal disease at baseline (based in the BVAS renal component, including albuminuria; see section 4.1.5), the percent change in UACR from baseline over 52 weeks including the following timepoints: Weeks 1, 2, 4, 13, 26, 39, and 52.
7. In subjects with renal disease at baseline (based in the BVAS renal component; see section 4.1.5), the percent change in urinary MCP-1:creatinine ratio from baseline over 52 weeks including the following timepoints: Weeks 1, 2, 4, 13, 26, 39, and 52.
8. Change in Vasculitis Damage Index (VDI) from baseline over 52 weeks including the following timepoints: Weeks 26 and 52.

3.1.3 Efficacy Assessment

The BVAS version 3 will be used in this study and has been previously validated (Mukhtyar et al, 2009; Suppiah et al, 2011). BVAS provides a measure of current disease activity.

The Vasculitis Damage Index (VDI) was developed by Exley et al, 1997 and is for recording organ damage that has occurred in subjects since the onset of vasculitis. The VDI provides a measure of cumulative organ damage since the onset of the disease.

The GTI was developed to quantify toxicity associated with glucocorticoid use (Miloslavsky et al, 2016). The GTI version 2.0 will be used to quantify changes in glucocorticoid toxicity. Please refer to section 7.3.1 and Appendix, Section 15.1.3 for more detail.

Calculation of eGFR will be based on serum creatinine (Modification of Diet in Renal Disease [MDRD] equation for adults, and modified Schwartz equation for adolescents).

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

Japan unique formula for eGFR in Japanese adults is defined by Protocol Addendum Japan-specific as follows:

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

BVAS and VDI data are assessed and documented by the study investigators. The assessments performed by the study investigators will then be adjudicated by an Adjudication Committee (AC) comprised of experts in the field of vasculitis. The members of the AC are blinded to individual subject treatment assignment and their actions are governed by an adjudication charter. The adjudication charter specifies adjudications of the BVAS assessments over the course of the study, as well as whether BVAS=0 has been achieved at Week 4, remission has been achieved at Week 26, and sustained remission has been achieved at Week 52. The AC also adjudicates all potential relapses. The adjudicated data will be used in the primary analyses.

3.2 Safety Endpoints

3.2.1 Adverse Events

Safety endpoints include subject incidence of treatment-emergent serious adverse events, adverse events, and withdrawals due to adverse events.

An adverse event will be considered treatment-emergent (TEAE) if the start date of the event is on or after the date of administration of the first dose of study medication. All reported adverse events will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) (version 19.1).

The relationship of CCX168/placebo as well as the relationship of glucocorticoid use, cyclophosphamide, rituximab, and azathioprine or mycophenolate use to an adverse event will be determined by the Investigator. The sponsor will perform a safety analysis based on an aggregate analysis across the safety database as well as the assessment of individual cases of interest.

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires or prolongs hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or is an important and significant medical event that, based on appropriate medical judgment, may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the other outcomes defining serious.

In addition, certain safety endpoints of special interest including laboratory parameters and TEAEs will be presented by treatment group (see Section 8.3).

3.2.2 Safety Laboratory Evaluations

Safety endpoints include change from baseline and shifts from baseline in all safety laboratory parameters, including blood chemistry, hematology, and urinalysis. Visits to be listed and summarized include 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 (Follow-up).

Clinical safety laboratory assessments include 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 [LDH], aspartate aminotransferase [AST], alanine aminotransferase [ALT]), renal panel (blood urea nitrogen [BUN], creatinine), creatine phosphokinase (CPK), albumin, sodium, potassium, magnesium, bicarbonate, chloride, calcium, inorganic phosphorus, glucose, total protein, alkaline phosphatase, total cholesterol, uric acid, serum amylase, and serum lipase
- Hemoglobin A1c and LDL cholesterol (for use in the GTI)
- Urinalysis: At the central laboratory, nitrite, blood, and protein, will be tested. If positive, microscopy will be performed.

Laboratory assessments measured at the local laboratory include WBC counts prior to administration of cyclophosphamide or azathioprine for potential dose adjustments. Virology, serology, and complement are measured only at screening and may be measured at the local laboratory). Tuberculosis (TB) screen results will also be listed.

3.2.3 Vital Signs

Individual vital sign values including temperature, blood pressure and heart rate, and change from baseline will be calculated. Visits to be listed and summarized include Day 1, and Weeks 1, 2, 3, 4, 7, 10, 13, 16, 20, 26, 32, 39, 45, 52, and Week 60 (Follow-up).

3.2.4 Other Safety Assessments

3.2.4.1 ECG

ECG Interpretation (normal/abnormal), clinical significance (yes/no) and description of abnormality will be listed. Visits to be listed include Screening and Weeks 2, 7, 13, 26, 39, 52, and 60 (Follow-up).

3.2.4.2 Physical Exam

A complete physical examination (including evaluation of general appearance/mental status, HEENT [head, eyes, ears, nose, throat], and the following body systems: dermatologic, cardiovascular, respiratory, gastrointestinal, musculoskeletal and neurologic) for safety, BVAS, GTI, and VDI assessments will be performed at Screening, Day 1, Weeks 1, 2, 4, 10, 13, 16, 26,

39, 52, and 60 (Follow-up). Physical examinations are to be sufficiently comprehensive to include ALL components of the BVAS, VDI, and GTI. Any new or worsening findings upon physical examination are to be recorded as adverse events, and also captured in the BVAS, VDI, and GTI, as appropriate. Body weight is to be measured as part of the physical examinations. Height is to be recorded at screening only, except for adolescents (12-17 years old) in whom height is also to be included as part of all physical examinations. BMI will be calculated from the body weight and height measurements. Abnormalities in physical examination, body weight, height, and vital signs will be listed.

3.3 Pharmacokinetic Assessments

Concentrations of CCX168 (and metabolites) will be determined in plasma from samples obtained on Day 1, and Weeks 1, 2, 4, 7, 13, 26, 39, and 52. The samples on Day 1 will be collected prior to the first dose of CCX168/placebo on that day. Only for subjects 12 to 17 years of age, samples will also be taken at hours 0.5, 1, 2, 3, 4, and 6 following the first dose of CCX168/placebo on Day 1. The blood samples collected on the other study days do not need to be collected prior to the CCX168/placebo dose on those days. However, the date and time of the last dose of CCX168/placebo prior to the sample collections must be recorded in the EDC system. Population PK analysis will be performed based on the CCX168 and metabolite plasma concentrations.

Total plasma concentrations of CCX168 (and metabolites) will be determined using validated analytical methods. These plasma samples may also be used to measure cytokines, complement fragments, or other markers associated with AAV.

CCX168 (and metabolite) plasma concentration results will be used to calculate trough plasma concentrations (C_{min}) over the course of the clinical trial. If sufficient data are available, population PK analyses may also be performed to determine PK parameters for CCX168 and significant metabolites.

The C_{max}, T_{max}, and AUC_{0-6} will be determined for subjects 12 to 17 years old based on CCX168 and metabolite plasma concentration data on Day 1.

3.4 Pharmacodynamic Assessments

The following PD endpoints may be assessed if the PD analytes are measured:

1. Change and percent change from baseline in plasma biomarkers including, but not limited to, cystatin C, complement fragments, inflammatory chemokine and cytokine levels. The cystatin C levels may be used in calculating eGFR changes from baseline using the following equation:

   $eGFR_{cys}$ (mL/min/1.73 m^2) = 127.7 x (cystatin C in mg/L)$^{-1.17}$ x (Age)$^{-0.13}$ x (0.91 if female) x (1.06 if African-American/Black)

2. Change and percent change from baseline in urine biomarkers including, but not limited too, renal injury and inflammation markers (e.g., KIM-1 and NGAL), soluble CD163, complement fragments, inflammatory chemokine and cytokine levels;
3. Change from baseline in CBC count (especially WBCs, neutrophils, and lymphocytes) and lymphocyte subset counts including B cells, T cells, and natural killer cells;

4. Change from baseline in blood cell gene expressions such as neutrophil functional status markers.

The effect of polymorphism in genetic markers such as *HLA DPB1*0401*, *SERPINA1*, *PRTN3*, and *HLA-DQ*, as well as C5aR polymorphism may also be investigated.

4 STATISTICAL METHODOLOGY

4.1 Analysis Populations

4.1.1 Randomized Population

The Randomized Population will include all subjects who have provided written informed consent and are randomized in the study.

4.1.2 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will include all subjects who are randomized and have received at least one dose of study drug.

4.1.3 Safety Population

The Safety Population will include all subjects who are randomized and have received at least one dose of study drug; the Safety Population is identical to the ITT population.

4.1.4 Per Protocol Population

The Per Protocol (PP) Population will include all of the subjects in the ITT population who were compliant with taking CCX168/placebo and who did not have major protocol deviations that might significantly affect the interpretation of the study results.

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

- Subjects with significant protocol deviations regarding inclusion and exclusion criteria that may impact evaluation of the primary endpoints (see section 6.2).
- Subjects with significant lack of compliance of study medication administration (CCX168/placebo) defined as:
  - For the Week 26 primary endpoint: All subjects who were <75% compliant with taking CCX168/placebo from Day 1 through Week 26 based on study medication accountability records;
  - For the Week 52 primary endpoint: All subjects who were <75% compliant with taking CCX168/placebo from Day 1 through Week 52 based on study medication accountability records.
- Subjects administered non-allowed medications defined as:
  - For the Week 26 primary endpoint: All subjects who had received rituximab or cyclophosphamide, or a clinically significant dose of mycophenolate (except if used

instead of azathioprine per protocol), methotrexate, anti-TNF treatment, abatacept, alemtuzumab, belimumab, tocilizumab, eculizumab, or other experimental or immunosuppressive drugs other than protocol-specified use between Day 1 and Week 26;

  - For the Week 52 primary endpoint: In addition to those for the Week 26 primary endpoint, all subjects who had rituximab or cyclophosphamide, or a clinically significant dose of mycophenolate (except if used instead of azathioprine per protocol), methotrexate, anti-TNF treatment, abatacept, alemtuzumab, belimumab, tocilizumab, eculizumab, or other experimental or immunosuppressive drugs between Week 26 and 52 that was not associated with a relapse event.

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

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

Subjects who need to be taken into account for the PP population will be identified and documented prior to the database freeze and prior to unblinding of the database for the analysis of the primary endpoints.

For the analysis of the primary efficacy endpoints in the PP population, subjects with important deviations regarding inclusion criteria, e.g., no clear evidence of anti-PR3 or anti-MPO AAV at study entry, and subjects with missing Week 26 data will be excluded as a whole from the PP population. For lack of compliance and for non-allowed medications, non-responder imputation will be applied, i.e., not achieving remission at Week 26 and/or not achieving sustained remission at Week 52. Exploratory sensitivity analyses may be performed using other methodologies, e.g., total exclusion of subjects with major deviations from the study population.

Subjects who have received glucocorticoids at doses higher than those provided in the protocol guidance will be assessed through sensitivity analyses in the ITT population (see section 7.2.2).

4.1.5 Subjects with Renal Disease at Baseline

Since renal disease is one of the most important manifestations of AAV, most endpoints will be analyzed in the subgroup of subjects with renal disease at baseline. This is defined as subjects who have at least one of the renal components of the BVAS at the Screening visit:

- Hypertension
- Proteinuria >1+ or >0.2 g/g creatinine

- Hematuria ≥10 RBCs/hpf
- Elevated serum creatinine (≥125 μmol/L)
- Rise in serum creatinine >30% or fall in creatinine clearance >25% from previous assessment.

Whether a subject has renal disease will be based on the Investigators' assessment of BVAS at the Screening visit of this study.

For the endpoint of change from baseline in UACR, subjects must also have albuminuria at baseline, defined as UACR of at least 10 mg/g creatinine.

Subgroup analyses will also be performed in those subjects with no renal disease at baseline.

