A Randomized, Double-Blind, Active Comparator-Controlled Study to Evaluate the Effect of Obinutuzumab Versus Rituximab in PR3-Patients With Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis

NCT05376319

17OCT2023

Clinical Trial Protocol: PR3-AAV Resilient Remission or (PRRR)

Study Title:	A Randomized, Double-Blind, Active Comparator-Controlled Study to Evaluate the Effect of Obinutuzumab versus Rituximab in PR3-Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis
Brief Title:	PR3-AAV Resilient Remission or PRRR
Study Number:	21-012197
Study Phase:	2
Product Name:	Obinutuzumab
Indication:	Treatment of PR3-ANCA-Associated Vasculitis
Sponsor:	Ulrich Specks, MD
Genentech ID	ML43834
Protocol Co-Chair	Ulrich Specks, MD Mayo Clinic 200 First Street SW Rochester, MN 55905 Phone: (507) 284-2301 Fax: [redacted] Email: specks.ulrich@mayo.edu
Protocol Co-Chair	[redacted], MD, MPH Massachusetts General Hospital 55 Fruit Street/Yawkey 2 Boston, MA., 02114 Phone: [redacted] Fax: [redacted] Email: [redacted]
Sponsor Contact:	[redacted]
Medical Monitor:	Ulrich Specks, MD [redacted], MD, MPH
Protocol Version:	Version 3.0
Protocol Effective Date:	17OCT2023

Confidentiality Statement

REVISION LOG	DATE	CHANGES BY:
Version 1.0	25-JUN-2021	[redacted]
Version 1.0	03-FEB-2022	[redacted]
Version 2.0	14-NOV-2022	[redacted]
Version 2.1	02-MAR-2023	[redacted]
Version 3.0	23-AUG-2023	[redacted], PM, Tranquil Clinical Research

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SYNOPSIS

Sponsor:

Ulrich Specks, MD

Name of Target Finished Product:
Obinutuzumab for infusion

Name of Target Active Ingredient:

Obinutuzumab

Study Title:
A Randomized, Double-Blind, Active Comparator-Controlled Study to Evaluate the Effect of Obinutuzumab versus Rituximab in PR3-Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis

Brief Title:

PR3-AAV Resilient Remission (PRRR)

Study Number: 21-012197

Primary Objective(s):
The primary objective of this study is to determine the proportion of patients achieving both complete remission and seronegativity for ANCA at 6 months. Complete remission is defined as a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) of 0 without glucocorticoids beyond the prescribed prednisone taper. Seronegativity for ANCA is defined as a negative test for antibodies directed against serine proteinase 3 (i.e., a negative PR3-ANCA assay).

Secondary Objectives:
The secondary objectives of this study are:

- To compare the proportion of subjects who achieve sustained complete remission at month 6 after administration of obinutuzumab or rituximab. **Complete remission is defined as BVAS/WG = 0 without glucocorticoids.**
- To compare the proportion of subjects who achieve sustained complete remission at month 12 after administration of obinutuzumab or rituximab.
- To compare the proportion of subjects who achieve sustained complete remission at month 18 after administration of obinutuzumab or rituximab.
- To compare the time to treatment failure through month 18 by administration of obinutuzumab or rituximab; Patients will be considered treatment failures if the glucocorticoid dose has to be increased at any point during the 18-month study period because of a disease relapse. ***Disease relapse* is *defined* as an increase in the BVAS/WG of ≥ 1 point accompanied by a decision on the part of the investigator to increase treatment for PR3-AAV**

Follow-up in the trial will continue until all patients have been followed for 18 months.

Exploratory Objectives:

The exploratory objectives are to compare between the two treatment groups for following outcomes:

- The number of disease relapses as defined as an increase in the BVAS/WG of ≥1 point accompanied by a decision on the part of the investigator to increase treatment for PR3-AAV.
- The Glucocorticoid Toxicity Index (GTI) scores (Cumulative Worsening Score and Aggregate Improvement Score) over time;
- The cumulative glucocorticoid dose;
- The number of severe relapses. ***Severe relapse*** **is** ***defined*** **as at least one major BVAS/WG item or a BVAS/WG ≥3 and the investigator deems standard treatment for severe disease is necessary.**
- The changes from baseline in Vasculitis Damage Index (VDI) over time;
- The time to clinical remission;
- The changes in estimated glomerular filtration rate (eGFR);
- The proportion of patients achieving and maintaining complete peripheral blood B cell depletion (CD19+) at each study visit using high-sensitivity flow cytometry (HSFC);
- The kinetics of ANCA:
    - Time to negative testing for ANCA
    - Time to recurrence of a positive test for ANCA (after negative testing);
- The kinetic of recurrence of PR3-specific (autoantigen-specific) B cells after B cell depletion
- The changes from baseline on AAV patient reported outcome (AAV-PRO) assessment over time
- Vasculitis Clinical Research Consortium (VCRC) Granulomatosis with polyangiitis/ microscopic polyangiitis (WG/MPA) disease activity and transition assessment over time