5 GENERAL CONSIDERATIONS FOR DATA ANALYSIS

5.1 General Statistical Considerations

The analysis of the efficacy endpoints will be conducted when all randomized subjects have completed at least the Week 52 study visit (section 8.6 of the protocol). The database will be frozen when all data through Week 52 have been cleaned and verified. The Week 52 analysis is the primary analysis of the study. The data collected in the 8-week follow-up period (between the end of the treatment period at Study Week 52 and the end of the follow-up period at Study Week 60) will be described in the follow-up analysis. A final database lock will take place after all the follow-up data have been cleaned and verified. The follow-up analysis will not affect the primary efficacy analysis which is based on the Week 52 BVAS assessments. All study results will be included in a single Clinical Study Report.

Data will be summarized descriptively by treatment group. For continuous variables, numbers, means, medians, ranges, standard deviations, and standard error of means will be calculated. Geometric means will be calculated for UACR and urinary MCP-1:creatinine ratio, and other data that are not normally distributed. Frequency counts and percentages will be presented for categorical variables. Listings of raw and derived data will be included as part of an appendix to the Clinical Study Report (CSR).

In analysis tables and listings, the two treatment groups will be referred to as

- '**Prednisone + Standard of Care**', referenced in the protocol as Group A: CCX168-matching placebo plus cyclophosphamide/azathioprine or rituximab plus a full starting dose of prednisone
- '**Avacopan + Standard of Care'**, referenced in the protocol as Group B: CCX168 plus cyclophosphamide/azathioprine or rituximab plus prednisone-matched placebo

5.2 Study Day/Study Week

Study day or analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before will be Day -1. There will be no Day 0. Study week will be calculated in 7 day intervals from study Day 1.

The 4-week glucocorticoid free periods prior to Week 26 and Week 52 will be calculated from the actual dates of the Week 26 and Week 52 visits. This is important for measurement of BVAS remission endpoints.

5.3 Baseline Definition

Baseline is defined as the last value prior to start of dosing with study medication (typically the Day 1 pre-dose value). For ANCA positivity, BVAS, and VDI, baseline will be taken from the Screening visit. However, if the ANCA levels were not measured at the Screening visit but instead at the Day 1 visit, these Day 1 measurements may be used to assess ANCA status, if measured prior to administration of any study medication. In addition, if the BVAS and VDI were not completed at the Screening visit, but at the Day 1 visit and prior to administration of any study medication, these may be used in the data analyses.

5.4 Assessment Window

Scheduled visits will be assigned to analysis visits as recorded in the electronic data capture (EDC) system. If a scheduled visit is not available, unscheduled and early termination visits will be assigned to analysis visits using analysis visit windows based on the actual date the assessment took place. The start day of the analysis window will be calculated as the midpoint between the scheduled assessment and previously scheduled assessment for that parameter. The end day of the analysis window will be calculated as the midpoint between the scheduled assessment and the next scheduled assessment for that parameter. Where multiple measurements for a particular parameter appear within an analysis window, the scheduled visit will be used. If no scheduled visit appears in the analysis window, the result closest to the target day will be used. If equidistant and both are unscheduled and/or early termination visits, the later result will be used for the summary measure.

Though all measures may not be used in data summaries (e.g., two lab measures within the same analysis visit window), all measurements appear in the datasets and listings. For subjects where the event date is missing, the study day and analysis window will also be missing. See Table 1 below for an example of analysis windows.

Table 1. Analysis Window Example for SF-36

Analysis Window	Start Day	End Day	Target Day
Baseline		1	1
Day 1	1	1	1
Week 4	2	42	29
Week 10	43	92	71
Week 16	93	148	113
Week 26	149	228	183
Week 39	229	319	274
Week 52	320	420	365
Week 60 (Follow-up)	421	Last Day in double blind follow-up	NA

Note: Baseline is defined as the last value prior to start of dosing with study medication (typically the Day 1 pre-dose value). For BVAS and VDI, baseline will be taken from the Screening visit.

5.5 Handling of Missing Data

Dates will be printed in ISO 8601 date format (YYYY-MM-DD). If only year and month are available, date will be displayed as YYYY-MM. If only year, then just YYYY. Dates that are missing because they are not applicable for the subjects are output as "NA", unless otherwise specified.

For the primary endpoints, missing data at Week 26 and Week 52 will be imputed as not achieving remission (Week 26) or sustained remission (Week 52), respectively, for the ITT population analyses. No imputation will be performed for other time points.

No imputation will be performed for missing safety endpoints, including safety laboratory values, vital signs, electrocardiograms, etc.

Adverse events and prior/concomitant medications/procedures with incomplete start or stop dates will be imputed according to the rules stated in Section 15.2.

5.6 Other Data Handling Approaches

For continuous variables, the estimated mean and median for a set of values will be printed out to one more decimal place than the individual units of measurement, and the standard deviation will be printed out to 1 additional place. P-values will be given with 4 decimals (i.e., 0.xxxx). When a p-value is less than 0.0001, '<0.0001' will be printed.

All fractional numeric values will be printed with a zero to the left of the decimal point (e.g., 0.12, 0.3 etc.). Percentage values will be printed with 1 digit to the right of the decimal point (e.g., 52.3%, 8.9% etc.).

6 ANALYSIS OF DISPOSITION AND SUBJECT CHARACTERISTICS

6.1 Disposition and Analysis Populations

The number of subjects who were screened, who screen failed (by reason), who were randomized, who completed Week 26, Week 52, completed the study (Week 60), who withdrew early from the study, along with the reasons for withdrawal, and who prematurely discontinued blinded study drug, along with the reasons for discontinuation, will be presented by treatment group. These data will also be presented in a flow diagram in the CSR.

6.2 Protocol Deviations

Significant protocol deviations, i.e., those pertaining to GCP violations and those that may affect the efficacy evaluation, will be captured in the Study Management System as CSR Reportable deviations. These significant deviations will be listed and summarized by category. These deviations will be reviewed prior to database freeze to determine the potential impact on the interpretation of the efficacy outcomes. The effect of major protocol deviations will be assessed by conducting per-protocol analyses (see section 4.1.4). This will be determined and documented prior to unblinding the study for the Week 52 primary analysis. Any protocol deviations identified during the follow-up period will be included in the CSR.

6.3 Demographics and Baseline Characteristics

All subject baseline characteristics and demographic data, i.e., age, gender, race, ethnicity, weight, height, body mass index, anti-PR3 and anti-MPO antibody status, AAV type: granulomatosis with polyangiitis (GPA) vs. microscopic polyangiitis (MPA), newly diagnosed vs. relapsing disease, IV cyclophosphamide vs. oral cyclophosphamide vs. IV rituximab use, age at diagnosis of AAV, vasculitis disease duration (from time of diagnosis), renal disease at baseline, BVAS, VDI, SF-36 v2, EQ-5D-5L, eGFR, hematuria status, UACR, urinary

MCP-1:creatinine ratio, geographic region (North America vs. Europe, New Zealand and Australia vs. Japan) will be listed and summarized by treatment group.

Glomerular histopathology (if biopsy was taken) will be collected in a standardized histology CRF. Baseline and any follow-up data will be listed and summarized by treatment group. If sufficient data are available, the relationship between various categories of baseline renal disease based on histology and BVAS outcome will be examined.

6.4 Medical History

Medical history terms will be coded using MedDRA (version 19.1) and will be listed and summarized by system organ class, preferred term and treatment group with counts and percentages. Disease burden at baseline, e.g., cardiovascular disease, pulmonary disease, and renal disease, will be compared between treatment groups, and the potential relationship between imbalances and adverse event profiles will be evaluated. Additional summaries by background therapy with rituximab or cyclophosphamide will also be produced.

6.5 Concomitant Medications

All prior and concomitant medications (including vasculitis medication) will be listed and summarized by Anatomic Therapeutic Chemistry (ATC) classification. The numbers and percentages of subjects taking prior and concomitant medications will be summarized by treatment group, ATC class, and preferred term for the randomized population. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (Sep 2016E B2).

Prior medications are defined as any medication taken prior to the first dose of study medication. Concomitant medications are defined as any medication taken on or after the first dose of study medication. A medication can be classified as both prior and concomitant if it started during the screening period and continued into the treatment period.

6.5.1 Glucocorticoid Use

6.5.1.1 Study Supplied Glucocorticoid Use

Subjects who are randomized to the control group are to receive oral prednisone according to a standardized tapering schedule over the course of the study (see section 12.6.1 of the study protocol).

The duration of dosing, overall percent compliance, and total dose of study supplied prednisone will be listed for each subject. The exposure as measured by study period, duration of exposure,

total dose, average daily dose, and overall percent compliance will be summarized by treatment group.

6.5.1.2 Non-Study Supplied Glucocorticoid Use

Extra glucocorticoids, i.e., those that are not supplied as study drug, were to be avoided as much as possible during the study. The protocol outlines scenarios for which non-study supplied glucocorticoid use was permitted, including treatment for subjects with severe AAV during the screening period, adrenal insufficiency or persistence, and worsening or relapse of AAV during the treatment period. Glucocorticoid use as pre-medication for rituximab infusion (typically 100 mg methylprednisolone, or equivalent) was allowed during the study, and is classified as non-study supplied. If a subject received glucocorticoids during the Screening period, the dose needed to be tapered to not more than 20 mg prednisone equivalent by Day 1 of the study. Furthermore, the glucocorticoid dose needed to be tapered to zero by Week 4 of the study.

Non-study supplied glucocorticoids will be listed by study period, type of glucocorticoid, route of delivery (IV or oral), dose, unit, and frequency of administration, total prednisone-equivalent dose, start and end dates, and indication for administration. Glucocorticoid use will be presented as milligram (mg) prednisone equivalent (see Table 2 for conversion factors).

Table 2. Glucocorticoid Conversion Factors to Prednisone-Equivalent Dose

Preferred Term	Conversion
Prednisolone	1 mg prednisolone = 1 mg prednisone
Methylprednisolone Methylprednisolone Sodium Succinate	1 mg methylprednisolone = 1.25 mg prednisone
Hydrocortisone Hydrocortisone Sodium Succinate Hydrocortisone Sodium Phosphate	4 mg hydrocortisone = 1 mg prednisone
Cortisone	5 mg Cortisone = 1 mg prednisone
Betamethasone Betamethasone Sodium Phosphate	0.75 mg Betamethasone = 5.6 mg prednisone

For each subject, the non-study supplied glucocorticoid use will be listed for each of the following periods: Screening (Days -14 to -1), Days 1 through 29, Days 30 through 183, Four Weeks Prior to the Week 26 Endpoint, Days 184 – End of Treatment (Day 365 visit or time of dropout), Four Weeks Prior to the Week 52 Endpoint, Days 1 through 183, Days 1 through End of Treatment, and End of Treatment through Week 60.

Total non-study supplied glucocorticoid use will be summarized by treatment group for the following study periods: Screening (Days -14 to -1), Days 1 through 29, Days 30 through 183, Four Weeks Prior to the Week 26 Endpoint, Days 184 – End of Treatment, Four Weeks Prior to the Week 52 Endpoint, Days 1 through 183, Days 1 through End of Treatment, and End of Treatment to Week 60.

6.5.1.3 Total Glucocorticoid Use

Total glucocorticoid use includes both study supplied and non-study supplied glucocorticoids, including rituximab pre-medication glucocorticoid use.

Total glucocorticoid use will be listed by study subject, by study day, by study supplied vs. non-study supplied glucocorticoid use (by route). To facilitate review, by subject graphs may be generated showing the cumulative amount of glucocorticoid use (separated by study-supplied and non-study supplied glucocorticoids) over the course of the study. These graphs will be presented by Week 26 BVAS remitters vs. non-remitters and Week 52 sustained remitters vs. non-remitters.

The number and percentage of subjects who used prior glucocorticoids and glucocorticoids during the study will be summarized. Total glucocorticoid use will be summarized by treatment group for the following study periods: Screening (Days -14 to -1), Days 1 through 29, Days 30 through 183, Four Weeks Prior to the Week 26 Endpoint, Days 184 – End of Treatment, Four Weeks Prior to the Week 52 Endpoint, Days 1 through 183, Days 1 through End of Treatment, and End of Treatment to Week 60 (only for Non-Study supplied).

6.5.2 Other Non-Study Supplied Treatments for AAV

Non-study specified or supplied treatments for AAV (other than glucocorticoids) will be listed and summarized by treatment group. These treatments include non-protocol allowed rituximab, cyclophosphamide, mycophenolate (except if used instead of azathioprine per protocol), methotrexate, anti-TNF treatment, abatacept, alemtuzumab, IVIg, belimumab, tocilizumab, eculizumab, or other experimental or immunosuppressive drugs.

7 ANALYSIS OF EFFICACY

The overall efficacy hypothesis in this study is that CCX168 treatment will be effective in treatment of subjects with AAV based on inducing remission, and then sustaining remission without requiring chronic oral prednisone treatment at the levels currently used in Standard of Care treatment regimens.

7.1 Covariates and Subgroups

The analysis of the efficacy endpoints may be adjusted by the following variables in the form of covariate analysis and/or subgroup analysis:

Stratification factors [1]:

- Subjects receiving IV rituximab background therapy
- Subjects receiving IV or oral cyclophosphamide therapy [2]
- Subjects with PR3 ANCA positivity
- Subjects with MPO ANCA positivity
- Subjects with newly diagnosed AAV
- Subjects with relapsed AAV

[1] The stratification factor values as collected in the electronic case report forms (eCRFs) will be used for all stratified efficacy analyses, subgroup analyses and summaries of baseline characteristics.

[2] IV and oral cyclophosphamide use will be combined due to the low number of subjects in the oral cyclophosphamide group.

Subgroups and Covariates

- Subjects with renal disease at baseline (based on BVAS renal component)
- Subjects without active renal disease at baseline
- Subjects with Granulomatosis with Polyangititis (Wegener's)
- Subjects with Microscopic Polyangitis
- Subjects in North America
- Subjects in Europe and Rest of World except Japan
- Subjects in Europe
- Subjects in Japan
- Sex (Male, Female)
- BMI (<30, ≥30 kg/m^2) at baseline
- Age at diagnosis of AAV (≤50, >50 years old)
- Duration of AAV (<1 year, ≥1 year) at baseline
- Subject's age at baseline (12-17, 18-50, 51-64, 65-74, ≥75 years old), race (Asian, Black/African American, White/Caucasian, Other), and ethnicity (Hispanic, Non-hispanic, Unknown/Not reported)
- Baseline BVAS (<15, ≥15)
- Baseline VDI (0, >0)
- Baseline eGFR (<30, 30-59, >59 mL/min/1.73 m^2)
- Baseline hematuria (<10 RBCs/hpf, ≥10 RBCs/hpf)
- Baseline UACR (<10 mg/g, 10-300 mg/g, >300 mg/g creatinine)
- Baseline urinary MCP-1:creatinine ratio (<median of all subjects in study, ≥median of all subjects in study)

7.2 Primary Efficacy Analysis

The primary efficacy endpoints are:

1. The proportion of subjects in disease remission at Week 26. The proportion of subjects achieving disease remission at Week 26 is defined as a BVAS score of 0 and not taking glucocorticoids for treatment of AAV within 4 weeks prior to Week 26. Achievement of this endpoint will be based on assessment by the blinded AC that disease remission has been

achieved at Week 26. The AC will assess remission based on BVAS=0 at Week 26, and having not received any glucocorticoids for treatment of AAV during the 4-week period preceding and including the Week 26 visit.

The number of subjects adjudicated as having achieved remission at Week 26 will be divided by the total number of subjects in the respective treatment group in the ITT or PP population.

- Subjects who discontinue the study prior to Week 26 will be assessed as not in remission for assessment of the endpoint for the ITT and PP analyses.
- Subjects who permanently discontinue treatment with blinded study drug prior to Week 26 for any reason, but who remain in the study will be assessed as remission or no remission based on adjudication for the ITT analysis. They will be assessed as not in remission for the Per Protocol Analysis if their compliance with taking study medication (CCX168/placebo) was <75% during the first 26 weeks of the study (see Section 4.1.4).
- Subjects with missing data at Week 26 will be assessed as no remission for the ITT but these subjects will be excluded from the PP analyses.

2. The proportion of subjects achieving sustained remission. The proportion of subjects achieving sustained disease remission at Week 52 is defined as remission at Week 26 without relapse to Week 52 (BVAS of 0 and not taking glucocorticoids for treatment of AAV within 4 weeks prior to Week 52). Achievement of this endpoint will be based on assessment by the blinded AC that disease remission has been achieved at Week 26, that disease remission has been achieved at Week 52, and that no relapse has occurred between Weeks 26 and Week 52. The proportion will be calculated as the number of subjects who achieved sustained remission divided by the total number of subjects in the respective treatment group in the ITT or PP population.

    - Subjects who discontinue the study prior to Week 52 will be assessed as not in sustained remission for assessment of this endpoint for the ITT and PP analyses.
    - Subjects who permanently discontinue treatment with blinded study drug prior to Week 52 for any reason, but who remain in the study, will be assessed as having achieved sustained remission or not having achieved sustained remission based on adjudication for the ITT analysis. They will be assessed as not achieving sustained remission for the Per Protocol Analysis if their compliance with taking study medication (CCX168/placebo) was <75% during the 52-week treatment period (see Section 4.1.4).
    - Subjects with missing data at Week 52 will be assessed as no sustained remission for the ITT but these subjects will be excluded from the PP analyses.

Statistical Hypothesis Testing and Procedure

For the two primary efficacy endpoints, the proportion of subjects achieving disease remission at Week 26 and sustained disease remission at Week 52, and the two-sided 95% confidence intervals for the difference in proportions (CCX168 minus control) will be estimated for the comparison between the CCX168 group and the control group. For both the non-inferiority and superiority tests, the 1-sided p-values will be presented. They will be compared to the 1-sided type-I error of 0.025 for statistical significance.

Confidence intervals for the stratified analysis will be calculated as follows:

Summary score estimate of the common difference in remission rates (Agresti 2013, p. 231) by using inverse-variance stratum weights and Miettinen-Nurminen (score) confidence limits for the common difference in remission rates will be provided for the stratified contingency tables at Weeks 26 and 52. Summary score test will be used for both non-inferiority and superiority test of the stratified analysis at Weeks 26 and 52. The stratification factors will come from the stratification values collected in the eCRFs. For unstratified analysis, the Wald confidence limits for the difference in remission rates at Weeks 26 and 52 will be calculated. The Wald test will be used for both non-inferiority and superiority test of the difference in remission rates at Weeks 26 and 52.

The Clopper–Pearson exact interval will be provided for single proportion data.

The following hypotheses will be tested for the first primary efficacy endpoint:

- The non-inferiority null hypothesis ($H1_0$) is that the CCX168 group is inferior to the control group when comparing the remission rate based on BVAS at Week 26.
- The non-inferiority alternative hypothesis ($H1_1$) is that the CCX168 group is not inferior to the control group when comparing the remission rate at Week 26.
- The superiority null hypothesis ($H2_0$) is that the CCX168 group is not different from the control group when comparing the remission rate at Week 26.
- The superiority alternative hypothesis ($H2_1$) is that the CCX168 group is superior to the control group when comparing the remission rate at Week 26.

The following hypotheses will be tested for the second primary efficacy endpoint:

- The non-inferiority null hypothesis ($H3_0$) is that the CCX168 group is inferior to the control group when comparing the sustained remission rate based on remission at Week 26 without relapse to Week 52.
- The non-inferiority alternative hypothesis ($H3_1$) is that the CCX168 group is not inferior to the control group when comparing the sustained remission rate based on remission at Week 26 without relapse to Week 52.
- The superiority null hypothesis ($H4_0$) is that the CCX168 group is not different from the control group when comparing the sustained remission rate based on remission at Week 26 without relapse to Week 52.
- The superiority alternative hypothesis ($H4_1$) is that the CCX168 group is superior to the control group when comparing the sustained remission rate at Week 26 without relapse to Week 52.

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

1. Test for non-inferiority ($H1_0$) of the CCX168 group compared to the control group regarding remission at Week 26; if the p-value for non-inferiority for the 1-sided test is < 0.025, proceed to step 2;

2. Test for non-inferiority ($H3_0$) of the CCX168 group compared to the control group regarding sustained remission at Week 52; if the p-value for non-inferiority for the 1-sided test is < 0.025, proceed to step 3;
3. Test for superiority ($H4_0$) of the CCX168 group compared to the control group regarding sustained remission at Week 52; if the p-value for superiority for the 1-sided test is < 0.025, proceed to step 4;
4. Test for superiority ($H2_0$) of the CCX168 group compared to the control group regarding remission at Week 26.

For the non-inferiority test of the first primary efficacy endpoint, if the lower bound of the 2-sided 95% confidence interval is greater than -0.20 (the non-inferiority margin) and the control group disease remission rate is at least 40% at Week 26 (if the observed rate of CCX168 is lower than that of the control group), the CCX168 group will be considered not inferior to the control group. For the superiority test, if the lower bound of the 2-sided 95% confidence interval is greater than 0.0, the CCX168 group will be considered superior to the control group in achieving the disease remission at Week 26.

In deriving the non-inferiority margin, the historical disease remission rate at Week 26 in the control group is based on a meta-analysis of 20 published studies in subjects treated with rituximab plus glucocorticoids or cyclophosphamide plus glucocorticoids. The lower bound of the 95% confidence interval for the remission rate was approximately 60%. The non-inferiority margin of -0.20 was selected to demonstrate that the CCX168 group retains at least 50% of the control group benefit.

For the second primary endpoint, the proportion of subjects in sustained remission at Week 52 (disease remission at Week 26 without relapse to Week 52, as adjudicated by the AC) and the two-sided 95% confidence interval for the difference in proportion (CCX168 minus control) will be estimated for the comparison between the CCX168 group and the control group. For the non-inferiority test of the second primary endpoint, if the lower bound of the 95% confidence interval is greater than -0.20 and the control group disease remission rate is at least 40% at Week 26 (if the observed rate of CCX168 is lower than that of the control group), the CCX168 group will be considered not inferior to the control group. For the superiority test, if the lower bound of the 95% confidence interval is greater than 0.0, the CCX168 group will be considered superior to the control group in achieving the disease remission at Week 26 and sustained to Week 52.

A successful study will be declared if (at minimum) non-inferiority is achieved for the CCX168 group vs. the control group for remission at Week 26.

```
*******************************************************************************
Note:  TRTN = randomized treatment group
              1 = Placebo + Standard of Care, 2 = Avacopan + Standard of Care
       RESP = Value of response variable (Y/N)
       TRTREG = Standard of Care Treatment Regimen
          *IV rituximab
          *Cyclophosphamide followed by oral azathioprine [1]
       ANCAPOS = ANCA Positivity:  PR3 vs MPO
       AAVSTAT = AAV Status:  Newly diagnosed vs. relapsing disease

[1] IV and Oral Cyclophosphamide use will be combined due to the low number of
subjects in the Oral Cyclophosphamide group
```

```
*******************************************************************************
```

The SAS code used to generate estimates and difference in proportions and 1-sided p-value for superiority will be similar to the following:

Stratified

```
proc freq data=efficacy;
    tables TRTREG*ANCAPOS*AAVSTAT*TRTN*RESP /
           COMMONRISKDIFF(test=SCORE)  alpha=0.05; *Summary Score CI and p-values;
run;
```

Non-Stratified

```
ods listing close;
proc freq data=efficacy;
    tables TRTN*RESP / riskdiff(EQUAL) alpha=0.05;
    ods output RiskDiffCol1=equalci;  *Estimate and CI for difference;
    ods output PdiffTest=equaltest;   *1-sided p-values for Superiority;
run;
ods listing;
```

The SAS code used to generate non-inferiority will be similar to the following:

Stratified

The common risk difference estimates and standard errors from the Stratified Analysis specified above will be used to calculate the non-inferiority p-value from the Z test.