Study Design:

This is a double-blind, randomized, active controlled multi-center phase 2 study to evaluate the efficacy and safety of obinutuzumab for the treatment of PR3-AAV. The study will enroll 30 patients who have clinical diagnoses of either granulomatosis with polyangiitis or microscopic polyangiitis. All patients enrolled must have positive serum assays for PR3-ANCA, manifestations of severe disease. ***Severe disease*** **is** ***defined*** **as at least one major BVAS/WG item or a BVAS/WG ≥3 and the investigator deems standard treatment for severe disease is necessary.**

Patients who are positive for serum assays for ANCA directed against myeloperoxidase (MPO-ANCA) will be excluded.

Eligible patients will be randomly assigned in a 1:1 ratio to receive two intravenous doses of either rituximab or obinutuzumab (both drugs dosed at 1000 mg per infusion). Infusions will be given approximately two weeks apart, on day 0 and on day 14.

All randomized patients will be prescribed a specified glucocorticoid regimen, to include:

- One to three intravenous pulses of methylprednisolone (1000 mg each) starting on or within 10 calendar days of study day 0. Decision on number of pulses of methylprednisolone per investigator.

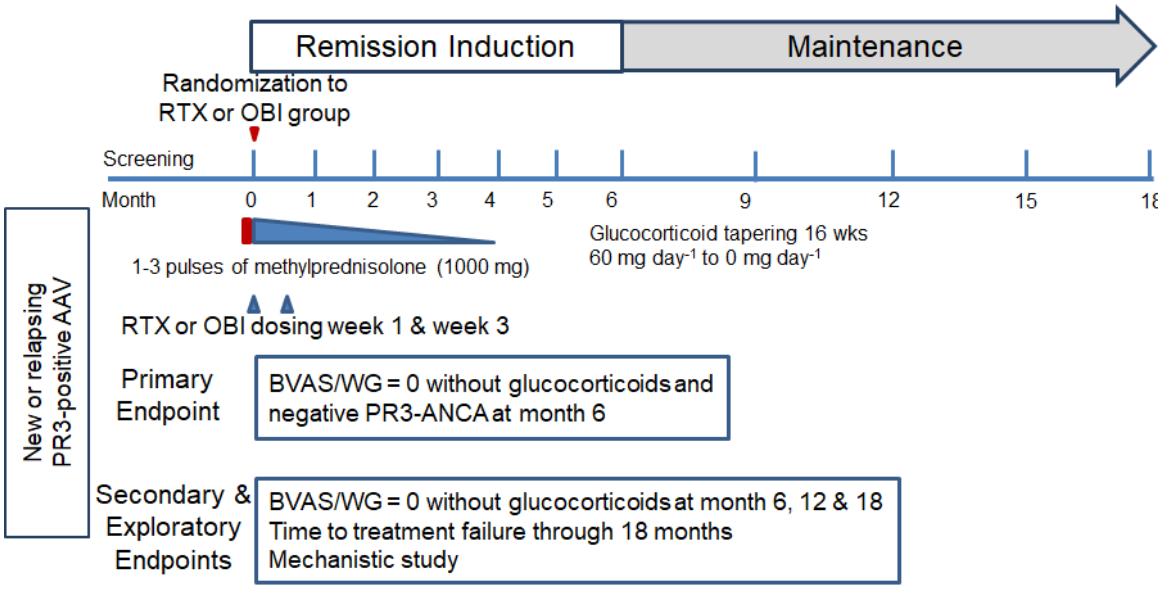
- The intravenous methylprednisolone will be followed by oral prednisone at a dose of 60 mg per day. The glucocorticoid dose will be tapered so that by week 2 of glucocorticoid treatment taper, the patients will take 30 to 40 mg/day prednisone equivalent. All patients who have a remission without disease flares will be off glucocorticoids completely by week 16. Patients will complete clinic visits at months 1, 2, 4, and 6 after the first infusion of study drug has been administered.

Patients who have received intravenous methylprednisolone and/or have started their oral glucocorticoid treatment as a part of standard of care will not repeat this therapy as a part of protocol requirements. Once patients are enrolled, they will continue oral glucocorticoid therapy according to the protocol specified tapering schedule.

Patients who achieve clinical remission will enter the maintenance phase and be evaluated every 3 months after the 6-month primary outcome assessment for a total of 18 months from the first dose.