Z=(Common Risk Difference estimates – (margin))/standard error

The non-inferiority test p-value will be 1-sided from the Z test above: Pr > Z. The margin is -20%.

Non-Stratified

```
ods listing close;
proc freq data=efficacy;
    tables TRTN*RESP/ riskdiff(noninf margin=0.2 norisks) alpha=0.025;
 ods output PdiffNoninf=noninf; *p-values for non-inferiority;
 run;
 ods listing;
```

Subjects who relapse after Week 26 and before Week 52 will be adjudicated as treatment failures for the sustained remission analysis at Week 52, per the Adjudication Charter. A relapse is defined as worsening of disease that involves at least one major item, or three or more minor items, or one or two minor items recorded at two consecutive visits in the BVAS, after having previously achieved remission (BVAS = 0) at Week 26 in the study. In all cases the decision of the Adjudication Committee supersedes other data.

7.2.1 Primary Analysis

The primary analysis will be based on the stratified analyses comparing the remission rates described above for the two primary efficacy endpoints for the ITT population. The stratification factors include the following:

1. Standard of Care Treatment Regimen:
    a. Rituximab
    b. Cyclophosphamide use (IV and oral cyclophosphamide use will be combined due to the low number of subjects in the oral cyclophosphamide group)
2. ANCA Positivity
    a. anti-proteinase 3 (PR3)
    b. anti-myeloperoxidase (MPO)
3. AAV Status
    a. Newly diagnosed
    b. Relapsing disease

The primary analyses are adjusted for the potential confounding effects from the stratification variables that were collected in the eCRFs. The overall adjusted results will be presented. The same hypothesis tests described for the primary analysis will be applied to the sensitivity analyses.

7.2.2 Sensitivity Analyses

7.2.2.1 Unstratified Analyses

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

7.2.2.2 Sensitivity Analyses for High Non-Study Supplied Glucocorticoid Use

Sensitivity analyses (stratified) will also be performed to assess the impact of non-study-supplied glucocorticoid use on the secondary 4-week efficacy endpoint (BVAS = 0 at Week 4), and the primary 26-week and 52-week efficacy endpoints for the ITT populations. Analyses will be based on adjudicated BVAS and relapse data:

1. For the BVAS = 0 at Week 4 endpoint:
    a. Subjects who used more than 900 mg prednisone equivalent within the first 4 weeks of the study will be considered not to have achieved the BVAS = 0 endpoint at Week 4 (BVAS=0 would be 'No' for these subjects and denominator would be the ITT population);
    b. Subjects who used more than 900 mg prednisone equivalent within the first 4 weeks of the study will be excluded from the analysis (denominator would be the ITT population minus subjects excluded from the analysis).

The rationale for selection of a 900-mg threshold is as follows: Pre-medication with glucocorticoids for IV rituximab use to avoid hypersensitivity reactions is common. The glucocorticoid dose typically used for this purpose is 100 mg methylprednisolone IV (i.e., 125 mg prednisone equivalent) for each of 4 IV rituximab doses given within the first 4 weeks of the study. This is the prednisone equivalent of 500 mg, i.e., 125 mg x 4. The protocol also allows (section 12.6.2.3) for tapering of oral glucocorticoids from ≤20 mg on Day 1 to zero by the end of 4 weeks. The equates to up to 400 mg prednisone equivalent dose over the first 4 weeks (see subject 101-003, for example). Therefore, the total prednisone equivalent dose over the first 4 weeks could be up to 900 mg, i.e., 500 mg for rituximab pre-medication plus 400 mg for oral glucocorticoid tapering over the first 4 weeks.

2. For the BVAS remission at Week 26 endpoint:
    a. Subjects who used more than 1460 mg prednisone equivalent within the first 26 weeks of the study will be considered not to have achieved the BVAS remission at Week 26 endpoint (Remission would be 'No' for these subjects and denominator would be the ITT population);
    b. Subjects who used more than 1460 mg prednisone equivalent within the first 26 weeks of the study will be excluded from the analysis (denominator would be the ITT population minus subjects excluded from the analysis).

    The rationale for selection of a 1460-mg threshold is as follows: As discussed in (1) above, up to 900 mg prednisone equivalent could be used within the first 4 weeks of the study. The protocol also allows for short bursts of low dose glucocorticoids to treat non-major manifestations of AAV (doses up to 20 mg for up to 14 days). Two such short bursts equate to 560 mg prednisone equivalent, i.e., 20 mg x 14 days x 2 bursts. Therefore, the total prednisone equivalent dose over the first 26 weeks could be up to 1460 mg in subjects who do not have major manifestations of AAV over the first 26 weeks of the study, i.e., 900 mg over the first 4 weeks plus 560 mg for two short bursts of glucocorticoids.

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

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

    Exploratory sensitivity analyses may be performed to evaluate alternative glucocorticoid thresholds for each of the Week 4, Week 26, and Week 52 endpoints.

7.2.2.3Alternative Endpoints

The following preplanned analyses based on BVAS=0 will be done:

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

Analyses for the alternative endpoints will be based on adjudicated BVAS data.

7.2.2.4Adjudicated vs Non-Adjudicated Results

The primary endpoint analyses will be based on the adjudicated BVAS remission at Week 26, and adjudicated BVAS sustained remission at Week 52 results. The secondary endpoint of BVAS = 0 at Week 4 will also be based on adjudicated Week 4 BVAS results.

Sensitivity analyses will be conducted on the Investigator-assessed BVAS data (non-adjudicated results) for the two primary endpoints, BVAS remission at Week 26 and BVAS sustained remission at Week 52, as well as the BVAS = 0 at Week 4 secondary endpoint.

7.2.2.5Analysis Excluding Japan

When the clinical trial was launched, Japan was not included. Japan was added later to the trial and therefore Japanese subjects were enrolled towards the end of the enrollment period. In order to evaluate the efficacy of the regions included at study initiation, a sensitivity analysis will be conducted for the two primary endpoints, BVAS remission at Week 26 and BVAS sustained remission at Week 52, as well as the BVAS = 0 at Week 4 secondary endpoint, excluding subjects enrolled in Japan.

7.2.3 Subgroup Analyses

For both primary efficacy endpoints, the proportion of subjects achieving adjudicated disease remission at Week 26 and proportion of subjects achieving adjudicated sustained remission at Week 52 will be presented by the following subgroups for the ITT population. No p-values will be provided, since the sample size will be small in several subgroups.

- Subjects receiving IV Rituximab background therapy
- Subjects receiving IV or Oral Cyclophosphamide therapy
- Subjects with PR3 ANCA positivity
- Subjects with MPO ANCA positivity
- Subjects with newly diagnosed AAV
- Subjects with relapsed AAV
- Subjects with renal disease at baseline (based on BVAS renal component)
- Subjects without active renal disease at baseline

- Subjects with Granulomatosis with Polyangititis (Wegener's)
- Subjects with Microscopic Polyangitis
- Subjects in North America
- Subjects in Europe and Rest of World except Japan
- Subjects in Europe
- Subjects in Japan
- Sex (Male, Female)
- BMI (<30, ≥30 kg/m^2)
- Age at diagnosis of AAV (≤50, >50 years old)
- Duration of AAV (<1 year, ≥1 year)
- Subject's age (12-17, 18-50, 51-64, 65-74, ≥75 years old), race (Asian, Black/African American, White/Caucasian, Other), and ethnicity (Hispanic, Non-hispanic, Unknown/Not reported)
- Baseline BVAS (<15, ≥15)
- Baseline VDI (0, >0)
- Baseline eGFR (<30, 30-59, >59 mL/min/1.73 m^2)
- Baseline hematuria (<10 RBCs/hpf, ≥10 RBCs/hpf)
- Baseline UACR (<10 mg/g, 10-300 mg/g, >300 mg/g creatinine)
- Baseline urinary MCP-1:creatinine ratio (<median of all subjects in study, ≥median of all subjects in study)

7.2.4 Per-Protocol Analyses

The same analyses as described for the Primary Analysis will also be conducted for the Per-Protocol population.

7.3 Secondary Efficacy Analyses

The secondary endpoints will be tested in parallel and nominal p-values will be provided.

7.3.1 Glucocorticoid Toxicity Index

7.3.1.1 Primary Analysis

Glucocorticoid toxicity will be analyzed by the Glucocorticoid Toxicity Index (GTI) version 2.0 (Ehlers et al, 2019a, Ehlers et al, 2019b), an instrument upgrade from the original GTI version 1.0 (Miloslawsky et al, 2017). The GTI 2.0 instrument uses two GTI scores: the Cumulative Worsening Score (CWS) and the Aggregate Improvement Score (AIS). These scores are referred to respectively as:

- The GTI-CWS

- The GTI-AIS

The two scores are outlined briefly below.

The Cumulative Worsening Score

The GTI-CWS serves as a lasting record of any glucocorticoid toxicity that occurs over the course of a trial. The 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. The GTI-CWS can only increase or remain the same over time. Thus, if an investigational agent is effective at decreasing glucocorticoid toxicity over time, the GTI-CWS will be lower in the investigational treatment arm.

The Aggregate Improvement Score

In contrast to the CWS, with the GTI-AIS, toxicities are removed if improvement occurs. Toxicities can also be added in the GTI-AIS if a new toxicity event occurs or if worsening in a specific item of toxicity compared to baseline occurs. The rationale for the GTI-AIS is that in a clinical trial in a disease in which patients are anticipated to have some glucocorticoid toxicity at baseline, the GTI-AIS is important in establishing that the new therapy is effective at diminishing any baseline glucocorticoid toxicity over time.

If an item of toxicity that is present at baseline or occurs during the trial resolves over the course of follow-up, then that improvement is reflected in a negative GTI-AIS for that item during that interval. If an investigational agent is effective at decreasing glucocorticoid toxicity over time, the GTI-AIS will decrease over the course of the trial in the investigational treatment arm.

The GTI domains and weights of individual items are shown in Section 15.1.3.

The primary analysis of total GTI-CWS and GTI-AIS at Week 13 and 26 will be performed in the ITT population using a mixed effects model for repeated measures (MMRM). Separate models for GTI-CWS and GTI-AIS will incorporate treatment group, visit, treatment-by-visit interaction and stratification factors as covariates. The stratification factors will come from the stratification values collected in the eCRFs. Subjects will be considered as repeated measure units over visits. Linear contrast from the model will be used to test the treatment difference at week 13 and 26 separately. Test p-values, point estimates and corresponding 95% confidence intervals of treatment difference will be provided at Week 13 and Week 26 separately for GTI-CWS and GTI-AIS.

In the MMRM model, missing data will not be imputed. This analysis is unbiased under the missing at random (MAR) assumption. A Toeplitz covariance matrix will be used to model the within-subject variance-covariance structure for the model errors. If the model does not converge using the Toeplitz covariance matrix, AR(1) covariance matrix will be used. If convergence is still not met, then compound symmetry (CS) will be used.

The code used to generate the MMRM analysis will be similar to the following:

```
*******************************************************************************
Note:  TRTN = randomized treatment group (numeric)
                1 = Placebo + Standard of Care, 2 = Avacopan + Standard of Care
       TRTREG = Standard of Care Treatment Regimen
               *IV rituximab
               *Cyclophosphamide followed by oral azathioprine [1]
```

```
       ANCAPOS = ANCA Positivity:  PR3 vs MPO
       AAVSTAT = AAV Status:  Newly diagnosed vs.relapsing disease
       VISITN = Visit Number       RESP = Value of continuous response variable
 [1] IV and Oral Cyclophosphamide use will be combined due to the low number of
subjects in the Oral Cyclophosphamide group
*******************************************************************************

    proc mixed data=MMRMDATA;
      class SUBJECT TRTN VISITN TRTREG ANCAPOS AATSTAT;
      model RESP = TRTN VISITN TRTN*VISITN TRTREG ANCAPOS AATSTAT / ddfm=kr;
      repeated VISITN/subject=SUBJECT type=TOEP;
      lsmeans TRTN*VISITN /cl diff=control("1");
   run;
```

If GTI data are not normally distributed, the GTI change will be classified into two categories, for example, > 0 vs ≤0. The generalized linear mixed model with logistic link function will be used to analyze the dichotomized GTI data. The linear contrast will be similar to the primary analysis.