Patients will be considered treatment failures if the glucocorticoid dose has to be increased either during the prednisone taper or after remission because of a disease relapse or if any other treatment for ANCA-associated vasculitis is prescribed to treat a disease relapse. The patients who experienced treatment failure with detectable B cells (≥5 cells/µl) will be offered open-label obinutuzumab accompanied by one to three intravenous methylprednisolone pulses (1000 mg each) starting on or within 10 calendar days of obinutuzumab followed by oral glucocorticoid dosing at the discretion of the investigator (but not to exceed the original specified glucocorticoid tapering regimen) to control the disease. Patients who experience a treatment failure and B cells are still depleted should be treated according to best medical judgment. Patients who respond to the re-treatment and achieve clinical remission will enter the maintenance phase and be evaluated every 3 months until the study completes. Any patient who experiences treatment failure should continue with study follow-up visits per the schedule of assessments through the end of study.

The study is completed when all randomized patients have been followed up for 18 months or have withdrawn prematurely. The study design is illustrated below.



Study Population:
30 patients with newly diagnosed or recurring PR3-AAV are planned. Each patient must meet the following criteria to be enrolled in this study.

1. Fulfillment of the definitions of the Second Chapel Hill Consensus Conference for ANCA-associated vasculitis (either granulomatosis with polyangiitis or microscopic polyangiitis).
2. Positivity for ANCA, directed against proteinase-3 (PR3).
3. Severe newly-diagnosed disease or relapsing disease.
4. Minimum BVAS/WG of 3 and the investigator deems standard treatment for severe disease is necessary.
5. Relapsing patients must have B cells detectable in the peripheral blood.
6. Patients must have completed the COVID-19 vaccination per current recommended CDC guidelines at least 4 weeks prior to enrollment. Patients who have recovered from COVID-19 prior to screening with a positive spike protein antibody test result but have not been vaccinated are also eligible.

Test Product, Dose, and Mode of Administration:
For patients assigned to the obinutuzumab arm: two infusions of obinutuzumab of 1000 mg each, administered 2 weeks apart

For patients assigned to the rituximab arm: two infusions of rituximab of 1000 mg each, administered 2 weeks apart

For patients who require re-treatment: two infusions of obinutuzumab of 1000 mg each, administered 2 weeks apart

Duration of Treatment with rituximab or obinutuzumab:
For all randomized patients: one course of treatment (2 infusions) completed in < 3 weeks.

For patients who require re-treatment: two courses of treatments, each course completed in < 3 weeks.

Efficacy Assessments:

- BVAS/WG
- PR3-ANCA assay

Exploratory Assessments:

- Mechanistic study comparing obinutuzumab and rituximab effects on changes in the peripheral blood cells by flow cytometry. The biomarker samples are intended to profile B cells and other relevant cell populations in patients with PR3-AAV before and after administration of obinutuzumab or rituximab.

Safety Assessments:

- Treatment-emergent adverse events
- Electrocardiogram
- Clinical laboratory testing
- Glucocorticoids Toxicity Index 2.0 assessment
- Vasculitis Damage Index assessment

Statistical Methods:
PRRR is an exploratory proof-of-concept study to evaluate the potential utility of obinutuzumab for the treatment of PR3-ANCA associated vasculitis. The planned sample size of 30 patients in two equal size groups is not powered to test the hypothesis that obinutuzumab is superior to rituximab. No sensitivity analyses (e.g., to account for missing data) and no adjustment for multiple comparisons will be conducted. Nominal p-values will be used to examine any trends in the endpoint.

The primary efficacy endpoint is defined as the proportion of patients achieving complete remission and ANCA negativity at month 6. Complete remission is defined as:

- BVAS/WG of 0; and
- No requirement for glucocorticoids beyond the prescribed 16-week prednisone taper.

Patients must achieve a complete remission as defined above and be ANCA-negative at month 6 in order to meet the primary efficacy endpoint.

The primary efficacy analysis is to compare the proportion of patients assigned to the obinutuzumab group who meet the primary efficacy endpoint criteria at month 6 to the proportion of patients assigned to the rituximab group who meet the primary efficacy endpoint criteria at month 6. Descriptive statistics (number and percent of subjects meet the primary efficacy endpoint criteria) will be reported by treatment group.

The following null (H_0) and alternative (H_a) hypotheses will be tested using Fisher's Exact test:

$$H_0: \pi \text{ obinutuzumab} - \pi \text{ rituximab} = 0$$
$$H_a: \pi \text{ obinutuzumab} - \pi \text{ rituximab} \neq 0$$

π obinutuzumab: proportion of patients assigned to the obinutuzumab group who achieve complete remission and ANCA negativity at month 6 month
π rituximab: proportion of patients assigned to the rituximab group who achieve complete remission and ANCA negativity at month 6

Two-sided Newcombe-corrected 95% confidence intervals of the risk difference between treatments with respect to the primary efficacy endpoint success rate will also be presented. It is not expected that the null hypothesis will be rejected at a two-sided 0.05 level of significance given the proof-of-concept nature of the study and given the small sample size; trends seen between treatment groups in the primary endpoint rate will be used to define future studies.

The above analyses on the primary efficacy endpoint success rate will be performed when all subjects have completed 6 months of follow-up (or would have completed 6 months of follow-up) had they not prematurely withdrawn.

Safety data includes adverse events (AEs), vital signs, ECG results, and clinical lab results including serum chemistry, hematology, and urinalysis.

The secondary endpoints are:

- To compare the proportion of subjects who achieve sustained complete remission at months 6, 12, and 18 (BVAS/WG = 0 without glucocorticoids) by administration of obinutuzumab or rituximab. These comparisons will be carried out using Fisher's Exact test.

- To compare the time to treatment failure through month 18 by administration of obinutuzumab or rituximab; patients will be considered treatment failures if the glucocorticoid dose has to be increased because of a disease relapse either during the prednisone taper or after the remission is achieved. A disease relapse is defined as an increase in the BVAS/WG of 1 point or more accompanied by a decision on the part of the investigator to increase treatment for PR3-AAV. Time-to-treatment failure will be compared between treatments using the log-rank test; Kaplan-Meier plots of time to treatment failure through 18 months will be generated for each randomized treatment group; patients not experiencing treatment failure will be censored at last known follow-up for these analyses.

The exploratory objectives are to be analyzed as comparison between the two treatment arms. Descriptive statistics will be reported by treatment group.

The exploratory biomarker samples and results will be analyzed and reported separately.

Study Conduct:

The clinical trial will be conducted in compliance with regulations (21 CFR 312, 50, and 56), guidelines for Good Clinical Practice (ICH Guidance E6), and in accordance with general ethical principles outlined in the Declaration of Helsinki; informed consent will be obtained from all participating patients; the protocol and any amendments will be subject to approval by the designated IRB prior to implementation, in accordance with 21 CFR 56.103(a); and subject records will be stored in a secure location and subject confidentiality will be maintained. The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

Date of Original Approved Protocol: Version 11JAN2021

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations	
AAV	ANCA-associated vasculitides
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
ANCA	antineutrophil cytoplasmic antibody
BVAS/WG	Birmingham Vasculitis Activity Score for Wegener's Granulomatosis
CD20	pan-B cell antigen
CDC	complement-dependent cytotoxicity
CLL	chronic lymphocytic leukemia
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DMARDs	disease-modifying antirheumatic drugs
ECG	electrocardiograms
eGFR	estimated glomerular filtration rate
FL	follicular lymphoma
FSH	follicle-stimulating hormone
GBM	glomerular basement membrane
GClb	obinutuzumab, in combination with chlorambucil
GPA	granulomatosis with polyangiitis
GTI	Glucocorticoids Toxicity Index
HACA	human anti-chimeric antibodies
HSFC	high-sensitivity flow cytometry
ICH	International Council for Harmonisation
IRR	infusion related reactions
IWRS	Interactive Web Response system
MDRD	Modification of Diet in Renal Disease
MPA	microscopic polyangiitis
MPO	myeloperoxidase
PBMC	peripheral blood mononuclear cells
PML	progressive multifocal leukoencephalopathy
PR3	proteinase 3
RTX	rituximab
SAE	serious adverse event
SF-36	Short-Form Health Survey
SUSAR	suspected unexpected serious adverse reaction

TB	tuberculosis
VDI	Vasculitis Damage Index
Definition of Terms	
Severe disease	at least one major BVAS/WG item or a BVAS/WG score ≥ 3 and the investigator deems standard treatment for severe disease is necessary.
Relapse	An increase in the BVAS/WG of ≥ 1 point accompanied by a decision on the investigator to increase treatment for PR3-AAV.
Severe relapse	at least one major BVAS/WG item or a BVAS/WG score ≥3 and the investigator deems standard treatment for severe disease is necessary.
Infusion related reactions (IRR)	any AEs during infusion or within 24 hours of completing the infusion that are considered related to the investigational products by the investigator
Complete remission	complete remission is defined as BVAS/WG = 0 without glucocorticoids

1 INTRODUCTION

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis or AAV are rare autoimmune diseases of unknown cause, characterized by inflammatory cell infiltration causing necrosis of blood vessels. The AAV comprise granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). The two ANCA specificities relevant to systemic vasculitis are myeloperoxidase (MPO) and proteinase 3 (PR3). The prevalence of AAV is estimated to be between 46 and 184 cases per million. These diseases are slightly more common in men than in women and are also more common among individuals older than 60 years of age, but the AAV are known to occur in individuals of all ages (Kitching et al., 2020).

Despite treatment advances over the past ten years, the AAV remain among the most aggressive forms of autoimmune disease. As discussed below, GPA is the form of AAV associated with the greatest unmet medical need. GPA, typically linked to the presence of anti-PR3-ANCA, can target virtually any organ but has particular predilections for the lungs, kidneys, peripheral nerves, eyes, and upper respiratory tract. If not diagnosed promptly and treated aggressively, PR3-AAV consistently leads to organ failure (e.g., mechanical ventilation, renal replacement therapy, crippling neuromuscular dysfunction), other major organ dysfunction, and death (Kitching et al., 2020; Yates and Watts, 2017).