7.3.1.2Secondary Analysis

Summary statistics including number, mean, standard deviation (SD), standard error of mean (SEM), minimum, median and maximum for individual components of the GTI, including Body Mass Index (BMI), glucose tolerance, blood pressure, lipids, steroid myopathy, skin toxicity, neuropsychiatric toxicity, and infection will be presented by treatment group for the ITT population.

The number and percentage of subjects with "specific list" items, including all subjects with at least one specific list item, as well as each specific list item (endocrine, gastrointestinal, musculoskeletal, and ocular manifestations of glucocorticoid use) will be summarized by timepoint and treatment group.

7.3.1.3Subgroup Analyses

Summary statistics including number, mean, standard deviation (SD), standard error of mean (SEM), minimum, median and maximum for GTI-CWS and GTI-AIS will be presented by treatment group at Week 13 and Week 26 for the following subgroups in the ITT population:

1. Subjects receiving IV Rituximab background therapy
2. Subjects receiving IV or Oral Cyclophosphamide therapy
3. Subjects with PR3 ANCA positivity
4. Subjects with MPO ANCA positivity
5. Subjects with newly diagnosed AAV
6. Subjects with relapsed AAV
7. Subjects with renal disease at baseline
8. Subjects without renal disease at baseline

9. Subjects with Granulomatosis with Polyangititis (Wegener's)
10. Subjects with Microscopic Polyangitis
11. Male Subjects
12. Female Subjects
13. Subjects in North America
14. Subjects in Europe and Rest of World excluding Japan
15. Subject in Europe
16. Subjects in Japan

7.3.1.4 Exploratory Analyses

Exploratory analyses may be conducted to evaluate the relationship between GTI CWS and GTI AIS and the glucocorticoid cumulative dose and average daily dose over the first 26 weeks of the study by treatment group.

7.3.2 Early Disease Remission

The proportion of subjects with early remission, defined as BVAS of 0 at Week 4, regardless of receiving glucocorticoids, will be presented by treatment group for the ITT population. Summary by subgroup will also be provided. Early remission data will be analyzed similarly to the primary endpoint analysis.

An exploratory analysis includes time to remission using the Kaplan-Meier estimate. For each subject, time to remission is defined as the time from first day of study medication dosing to the time when BVAS of 0 is achieved during the 52 week treatment period. For the subjects who did not achieve BVAS of 0, the subjects' time to remission is censored at last time of BVAS assessment during the treatment period. Log-rank test will be used to test the difference of time to remission in two treatment groups. The median time to remission and its associated 95% CI will be provided for each treatment group. The hazard ratio and its 95% CI will also be provided.

7.3.3 SF-36 v2 and EQ-5D-5L VAS and Index - Change from Baseline

7.3.3.1 Primary Analysis

The primary analysis of change from baseline over 52 weeks in the physical component score, mental component score, and eight domains of the SF-36 v2, and the visual analogue scale and index of the EQ-5D-5L will be performed in the ITT population using an MMRM with treatment group, visit, treatment-by-visit interaction, and randomization strata (IV rituximab, IV or oral cyclophosphamide, anti-PR3 or anti-MPO ANCA, and newly-diagnosed AAV or relapsed AAV) as factors, and baseline as covariate. Subjects will be considered as repeated measure units over visits. P-values, point estimates, and corresponding 95% confidence intervals will be estimated for the difference across 52 weeks using a simple contrast from the model. SF-36 v2 and EQ-5D-5L are computed at Baseline, Weeks 4, 10, 16, 26, 39, and 52 during the treatment period.

In the MMRM model, missing data will not be imputed. This analysis is unbiased under the missing at random (MAR) assumption. A Toeplitz covariance matrix will be used to model the

within-subject variance-covariance structure for the model errors. If the model does not converge using the Toeplitz covariance matrix, AR(1) covariance matrix will be used. If convergence is still not met, then compound symmetry (CS) will be used.

The code used to generate the MMRM analysis will be similar to the following:

```
*******************************************************************************
Note:  TRTN = randomized treatment group (numeric)
                1 = Placebo + Standard of Care, 2 = Avacopan + Standard of Care
       TRTREG = Standard of Care Treatment Regimen
               *IV rituximab
               *Cyclophosphamide followed by oral azathioprine [1]
       ANCAPOS = ANCA Positivity:  PR3 vs MPO
       AAVSTAT = AAV Status:  Newly diagnosed vs.relapsing disease
       VISITN = Visit Number       RESP = Value of continuous response variable
       BASERESP = Baseline value of response
[1] IV and Oral Cyclophosphamide use will be combined due to the low number of
subjects in the Oral Cyclophosphamide group
*******************************************************************************

    ods listing close;
    proc mixed data=MMRMDATA;
      class SUBJECT TRTN VISITN TRTREG ANCAPOS AATSTAT;
      model RESP= TRTN BASERESP VISITN TRTN*VISITN TRTREG ANCAPOS AATSTAT / ddfm=kr;
      repeated VISITN/subject=SUBJECT type=TOEP;
      lsmeans TRTN*VISITN /cl diff=control("1");
   run;
```

7.3.3.2 Subgroup Analyses

The subgroup analysis of change from baseline over 52 weeks in components of the SF-36 v2 and EQ-5D-5L will be performed as described above for the subgroup analysis of GTI for the ITT population (section 7.3.1.3).

7.3.4 Relapses up to Week 52

7.3.4.1 Proportion of subjects experiencing a relapse after achieving remission at Week 26 and prior to Week 52

The proportion of subjects experiencing a relapse after achieving remission at Week 26, and the time to relapse, will be summarized. The proportion of subjects will be calculated as the number of subjects experiencing a relapse after achieving remission at Week 26 divided by the number of subjects who have adjudicated remission at Week 26. The assessment of remission at Week 26 and the relapse after Week 26 are both based on the assessment by the AC.

7.3.4.2 Time to relapse after achieving remission at Week 26

In subjects who achieved remission at Week 26, time to relapse will be analyzed by Kaplan Meier methodology and log rank testing of the differences between treatment groups. The time to adjudicated relapse will be assessed from Week 26, independent of whether BVAS=0 was achieved at an earlier timepoint.

For subjects not achieving relapse on or before Week 52, time to relapse will be the time from the date of Week 26 BVAS assessment to the date of the last BVAS assessment during the 52 week treatment, and is censored.

The code used to generate the survival analysis will be similar to the following:

```
*******************************************************************************
Note:  TRTN = randomized treatment group (numeric)
                1 = Placebo + Standard of Care, 2 = Avacopan + Standard of Care
       TIME = Time to Remission at Week 26 to Relapse in Days
       VISITN = Visit Number in Weeks
*******************************************************************************
              proc lifetest data=SURVDATA method=km;
                  time TIME * censor(0);
                  strata TRTN;
              run;
```

An exploratory analysis includes time to relapse from the first time point when BVAS of 0 was achieved. Time to relapse will be from the Kaplan-Meier estimate. For each subject, time to relapse is defined as the time from when BVAS = 0 was first achieved up to the time when a relapse occurred during the 52 week treatment period. For this analysis, BVAS = 0 and relapse will be based on the Adjudicators' assessment of BVAS = 0 and relapse. For the subjects who did not relapse, the subjects' time to relapse will be censored using the last time of BVAS assessment during the 52 week treatment period as the relapse date. Log-rank test will be used to test the difference of time to relapse in two treatment groups. The median time to relapse and its associated 95% CI will be provided for each treatment group. The hazard ratio and its 95% CI will also be provided. The adjudicated BVAS and adjudicated relapse assessments will be used in this analysis.

7.3.5 eGFR (in Subjects with Renal Disease at Baseline) - Change from Baseline

7.3.5.1 Primary Analysis

The primary analysis of change from baseline over 52 weeks in eGFR (in subjects with renal disease at baseline) will be performed in the ITT population using an MMRM as described above for primary analysis of SF-36 v2 and EQ-5D-5L (section 7.3.3.1) with treatment group, visit, and treatment-by-visit interaction as factors, and baseline as covariate. eGFR is computed at Baseline, Weeks 1, 2, 3, 4, 7, 10, 13, 16, 20, 26, 32, 39, 45, and 52 during the treatment period.

7.3.5.2 Subgroup Analyses

If sample size permits, the subgroup analysis of change from baseline over 52 weeks in eGFR (in subjects with renal disease at baseline) will be performed using summary statistics as described above for the subgroup analysis of GTI for the ITT population (section 7.3.1.3). Change from baseline in eGFR over 52 weeks may be assessed based on baseline eGFR (<30, 30-59, >59 mL/min/1.73 m^2), if there are sufficient subject numbers in these subgroups.

7.3.6 UACR (in Subjects with Renal Disease at Baseline) – Percent Change from Baseline

7.3.6.1 Primary Analysis

The primary analysis of percent change from baseline over 52 Weeks in UACR (in subjects with renal disease at baseline and with albuminuria [UACR ≥10 mg/g creatinine] at baseline) will be performed using MMRM as described above for primary analysis of eGFR for the ITT population. To alleviate the skewness of the data, the UACR will be $\log_e$-transformed before entering into the MMRM analysis. Least squares mean differences between CCX168 and the control group in the change from baseline to Week 52 log(UACR) will be back transformed to obtain the estimate for the baseline-adjusted percent reduction from control in UACR. UACR is computed at Baseline, Weeks 1, 2, 4, 13, 26, 39, and 52 during the treatment period.

7.3.6.2 Subgroup Analyses

If sample size permits, the subgroup analysis of change from baseline over 52 Weeks in UACR (in subjects with renal disease at baseline and with albuminuria [UACR ≥10 mg/g creatinine] at baseline) will be performed using summary statistics as described above for the subgroup analysis of GTI for the ITT population (section 7.3.1.3). Percent change from baseline in UACR over 52 weeks will be assessed based on baseline UACR (<10 mg/g, 10-300 mg/g, >300 mg/g), depending on subject numbers in each subgroup.

7.3.7 MCP-1:creatinine ratio (in Subjects with Renal Disease at Baseline) – Percent Change from Baseline

7.3.7.1 Primary Analysis

The primary analysis of percent change from baseline over 52 weeks in MCP-1:creatinine ratio (in subjects with renal disease at baseline) will be performed using MMRM as described above for UACR. Urinary MCP-1:creatinine ratio is computed at Baseline, Weeks 1, 2, 4, 13, 26, 39, and 52 during the treatment period.

7.3.7.2 Subgroup Analyses

The subgroup analysis of change from baseline over 52 weeks in MCP-1:creatinine ratio will be performed as described above for the subgroup analysis of GTI for the ITT population (section 7.3.1.3).

Urinary MCP-1:creatinine ratio will be log-transformed prior to analysis, similar to the UACR (section 7.3.6.1).

7.3.8 VDI - Change from Baseline to Week 52

7.3.8.1 Primary Analysis

The primary analysis of change from baseline over 52 weeks in VDI will be performed as described above for primary analysis of SF-36 v2 and EQ-5D-5L (section 7.3.3.1) including incorporation of the baseline VDI score in the model. VDI is computed at Baseline, Weeks 26 and 52 during the treatment period. The primary analysis is based on adjudicated data.

A frequency distribution table will also be provided for the number and percentage of subjects in each of the following categories of change from baseline (0, 1, 2-3, and >3).

7.3.8.2 Sensitivity Analysis

A sensitivity analysis will be conducted to include the Investigator-assessed VDI data.

7.3.8.3 Subgroup Analyses

The subgroup analysis of change from baseline over 52 Weeks in VDI will be performed as described above for the subgroup analysis of GTI for the ITT population (section 7.3.1.3).