The current treatment options for induction of remission in AAV include high doses of glucocorticoids accompanied by either rituximab or cyclophosphamide. We have conducted a randomized, double-blind, double-dummy controlled trial known as the RAVE trial, in which rituximab dosed at 375 mg m^{-2} once a week for four infusions plus glucocorticoids was shown to be non-inferior to cyclophosphamide plus glucocorticoids. The RAVE trial involved 197 AAV patients. The rituximab regimen in RAVE was shown to be non-inferior to the cyclophosphamide regimen, with 64% of the subjects in the rituximab group (compared to 53% in the cyclophosphamide group) achieving the primary outcome of complete remission at 24 weeks (Stone et al, 2010; Specks et al, 2013).

PR3-AAV is associated with high unmet medical need. Despite the overall success of rituximab in RAVE in comparison to the previous standard of care (cyclophosphamide), the subset of patients with PR3-AAV continues to experience major unmet need with regard to therapeutics. Several pieces of data illustrate this point:

- The RAVE trial showed that 29% of the PR3-AAV patients failed the primary outcome because of active disease, **despite** pulse methylprednisolone (1000 mg) times three doses, a prednisone taper of 5.5 months, and either rituximab or cyclophosphamide.
- The PR3-AAV patient population is at the highest risk for relapse following successful remission induction, thus requiring frequent retreatment with glucocorticoids and other agents exposing patients to cumulative morbidity and organ damage from cumulative glucocorticoid exposure and disease activity. The RAVE trial results confirmed this clearly:
- All 10 early treatment failures were PR3-ANCA+
- 11 of the 12 severe flares were PR3-ANCA+
- 17 of the 25 limited flares were PR3-ANCA+

- Only 23 of 65 PR3-ANCA+ patients achieved the outcome of complete clinical and serological remission at 24 weeks.

The achievement of ANCA negativity predicts long term disease control. In the RAVE trial only 1 (non-severe/limited) relapse was recorded when ANCA was still undetectable after rituximab treatment (Specks et al., 2013); all other relapses occurred in patients who did not achieve ANCA-negativity. Several other studies have confirmed that ANCA-negativity portends stable sustained clinical remission. A recent report from the UK showed that the PR3-ANCA-negative status after remission induction with rituximab is significantly associated with a longer time to relapse (PR3-ANCA-negative status: hazards ratio, 0.08 [95% confidence interval, 0.01-0.63, p = 0.016] (McClure et al., 2019). Another study from the Netherlands reported that patients who achieved and maintained PR3-ANCA negativity after remission induction with rituximab (n = 29) had few relapses (3%), whereas persistent PR3-ANCA positivity (n = 49) and reappearance of PR3-ANCA (n = 10) associated significantly with more relapses (37%, P = 0.002 and 50%, P = 0.002) (van Dam et al., 2020).

Obinutuzumab (GAZYVA™, GAZYVARO™), a humanized, glycoengineered Type II anti-CD20 monoclonal antibody (mAb), is directed to CD20, a membrane protein expressed on B lymphocytes. Obinutuzumab is licensed for use in oncology indications. Obinutuzumab, in combination with chlorambucil (GClb), has received regulatory approval for the treatment of previously untreated patients with chronic lymphocytic leukemia and for follicular lymphoma.

The properties of obinutuzumab include increased direct cell death induction and reduced complement-dependent cytotoxicity (CDC) activity as compared to rituximab, a chimeric Type I CD20 antibody. Obinutuzumab is the product of glycoengineering that results in increased binding affinity for FcγRIII, which leads to significantly improved cellular cytotoxicity in *in vitro* antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP)-based assays. In particular, the binding affinity of obinutuzumab to the low affinity FcγRIIIa (F158) is substantially increased, such that it exceeds that of rituximab for the high affinity FcγRIIIa (V158) receptor. As a result of improved direct cell death induction and ADCC/ADCP potency, obinutuzumab has the potential to deplete CD20+ B-cells, including tissue-resident CD20+ B-cells, to a greater degree than other anti-CD20 antibodies. The potency of obinutuzumab with regard to its ability to kill B-cells is approximately 100 times the potency of rituximab. This feature may lead to greater clinical efficacy (Gagez and Cartron et al, 2014).

In *ex vivo* autologous whole blood B-cell depletion studies with blood from healthy volunteers as well as CLL patients, obinutuzumab mediates superior B-cell depletion. In line with these findings, obinutuzumab showed superior ex vivo B-cell depletion relative to rituximab in blood samples from autoimmune patients with rheumatoid arthritis or systemic lupus erythematosus. Obinutuzumab was at least twofold more efficient than rituximab at inducing B-cell cytotoxicity in *in vitro* whole blood assays. The data generated to date imply that obinutuzumab is representative of a novel class of therapeutic anti-CD20 antibodies that may have superior efficacy compared with classical Type I and non-ADCC enhanced CD20 antibodies. Based on these nonclinical data, it can be anticipated that the combination of the recognition of a Type II epitope together with improved ADCC and ADCP potency exclusive to obinutuzumab might translate

into superior clinical efficacy for the treatment of autoimmune diseases where B-cell depletion may be effective. Details of the clinical experience of obinutuzumab are available in the Investigator's Brochure.

Results of a randomized, placebo-controlled phase II trial in patients with lupus nephritis (NOBILITY, NCT02550652) showed that obinutuzumab was superior to placebo for the achievement of complete and overall renal responses at week 52 when added to mycophenolate and glucocorticoids and that improved renal responses with obinutuzumab compared to placebo continued through week 104. No increase in the incidence of serious adverse events, serious infections or death compared with placebo were observed in this study (Furie et al., 2022).

A recent case report indicated that obinutuzumab was well tolerated, effectively depleted B-cells and induced remission in 3 patients with AAV in whom rituximab was contraindicated because of a previous anaphylactic reaction to rituximab (Amudala et al 2021). These properties have led to the hypothesis that obinutuzumab has greater efficacy compared to rituximab for the treatment of certain immune-mediated conditions, and that obinutuzumab will achieve this greater efficacy through deeper and more sustained depletion of pathogenic B-cells in secondary lymphoid organs and tertiary lymphoid structures.

This randomized, double-blind, active controlled study is designed to demonstrate that treating patients diagnosed with PR3-ANCA AAV with obinutuzumab may result with a sustained remission and proof the concept that a more complete B-cell depletion may predict a better clinical outcome.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to determine the proportion of patients achieving both complete remission and seronegativity for ANCA at 6 months. Complete remission is defined as a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) of 0 without glucocorticoids beyond the prescribed prednisone taper. Seronegativity for ANCA is defined as a negative test for antibodies directed against serine proteinase 3 (i.e., a negative PR3-ANCA assay).

2.2 Secondary Objectives

The secondary objectives of this study are:

- To compare the proportion of subjects who achieve sustained complete remission at month 6 after administration of obinutuzumab or rituximab. ***Complete remission* is *defined* as BVAS/WG = 0 without glucocorticoids**
- To compare the proportion of subjects who achieve sustained complete remission at month 12 after administration of obinutuzumab or rituximab.
- To compare the proportion of subjects who achieve sustained complete remission at month 18 after administration of obinutuzumab or rituximab.

- To compare the time to treatment failure through month 18 by administration of obinutuzumab or rituximab; Patients will be considered treatment failures if the glucocorticoid dose has to be increased at any point during the 18-month study period because of a disease relapse. ***Disease relapse* is *defined* as an increase in the BVAS/WG of ≥ 1 point accompanied by a decision on the part of the investigator to increase treatment for PR3-AAV**
- Time to treatment failure. ***Treatment failure* is *defined* as the event when the glucocorticoid dose has to be increased at any point during the 18-month study period because of a disease relapse.**

Follow-up in the trial will continue until all patients have been followed for 18 months.

2.3 Exploratory Objectives

The exploratory objectives are to compare between the two treatment groups for following outcomes:

- The number of disease relapses as defined in section 2.2.
- The Glucocorticoid Toxicity Index (GTI) scores (Cumulative Worsening Score and Aggregate Improvement Score) over time;
- The cumulative glucocorticoid dose administered orally;
- The cumulative glucocorticoid dose administered via intravenous or oral route;
- The number of severe relapses**. *Severe relapse* is *defined* as the occurrence of life- or organ-threatening disease manifestation(s); marked by an increase in the major BVAS/WG items of ≥ 3 at months 6, 12, 18 and the investigator deems standard treatment for severe disease is necessary.**
- The changes from baseline in Vasculitis Damage Index (VDI) over time;
- The time to clinical remission;
- The changes in estimated glomerular filtration rate (eGFR) based on CKD-Epi equation without correcting for race;
- The proportion of patients achieving and maintaining complete peripheral blood B cell depletion (CD19+) at each study visit by high sensitive flow cytometry (HSFC)
    - Proportion of patients achieving B-cell depletion (HSFC) at specified timepoints.
    - Proportion of patients with sustained B-cell depletion (HSFC) over time.
- The kinetics of ANCA:
- Time to negative testing for ANCA
- Time to recurrence of a positive test for ANCA (after negative testing);
- The kinetic of recurrence of PR3-specific (autoantigen-specific) B cells after B cell depletion
- The changes from baseline on AAV patient reported outcome (AAV-PRO) assessment over time
- Vasculitis Clinical Research Consortium (VCRC) Granulomatosis with polyangiitis/ microscopic polyangiitis (WG/MPA) disease activity and transition assessment over time