7.3.8.4 Summary of Change from Baseline Categories

Change from baseline in Adjudicated VDI scores will be categorized into the following groups:

0, 1, 2-3, >3 and summarized at Week 26, Week 52, End of Treatment and Week 60. van Elteren's test will be used to compare the two treatment groups.

```
*******************************************************************************
Note:  TRTN = randomized treatment group
              1 = Placebo + Standard of Care, 2 = Avacopan + Standard of Care
       RESP = Value of response variable (Y/N)
       TRTREG = Standard of Care Treatment Regimen
          *IV rituximab
          *Cyclophosphamide followed by oral azathioprine [1]
       ANCAPOS = ANCA Positivity:  PR3 vs MPO
       AAVSTAT = AAV Status:  Newly diagnosed vs. relapsing disease

[1] IV and Oral Cyclophosphamide use will be combined due to the low number of
subjects in the Oral Cyclophosphamide group
*******************************************************************************
```

The SAS code used will be similar to the following:

```
  ods listing close;
    proc freq data=VDI;
      by VISITN;
      tables TRTREG*ANCAPOS*AAVSTAT*TRTN*CHG / cmh alpha=0.05 scores=modridit
          noprint;
      ods output cmh=CMH_RMS;  * p-value for Row Mean Scores;
     run;
    ods listing;
```

7.4 8-week Follow-Up Period Data

After the 52-week treatment period, there is an 8-week follow-up period during which subjects are not receiving any study treatment. Subjects visit the study centers at Week 60 for the final study visit. Data collected at the follow up visit will be listed by subject and summarized by

treatment group. The number (and percentage) of subjects who have worsening of AAV (based on BVAS and relapse data) will be summarized by treatment group. No inferential statistical analyses will be conducted on the follow-up period data.

8 ANALYSIS OF SAFETY

8.1 Population

All safety parameters will be summarized using the Safety Population.

8.2 Extent of Exposure

Subject drug exposure will be calculated based on the study drug dispensing and return records (based on drug accountability). CCX168 plasma concentrations over the course of the study may also be used to assess compliance. The CCX168/placebo and prednisone/placebo compliance will be calculated comparing the study drug dispensed and the study drug returned. The study drug exposure (duration, total dose, and average daily dose) and compliance will be summarized and listed. If date of last dose is not available, the date of discontinuation from study will be used.

Duration of exposure is defined as the date of the last dose of study medication minus the date of the first dose of study medication plus 1. Duration of exposure to study medication will be summarized with descriptive statistics and also in a contingency table for the safety population and presented by treatment group. Exposure data will be provided for the following intervals, defined to align with the efficacy endpoints: Days 1-29; Days 30-183; Day 184-365; Total Days 1-183 and Total Days 1-365.

Percent compliance to study drug will be calculated as follows:

CCX168/placebo:

Number of capsules taken / (6 x number of days in the randomized treatment period) x 100.

For adolescents, the formula will be altered to be consistent with the number of capsules taken daily, e.g., if the CCX168 dose was 10 mg twice daily, the formula would be:

Number of capsules taken / (2 x number of days in the randomized treatment period) x 100.

Number of days in the randomized treatment period is the Week 52 visit date (or the early termination visit date) minus first dose date +1.

Prednisone/placebo:

Number of capsules taken / (number of expected doses in randomized treatment period*) x 100

*The number of expected doses during the treatment period is based on the Prednisone/Matching Placebo schedule in the protocol. See Protocol Section 12.6.1, Tables 6 and 7, for further details.

8.3 Adverse Events

An adverse event (AE) is considered treatment-emergent if the start date/time of the event is on or after the date/time of first dose of study drug through 56 days following the last dose administered during the randomized treatment period.

An overview of treatment-emergent adverse events (TEAEs) will be prepared that presents all TEAEs, serious adverse events (SAEs), TEAEs leading to study drug discontinuation, events related to study medication, glucocorticoid use, IV cyclophosphamide, oral cyclophosphamide, rituximab, azathioprine, or mycophenolate and TEAEs by maximum severity.

Adverse events will be coded using MedDRA and TEAEs will be summarized by system organ class and preferred term and by preferred term, in descending order of frequency. Similar summaries by system organ class and preferred term will be prepared for TEAEs considered possibly related by the study investigators to study medication, glucocorticoids, cyclophosphamide, rituximab, azathioprine, or mycophenolate use, TEAEs by maximum severity, treatment emergent serious adverse events (TESAEs), possibly study treatment related TESAEs and TESAEs leading to discontinuation of study medication. Adverse events will be listed by treatment group, including all available information of interest such as onset and resolution dates, study day of onset and resolution relative to first dosing day, duration, severity, seriousness, causal relationship to study medication per the investigator, glucocorticoids, cyclophosphamide, rituximab, azathioprine or mycophenolate use, action taken, and outcome. Separate listings will be provided for non treatment-emergent AEs and SAEs. Separate listings will be provided for treatment emergent deaths, TESAEs, TESAEs and TEAEs leading to discontinuation of study drug, TESAES and TEAEs leading to withdrawal from study, and TEAEs of special interest.

TEAEs of special interest include infections, hepatic enzyme elevations, neutropenia and lymphopenia, and hypersensitivity/ angioedema.

The subject incidence of infections, serious infections, severe infections (i.e., Grade 3+), and infections leading to subject withdrawal from the study will be summarized by treatment group. Infections will be identified by selecting terms with the Adverse Event System Organ Class of 'Infections and Infestations'.

The subject incidence of adverse events potentially associated with liver injury will be summarized by treatment group – preferred terms in the category will include hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased, liver function test increased, blood bilirubin increased, alanine aminotransferase abnormal, liver function test abnormal, hepatic function abnormal, hepatocellular injury, drug-induced liver injury, and similar. The list, finalized prior to unblinding, is presented in Appendix 15.3. Any events occurring during the 8-week follow-up period will be included in the CSR. Shift tables for increases in liver tests and CPK based on the Central Laboratory analyses will be provided.

For serious adverse events where the preferred term indicates elevated liver enzymes, the laboratory values may be from the local laboratories or hospitalizations and will not be represented in the shift tables. Therefore, individual case assessments will be presented for subjects with SAEs where the preferred term indicates an increase in liver enzymes.

The subject incidence of adverse events associated with low WBC count, absolute granulocytes, neutrophils, or low lymphocytes will be summarized by treatment group – preferred terms in the category will include 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. The list, finalized prior to unblinding, is presented in Appendix 15.4. Any events occurring during the 8-week follow-up period will be included in the CSR.

For serious adverse events where the preferred term indicates neutropenia, the laboratory values may be from the local laboratories or hospitalizations and will not be represented in the shift tables. Therefore, individual case assessments will be presented for subjects with SAEs where the preferred term indicates neutropenia.

The subject incidence of adverse events associated with hypersensitivity/angioedema will be summarized by treatment group. Terms will be based on the Standardized MedDRA Query for hypersensitivity. Hypersensitivity events caused by drugs or factors other than study drug (avacopan/placebo) will be excluded from this analysis.

Exploratory analyses include TEAEs potentially associated with glucocorticoid use based on mechanism, consistent with The European League Against Rheumatism (EULAR) recommendations (van der Goes et al, 2010; Duru et al, 2013). These TEAEs, finalized prior to unblinding, are presented in Appendix 15.5. For this analysis, a by-subject listing will be provided and data will be summarized by treatment group by system organ class and preferred term. 95% Clopper-Pearson's CIs and unconditional exact 95% CI for the difference in proportions (avacopan minus control) may be determined for these TEAEs.

8.4 Safety Laboratory Parameters

Laboratory parameter results and changes from baseline will be summarized by visit. Summaries will be limited to values assessed at the Central Laboratory. Listings of laboratory values collected at local laboratories will be provided, but not summarized. Shift tables from baseline to subsequent study visits will also be generated based on the Central Laboratory measurements. Counts and percentages of laboratory values outside the normal reference range will be summarized by laboratory parameter, treatment group and visit. The denominator for percentages will be the number of subjects in the particular treatment group with measurement at a specified visit. Laboratory values outside the reference ranges will be flagged in the listings.

The subject incidence of elevated laboratory values of ALT, AST, total bilirubin, alkaline phosphase, creatinine, and potassium, as assessed by the Central Laboratory, will be summarized by treatment group and Grade, as defined per Common Terminology Criteria for Adverse Events (CTCAE) Version 5. Shift from baseline to highest CTCAE grade during the study period will also be produced for these laboratory parameters based on the Central Laboratory measurements. The same summary by treatment and CTCAE grade will be produced for subject incidence of elevated creatine phosphokinase (CPK), low neutrophils, low lymphocytes, low leukocytes, low hemoglobin, and low platelets. Shift from baseline to highest CTCAE grade during the study period will also be produced for these laboratory parameters. A by-subject listing including all data for these laboratory parameters including CTCAE grade for subjects with any abnormality will be provided.

A listing of subjects whose study drug were permanently discontinued due to adverse events or laboratory values will be produced.

8.5 Vital Signs

Vital sign results and changes from baseline will be listed and summarized by study visit and treatment group.

8.6 ECG Parameters

Abnormal ECG findings will be listed by treatment group and study visit, and clinical significance of abnormalities indicated. Shifts from baseline in overall interpretation (Normal vs. Abnormal) will be summarized by treatment group and overall with counts and percentages at each study visit. The denominator for percentages will be the number of subjects in the particular treatment group with measurement at a specified visit.

8.7 Physical Examinations

Physical examination findings will be listed and summarized by treatment group and study visit, and clinical significance of abnormalities indicated.

8.8 Other Safety Parameters

Analysis of change from baseline in the GTI is discussed in Section 7.3.1.

8.9 Pharmacokinetic and Pharmacodynamic Marker Analysis

Individual plasma concentrations of CCX168 and significant metabolites will be listed, plotted, and summarized descriptively and graphically. PK parameters such as C_{max}, T_{max}, and $AUC_{0\text{-}6hr}$ will be calculated in adolescents for CCX168 based on plasma concentrations for samples collected on Day 1. Plasma levels of significant metabolites may also be determined and PK parameters calculated. Population PK modeling may be performed to calculate PK parameters.

Plasma and urinary PD markers will be summarized and may be analyzed using methods analogous to the efficacy parameters.

The relationship between PK parameters and renal function based on eGFR will also be evaluated. The data may also be used to evaluate the PK/PD relationship of CCX168 treatment. To this end, the change and/or percent change from baseline in eGFR, VDI, UACR, urinary MCP-1:creatinine ratio, or other biomarkers may be used as PD markers.

Details of the PK and PD analysis will be described in a separate analysis plan and will be reported in a separate report.

9 DATA MONITORING COMMITTEE

In addition to continuous safety monitoring by the Medical Monitor and clinical staff, an external Data Monitoring Committee (DMC) has been established to monitor the safety of subjects over the course of the study. The DMC consists of external physicians and a biostatistician. A DMC charter was developed before start of the study and the DMC functions according to the charter. The DMC has regular meetings, once every 3 to 6 months, depending on study enrollment rate. Ad hoc meetings may be scheduled if unanticipated safety events occur. After review of data at each meeting, the DMC makes recommendations about further conduct of the study.

10 ADJUDICATION OF ENDPOINTS

An Adjudication Committee (AC) has been established to perform a blinded, independent adjudication of the BVAS and VDI data. The AC is composed of individuals who are independent of the Sponsor, recognized experts in AAV, and expert in the use of BVAS and VDI in clinical trial design and operationalization. The AC operates under a charter, which provides detailed guidance

In addition to BVAS and VDI, the following endpoints will be adjudicated by the AC:

1. Achievement of early disease remission at Week 4 (Secondary Endpoint)
2. Achievement of disease remission at Week 26 (Primary Endpoint)
3. Achievement of sustained disease remission at Week 52 (Primary Endpoint)
4. Occurrence of relapse during the 52 week treatment period and follow up.