2.4 Safety Objectives

To determine the safety profile of patients administered obinutuzumab by assessing:

- Treatment emergent adverse events
- Treatment emergent serious adverse events
- Laboratory testing
- Glucocorticoid use related toxicity using Glucocorticoids Toxicity Index (GTI) 2.0
- Treatment emergent adverse events of special interest including:
    - Infusion related reactions (IRR)
    - Grade 3 or higher infections
    - Hepatitis B reactivation
    - Progressive multifocal leukoencephalopathy (PML)
    - Drug-related neutropenia
    - Drug-related thrombocytopenia
    - Gastrointestinal perforations
    - Worsening of pre-existing cardiac conditions.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a double-blind, randomized, active controlled multi-center phase 2 study to evaluate the efficacy and safety of obinutuzumab for the treatment of PR3-AAV. The study will enroll approximately 30 patients who have clinical diagnoses of either granulomatosis with polyangiitis or microscopic polyangiitis. All patients enrolled must have positive serum assays for PR3-ANCA, manifestations of severe disease, and a BVAS/WG of ≥ 3 (Thompson et al., 2020). ***Severe disease* is *defined* as at least one major BVAS/WG item or a BVAS/WG>= 3 and the need for standard therapy for severe disease as per investigator.** Patients who are positive for serum assays for ANCA directed against myeloperoxidase (MPO-ANCA) will be excluded.

3.1.1 Remission Induction Period

Eligible patients will be randomly assigned in a 1:1 ratio to receive two doses of either rituximab or obinutuzumab (both drugs dosed at 1000 mg per infusion). Infusions will be given approximately two weeks apart, on day 0 and day 14. All randomized patients will be prescribed a specified glucocorticoid regimen. The glucocorticoid regimen will include one to three pulses of methylprednisolone (1000 mg each) starting on or within 10 calendar days of study day 0 followed by prednisone at a dose of 60 mg per day. The glucocorticoid dose will be tapered so that by week 2 of glucocorticoid treatment taper, the patients will take no more than 40 mg/day prednisone equivalent. All patients who have a remission without disease flares will be off glucocorticoids completely in 16 weeks. Patients will complete clinic visits at months 1, 2, 4 and 6 after the first infusion has been administered.

3.1.2 Maintenance Phase

Patients who respond to treatment and achieve clinical remission will enter the maintenance phase and be evaluated every 3 months after the 6-month primary outcome assessment for a total of 18 months from the first dose. Patients will be considered treatment failures if the glucocorticoid dose has to be increased either during the prednisone taper or after remission because of a disease relapse or if any other treatment for ANCA-associated vasculitis is prescribed to treat a disease relapse. The patients who experienced treatment failure with detectable B cells (≥5 cells/μl) will be offered open-label obinutuzumab accompanied by one to three intravenous methylprednisolone pulses (1000 mg each) starting on or within 10 calendar days of obinutuzumab followed by oral glucocorticoid dosing at the discretion of the investigator (but not to exceed the original specified glucocorticoid tapering regimen) to control the disease. Patients who experience a treatment failure and B cells are still depleted should be treated according to best medical judgment. Patients who respond to the re-treatment and achieve clinical remission will enter the maintenance phase and be evaluated every 3 months until the entire study completes. Any patient who experiences treatment failure should continue with study follow-up visits per the schedule of assessments through the end of study.

All patients will be followed until they will have completed 18 months of follow-up or withdraw from the study prematurely.

The specific visit schedule is presented in Section 7, Table 5. The study design is illustrated in Figure 1.