Note that assessment of glucocorticoid use for the purpose of assessing (2) and (3) above is also performed by the AC.

11 INTERIM ANALYSIS

Safety data from the study will be summarized for review by the DMC at various points over the course of the study (see Section 9). The DMC charter includes details of these reviews. No Type I error adjustment will be made based on the DMC review of the data, since these reviews will focus on safety assessments.

12 SAMPLE SIZE AND POWER CONSIDERATIONS

The proportion of subjects in the control group achieving clinical remission at Week 26 is estimated to be ~60%, a blended proportion of 64% and 53% observed in the rituximab and cyclophosphamide/azathioprine groups, respectively, in the largest prior registration study in AAV (Stone et al, 2010).

A non-inferiority margin of -20 percentage points has been derived for the difference between CCX168 and control groups, and a one-sided alpha level of 0.025. This non-inferiority margin is based on a thorough review and meta-analysis of all previous clinical trials conducted in subjects with AAV, as well as precedent (Stone et al, 2010).

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

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

13 CHANGES FROM PROTOCOL–SPECIFIED STATISTICAL ANALYSES

1. The protocol anticipates using the Glucocorticoid Toxicity Index version 1.0 (Miloslavsky et al 2016). Since the launch of this study, version 2.0 became available, which has distinct advantages over version 1.0, such as being validated in two patient cohorts (Ehlers et al 2019a; Ehlers et al 2019b) and expressing glucocorticoid toxicity in a cumulative manner with the Cumulative Worsening Score as well as in a two-directional manner with the Aggregate Improvement Score. Therefore, a decision was made by the Sponsor, in consultation with the developers of the GTI, prior to completion of this study, to use version 2.0 instead of version 1.0 for the final analysis.
2. The protocol states the analysis for the primary endpoint would be based on the stratified Newcombe hybrid-score method for the common difference in proportions. The primary endpoint analysis will be based on the stratified Summary score test and estimate for the common difference in proportions. Summary score estimate of the common difference in remission rates (Agresti 2013, p. 231) will be determined by using inverse-variance stratum weights and Miettinen-Nurminen (score) confidence limits for the common difference in remission rates. Results comparing different stratified analysis methods show that the Summary score method provides robust results for the data from the RAVE study (Stone et al, 2010), which is similar to this study.

14 REFERENCES

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15 APPENDICES

15.1 Data Derivation Details

15.1.1 BVAS

Only symptoms/signs ascribed to the presence of active AAV (GPA or MPA) will be recorded and entered into EDC. For the Week 4 BVAS assessment, the disease activity present within the 7 days prior to the visit was to be recorded. For all the other study visits, the disease activity present within the 28 days prior to the visit was to be recorded.

AAV Organ Systems and Activity Items in BVAS

There are 9 organ systems, plus an "Other" category in the BVAS. For study eligibility, a subject must have at least one major item, at least 3 minor items, or at least the two renal items of hematuria and proteinuria. If a subject has "other" items, not specified in the BVAS, these need to be discussed with the Medical Monitor before enrollment. The organ systems and items are provided in Table 3. Major items are indicated in bold italics.

Scoring of BVAS

The calculation of BVAS will be performed programmatically. A total score will be calculated from the individual organ system scores as described in Table 3. BVAS data recorded by investigators will be adjudicated, according to an adjudication charter, before data finalization and unblinding. The adjudicated data will be used in the final analysis.

Table 3. BVAS Organ Systems, Individual Items and Scoring

BVAS Items and Calculations	
Target Item	**Description**
General subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 3 (max score is 3 regardless if sum is above): Myalgia (1), Arthralgia or arthritis (1), Fever >= 38 (2), Weight loss >=2 kg (2)
Cutaneous subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 6 (max score is 6 regardless if sum is above): Infarct (2), Purpura (2), Ulcer (4), ***Gangrene*** (6), Other skin vasculitis (2)
Mucous membranes/eyes subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 6 (max score is 6 regardless if sum is above): Mouth ulcers / granulomata (2), Genital ulcers (1), Adnexal inflammation (4), Significant proptosis (4), ***Scleritis / Episcleritis*** (2), Conjunctivitis / Blepharitis / Keratitis (1), Blurred vision (3), Sudden visual loss (6), Uveitis (6), ***Retinal changes*** (6)
ENT subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 6 (max score is 6 regardless if sum is above): Bloody nasal discharge / crusts / ulcers / granulomata (4), Paranasal sinus involvement (2), Subglottic stenosis (6), Conductive hearing loss (3), ***Sensorineural hearing loss*** (6)
Chest subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 6 (max score is 6 regardless if sum is above): Wheeze (2), Nodules or cavities (3), Pleural effusion / pleurisy (4), Infiltrate (4), Endobronchial involvement (4), ***Massive haemoptysis / alveolar haemorrhage*** (6), ***Respiratory failure*** (6)
Cardiovascular subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 6 (max score is 6 regardless if sum is above): Loss of pulses (4), Valvular heart disease (4), Pericarditis (3), Ischaemic cardiac pain (4), Cardiomyopathy (6), Congestive cardiac failure (6)
Abdominal subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 9 (max score is 9 regardless if sum is above): Peritonitis (9), Bloody diarrhoea (9), ***Ischaemic abdominal pain*** (6)
Renal subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 12 (max score is 12 regardless if sum is above): Hypertension (4), Proteinuria (4), Haematuria (6), Serum creatinine 125-249 (4), Serum creatinine 250-499 (6), Serum creatinine >=500 (8), ***Rise in serum creatinine >30% or fall in creatinine clearance >25%*** (6)

BVAS Items and Calculations	
Target Item	**Description**
Nervous system subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 9 (max score is 9 regardless if sum is above): Headache (1), ***Meningitis*** (3), Organic confusion (3), Seizures (9), ***Cerebrovascular accident*** (9), ***Spinal cord lesion*** (9), ***Cranial nerve palsy*** (6), ***Sensory peripheral neuropathy*** (6), ***Mononeuritis multiplex*** (9)
Other	If RBC casts and/or glomerulonephritis is checked, it should be added to the Renal Organ System with a Score of 6. Haematuria is also in the Renal organ system (also given a score of 6). Only one or the other should be included in the Renal System. If additional Other Items are checked the applicable organ system and whether the item is major or minor is indicated. Minor items are given an score of 2 and Major items are given a Score of 4. The maximum score within an organ system is still applicable.
Total BVAS Score	Sum of all individual scores described above (General + Cutaneous + Mucous membranes / eyes + ENT + Chest + Cardiovascular + Abdominal + Renal + Nervous System)
Note: Major items are indicated in ***bold italics***.	

15.1.2 VDI

The Vasculitis Damage Index (VDI) is for recording organ damage that has occurred in subjects since the onset of vasculitis. Damage is defined as the presence of non-healing scars and does not give any indication of current disease activity. Damage items in the VDI are often the direct result of previous disease activity (captured in the BVAS). Damage is defined as having been present or currently present for at least 3 months. It is therefore possible for abnormalities to have occurred in the past, not be currently present, but to still count as damage.

Subjects often have co-morbidity before they develop vasculitis, which is not to be scored.

Features of active disease are recorded using the BVAS, not the VDI.

New subjects should usually have a VDI score of zero, unless:

a. They have had vasculitis for more than three months of onset of disease, and
b. The damage has developed or become worse since the onset of vasculitis.

The VDI item list can only deteriorate or be stable over time (damage is defined as irreversible in this scoring system). For each item in turn, all features which have occurred since the onset of vasculitis are recorded, regardless of the cause. For specific events, such as GI surgery, damage can be scored as positive if the procedure was undertaken at least three months prior to the assessment (and also must have occurred after the onset of the disease). The same time frame is applied to all the damage items. If the subject is seen for the first time, and their vasculitis onset date is within three months of the assessment, then by definition, the subject cannot be recorded as having any damage. However, any features which are observed can be recorded as ascribable to damage after the arbitrary time of three months has elapsed.

There are 11 organ systems in the VDI:

1. Musculoskeletal
    a. Significant muscle atrophy or weakness
    b. Deforming / erosive arthritis
    c. Osteoporosis / vertebral collapse
    d. Avascular necrosis
    e. Osteomyelitis
2. Skin/Mucous Membranes
    a. Alopecia
    b. Cutaneous ulcers
    c. Mouth ulcers
3. Ocular
    a. Cataract
    b. Retinal change
    c. Optic atrophy
    d. Visual impairment / diplopia
    e. Blindness in one eye
    f. Blindness in a second eye
    g. Orbital wall destruction

4. Ear, Nose & Throat
    a. Hearing loss
    b. Nasal blockage / chronic discharge/crusting
    c. Nasal bridge collapse / septal perforation
    d. Chronic sinusitis / radiological damage
    e. Subglottic stenosis (no surgery)
    f. Subglottic stenosis (with surgery)
5. Pulmonary
    a. Pulmonary hypertension
    b. Pulmonary fibrosis
    c. Pulmonary infarction
    d. Pleural fibrosis
    e. Chronic asthma
    f. Chronic breathlessness
    g. Impaired lung function
6. Cardiovascular
    a. Angina angioplasty
    b. Myocardial infarction
    c. Subsequent myocardial infarction
    d. Cardiomyopathy
    e. Valvular disease
    f. Pericarditis ≥3 months or pericardectomy
    g. Diastolic BP ≥95 or requiring antihypertensives
7. Peripheral Vascular Disease
    a. Absent pulses in one limb
    b. Second episode of absent pulses in one limb
    c. Major vessel stenosis
    d. Claudication >3 months
    e. Minor tissue loss
    f. Major tissue loss
    g. Subsequent major tissue loss
    h. Complicated venous thrombosis
8. Gastrointestinal
    a. Gut infarction / resection
    b. Mesenteric insufficiency / pancreatitis
    c. Chronic peritonitis
    d. Esophageal stricture / surgery
9. Renal
    a. Estimated / measured GFR ≤50
    b. Proteinuria ≥0.5 g/24 hours
    c. End stage renal disease

10. Neuropsychiatric

    a. Cognitive impairment
    b. Major psychosis
    c. Seizures
    d. Cerebrovascular accident
    e. 2nd Cerebrovascular accident
    f. Cranial nerve lesion
    g. Peripheral neuropathy
    h. Transverse myelitis

11. Other

    a. Gonadal failure
    b. Marrow failure
    c. Diabetes
    d. Chemical cystitis
    e. Malignancy
    f. Etc.

The number of positive items is added for the total VDI score. Any previously scored items on the VDI must be carried forward to subsequent visits. The VDI score cannot decrease over time. The calculation of VDI will be performed programmatically.

15.1.3 Glucocorticoid Toxicity Index (GTI)

The GTI was developed to quantitatively capture glucocorticoid toxicity and the glucocorticoid-sparing ability of other therapies. The index consists of components in Table 4:

Table 4. Glucocorticoid Toxicity Index Version 2.0 Items with Scoring and Specific List Items

Feature/Body System	Item Weight
Body Mass Index (BMI)	
Decrease of ≥5 BMI units	-36
Decrease of >2 but <5 BMI units	-21
No significant change in BMI (±2 BMI units)	0
Increase of >2 to <5 BMI units	21
Increase of 5 or more BMI units	36
Glucose tolerance	
Improvement in HbA1c AND decrease in medication	-44
Improvement in HbA1c OR decrease in medication	-32
No significant change	0
Increase in HbA1c OR increase in medication	32
Increase in HbA1c AND increase in medication	44
Blood pressure	
Improvement in BP AND decrease in medication	-44
Improvement in BP OR decrease in medication	-19
No significant change in blood pressure	0

Feature/Body System	Item Weight
Increase in BP OR increase in medication	19
Increase in BP AND increase in medication	44
Lipids	
Decrease in LDL AND decrease in medication	-30
Decrease in LDL OR decrease in medication	-10
No significant change in lipids	0
Increase in LDL OR increase in medication	10
Increase in LDL AND increase in medication	30
Steroid myopathy[1]	
Moderate weakness to none	-63
Moderate to Mild weakness	-54
Mild weakness to none	-9
No significant change	0
None to mild weakness	9
Mild to moderate weakness	54
None to Moderate weakness	63
Skin toxicity[1]	
Decrease in Skin Toxicity - Moderate to None	-26
Decrease in Skin Toxicity - Moderate to Mild	-18
Decrease in Skin Toxicity - Mild to None	-8
No significant change	0
Increase in Skin Toxicity - None to Mild	8
Increase in Skin Toxicity - Mild to Moderate	18
Increase in Skin Toxicity - None to Moderate	26
Neuropsychiatric (NP) toxicity[1]	
Decrease in NP Toxicity - Moderate to None	-74
Decrease in NP Toxicity - Moderate to Mild	-63
Decrease in NP Toxicity - Mild to None	-11
No significant change	0
Increase in NP Toxicity - None to Mild	11
Increase in NP Toxicity – Mild to Moderate	63
Increase in NP Toxicity - None to Moderate	74
Infection[1]	
No significant infection	0
Oral/vaginal candidiasis or uncomplicated zoster	19
Grade 3, 4 or 5 infection	93
[1] See Section 12.5.1 of the protocol for definitions of steroid myopathy, skin toxicity, neuropathy, and infection.	

Weighting of Improvement and Worsening in Items of Glucocorticoid Toxicity

As indicated by a review of Table 4, the GTI 2.0 permits an improvement in glucocorticoid toxicity to be accorded the same absolute weight as a worsening of glucocorticoid toxicity. The GTI 2.0 accomplishes this through the GTI-AIS (Aggregate Improvement Score). The GTI-AIS scores improvement in GC toxicity the same as a corresponding worsening of GC toxicity.

Example:

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

Application of GTI Scoring

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

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

The Skin and Neuropsychiatric Domains both have Sub-Items:

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

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

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

Scoring of Infections

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

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

15.1.3.1 Items in the specific list

The Specific List Items of the GTI are provided in Table 5.

Table 5. Specific List Items of the GTI

Feature/Organ System	Specific List
Body Mass Index	Major increase in BMI (>8 units and above 24.9 kg/m^2)
Glucose Tolerance	Diabetic retinopathy Diabetic nephropathy Diabetic neuropathy
Blood pressure	Hypertensive emergency (or posterior reversible encephalopathy syndrome) Posterior reversible encephalopathy syndrome
Steroid myopathy	Severe steroid myopathy or tendon rupture
Skin toxicity	Severe skin toxicity
Neuropsychiatric toxicity	Psychosis (hallucinations, delusions, or disorganized thought processes, occurring in the absence of mania, delirium, or depression) Glucocorticoid-induced violence towards self or others Other severe neuropsychiatric symptoms
Infections	Grade IV infection Grade V infection (death from infection)
Endocrine	Symptomatic adrenal insufficiency
Gastrointestinal	Perforation (occurring in the absence of regular nonsteroidal anti-inflammatory drug use) Peptic ulcer disease confirmed by endoscopy (excluding *H. pylori*)
Musculoskeletal	Avascular necrosis Tendon rupture Insufficiency fracture
Ocular	Central serous retinopathy New onset or worsened elevation of intraocular pressure requiring treatment or change in treatment. Posterior subcapsular cataract (or history of the same)

Explanations of Specific Items are provided below.

Hypertensive emergency: The blood pressure has reached levels that are damaging organs. Hypertensive emergencies generally occur at blood pressure levels exceeding 180 mmHg systolic OR 120 mmHg diastolic, but can occur at even lower levels in subjects whose blood pressure have not been elevated before. Complications can include: stroke, loss of consciousness, memory loss, myocardial infarction, hypertensive retinopathy or nephropathy, aortic dissection, angina, pulmonary edema.

Posterior reversible leukoencephalopathy syndrome (PRES): A clinical radiological entity. Clinical features may include headaches, altered mental status, seizures, and visual loss, depending on the affected neuroanatomy. Characteristic Magnetic Resonance Imaging (MRI) findings include vasogenic edema involving the white matter that predominantly affects the posterior occipital and parietal lobes of the brain, although other brain regions may also be affected. Confirmation by MRI is required as is exclusion of other potential causes (including hypertensive emergency).

Severe glucocorticoid myopathy: Grade 3 or worse myopathic weakness or respiratory myopathic weakness attributable to glucocorticoid myopathy.

Central serous retinopathy: a fluid detachment of macula layers from their supporting tissue. Requires formal ophthalmology examination, typically accompanied by optical coherence tomography and/or fluorescein angiography for diagnostic confirmation.

Grade 4 infection: Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis).

Diabetic nephropathy: Macroalbuminuria; i.e., a urinary albumin excretion >300 mg in a 24-hour collection or a urinary protein: creatinine ratio >300mg/g.

Diabetic neuropathy: Any of four types of peripheral neuropathy occurring in the setting of diabetes mellitus, namely: 1) a distal sensory polyneuropathy; 2) autonomic neuropathy (hypoglycemia unawareness, bladder or bowel problems, erectile dysfunction, and other autonomic nervous system issues); 3) diabetic amyotrophy (muscle infarction); or 4) mononeuritis (e.g., foot drop attributed to diabetic neuropathy).

15.1.4 EQ-5D-5L

Crosswalk value sets used in the calculation of the EQ-5D-5L Index Score are available for the following countries: Denmark, France, Germany, Japan, the Netherlands, Spain, Thailand, UK, US and Zimbabwe. For countries not listed above, reference data will used according to the following:

Country	EQ-5D-5L Crosswalk Value Country Set
US, Canada	US
Denmark, Sweeden	Denmark
France, Switzerland	France
Germany, Czech Republic, Austria	Germany
Japan	Japan
Netherlands, Belgium	Netherlands

Spain, Italy	Spain
UK, Ireland, Australia, New Zealand,	UK

15.2 Imputation for Missing/Partially Missing Adverse Event and Concomitant Medication Dates

15.2.1 Incomplete Adverse Event Start Date:

Partially missing AE start/stop dates will be imputed in the ADaM dataset for AEs, according to the rules below. However, listings of AE data will present the date as is, with missing date components left blank.

If the AE end date is complete with no missing year, month, or day, and a partially missing start date imputed by the rules below is after the AE end date, then the start date will be imputed by the AE end date.

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed. The corresponding AE will be included as TEAE.

15.2.2 Incomplete AE Stop Date:

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day
- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the last day of the month will be assigned to the missing day

15.2.1 Incomplete Start/Stop Dates for Prior/Concomitant Medications/Procedures

Partially missing start/stop dates for prior/concomitant medications and partially missing start dates for prior/concomitant procedures will be imputed in the ADaM dataset for prior/concomitant medications/procedures. However, listings of prior/concomitant medications/procedures data will present the date as is, with missing date components left blank.

For prior/concomitant medications, if the stop date is complete with no missing year, month, or day, and the partially missing start date imputed by the rule below is after the stop date, then the start date will be imputed by the stop date.

Partially missing prior/concomitant medication/procedure start dates will be imputed by the earliest possible date given the non-missing field(s) of the date, if the partial dates are either before or after the date of the first dose of the study drug. Otherwise, they will be imputed with the date of the first study drug dose.

Partially missing prior/concomitant medication stop dates will be imputed by the latest possible date given the non-missing field(s) of the date.

15.3 Preferred Terms of Adverse Events Potentially Associated with Liver Injury

Drug-induced liver injury

Hepatic function abnormal

Hepatocellular injury

Alanine aminotransferase increased

Aspartate aminotransferase increased

Blood bilirubin increased

Hepatic enzyme increased

Liver function test abnormal

Liver function test increased

Transaminases increased

Hepatitis cholestatic

15.4 Preferred Terms of Adverse Events Indicating WBC Count Decrease

Agranulocytosis

Bone marrow failure

Bone marrow toxicity

Febrile neutropenia

Leukopenia

Lymphopenia

Neutropenia

Pancytopenia

Neutropenic sepsis

Lymphocyte count decreased

Neutrophil count decreased

White blood cell count decreased

15.5 Preferred Terms of Adverse Events Potentially Associated with Glucocorticoid-Related Toxicity

Blood and lymphatic system disorders

Increased tendency to bruise

Cardiac disorders

Acute myocardial infarction

Angina pectoris

Cardiac failure

Cardiovascular insufficiency

Congestive cardiomyopathy

Myocardial infarction

Myocardial ischaemia

Endocrine disorders

Adrenal insufficiency

Cushing's syndrome

Cushingoid

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

Oedema

Oedema peripheral

Peripheral swelling

Systemic inflammatory response syndrome

Infections and Infestations (for the main analysis, only serious infections will be included)

Anal fungal infection

Aspergillus infection

Atypical pneumonia

Bacteraemia

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

Diarrhoea infectious

Diverticulitis

Ear infection

Ear infection fungal

Enteritis infectious

Epstein-Barr virus infection

Erysipelas

Escherichia infection

Escherichia urinary tract infection

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

Localised infection

Lower respiratory tract infection

Lower respiratory tract infection viral

Lung infection

Klebsiella test positive

Meningitis

Mucocutaneous candidiasis

Nasopharyngitis

Neutropenic sepsis

Oesophageal candidiasis

Ophthalmic herpes simplex

Oral candidiasis

Oral fungal infection

Oral herpes

Otitis externa

Otitis media

Otitis media acute

Otitis media chronic

Parainfluenzae virus infection

Paronychia

Periodontitis

Pharyngitis

Pharyngitis streptococcal

Pneumonia

Pneumonia bacterial

Pneumonia cytomegaloviral

Pneumonia haemophilus

Post procedural infection

Post procedural sepsis

Pulpitis dental

Pyuria

Rash pustular

Respiratory syncytial virus infection

Respiratory tract infection

Respiratory tract infection viral

Sepsis

Sinusitis

Subcutaneous abscess

Tinea cruris

Tinea pedis

Tinea versicolour

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

Metabolism and nutrition disorders

Central obesity

Diabetes mellitus

Diabetes mellitus inadequate control

Dyslipidaemia

Fluid retention

Glucose tolerance impaired

Hypercholesterolaemia

Hyperglycaemia

Hyperlipidaemia

Hypertriglyceridaemia

Hypervolaemia

Hypokalaemia

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

Confusional state

Depressed mood

Depression

Insomnia

Irritability

Libido decreased

Major depression

Mania

Mental status changes

Mood altered

Nervousness

Reproductive system and breast disorders

Gynaecomastia

Menorrhagia

Metrorrhagia

Skin and subcutaneous tissue disorders

Acne

Dermatitis acneiform

Ecchymosis

Hirsutism

Skin atrophy

Skin striae

Vascular disorders

Arteriosclerosis

Hypertension

Hypertensive emergency

Preferred Terms may be clustered according to EULAR terms (defined below).

Sponsor-defined GC-associated TEAE EULAR Terms and Cluster Designations		
Terms included in EULAR recommendations		**For analysis**
EULAR category/SOC	**EULAR event term**	**Cluster designation**
Cardiovascular	Dyslipidemia	Dyslipidemia
	Edema	Edema
	Ischemic CVD/atherosclerosis	CVD
Infectious	Infections	Infections
Gastro-intestinal	Peptic ulcer disease	Peptic ulcer disease
	Pancreatitis	Pancreatitis
Psychological	Mood disturbances	Mood disturbance
	Psychosis	Mood disturbance
Endocrine, metabolic	Diabetes/glucose intolerance	Hyperglycemia
	Body weight and fat redistribution	Body weight and fat redistribution
	Interference with hormone secretion	Interference with hormone secretion
Dermatological	Skin atrophy	Skin
	Acne, hirsutism, alopecia, bruisability	Skin
Musculoskeletal	Osteoporosis	Bone
	Osteonecrosis	Bone
	Myopathy	Myopathy
Ophthalmological	Cataract	Ophthalmological
	Glaucoma (intra-ocular pressure)	Ophthalmological