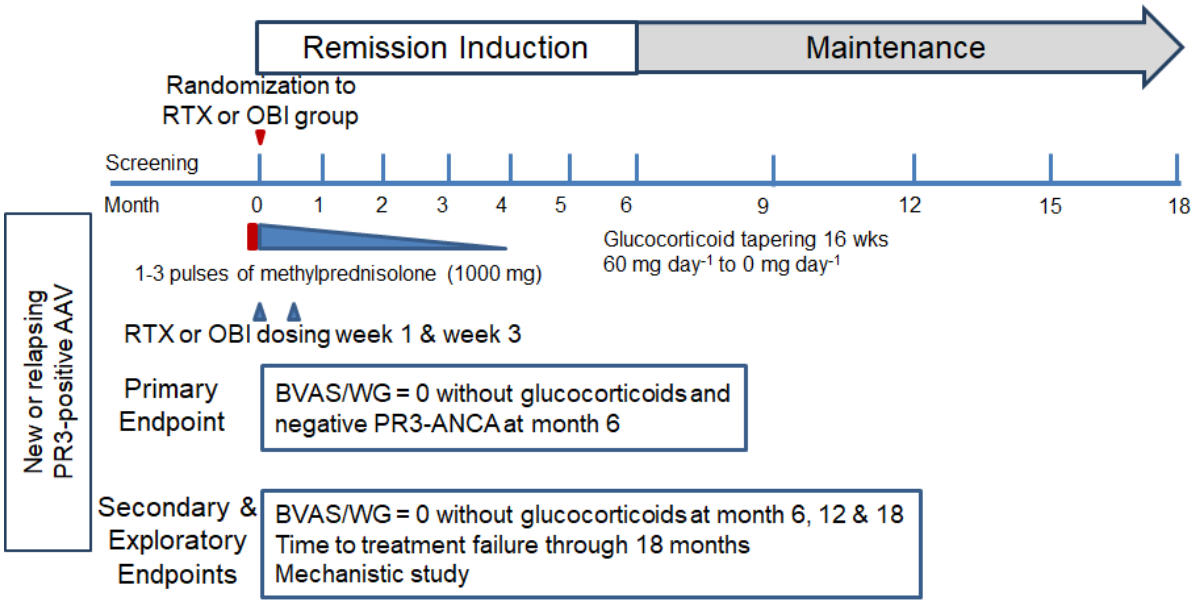


Figure -1 PRRR Study Design

3.1.3 Endpoint Analysis

The primary endpoint of comparing the proportion of patients who achieve complete remission and ANCA negativity will be conducted after all patients have completed the 6-month remission induction period. The data pertinent to the primary efficacy analysis will be source verified, locked and transferred to an independent statistician to perform the limited analysis. The statistical analysis plan will be developed and finalized prior to the analysis. This will be the only analysis to be conducted for the specified endpoint and the summary results without individual patient information will be available to a limited number of recipients. The investigators will continue to be blinded to the patient treatment assignment throughout the remainder of the follow-up period.

The 6-month analysis will be treated as an interim analysis with regard to the blinding and data handling. Since the treatment regimen will be completed after the second study drug infusion and the primary efficacy analysis is conducted once at the 6-month time point, no multiplicity adjustment will be used for the analysis.

3.2 Known and Potential Risks and Benefits to Participants

3.2.1 Risks Associated with Rituximab

No dose-limiting adverse effects were observed in phase I–III trials that evaluated the safety and efficacy of rituximab in participants with lymphoma. The most commonly observed infusion-

related adverse effects were chills or rigors, fever, fatigue, headache, hypotension, nausea, leukopenia, angioedema, and pruritus. Fever, chills, headache, nausea, vomiting, rhinitis, and mild hypotension occurred primarily during rituximab infusions; these adverse events typically responded to interrupting and then resuming the infusion at a slower rate. Infusion reactions were seen in 1 (1%) patient with AAV who was treated with rituximab in the RAVE study (Stone et al., 2010). Details of the risks associated with rituximab treatment are described in rituximab prescribing information. Management of IRRs follows routine clinical protocols consistent with the prescribing information and the approved use of rituximab and obinutuzumab for other indications.

3.2.2 Risks Associated with Obinutuzumab

Risks associated with obinutuzumab treatment are described in the obinutuzumab Investigator's brochure Section 6.3. The most frequently observed adverse drug reactions in patients receiving obinutuzumab were infusion related reactions (IRRs) which occurred predominantly during infusion of the first 1000 mg. A decreased incidence of IRRs was observed after prevention of IRRs including adequate glucocorticoid, oral analgesic/anti-histamine, omission of antihypertensive medication was implemented. The incidence and severity of infusion-related symptoms decreased substantially after the first 1000 mg was infused, with most patients having no IRRs during subsequent administrations of obinutuzumab. Management of IRRs follows routine clinical protocols consistent with the prescribing information and the approved use of rituximab and obinutuzumab for other indications.

In the majority of patients, irrespective of indication, IRRs were mild to moderate and could be managed by the slowing or temporary halting of the first infusion, but severe and life-threatening IRRs requiring symptomatic treatment have also been reported. IRRs may be clinically indistinguishable from IgE-mediated allergic reactions (e.g., anaphylaxis). The rates of Grade 3-4 IRRs were similar before and after mitigation measures were implemented.

3.2.3 Data and Safety Monitoring Board (DSMB)

An independent DSMB will include 2 to 3 physicians who are rheumatologists or experts in a related field and a statistician. It is the DSMB's responsibility to weigh risks and benefits throughout the study's duration. Specifically, this role includes: monitoring evidence for treatment harm such as toxicity, adverse events, serious adverse events or deaths. The sponsor medical team will prepare the safety summary and participate in the safety review discussion.

The DSMB will convene for safety data review meetings after 10 patients have been treated and completed the 1-month visit (V4) and once every 6 months until the study completion. Records for adverse events, laboratory values, vital signs and disease status will be reviewed. The DSMB may recommend the study protocol be modified if major safety concerns occur.

3.3 Rationale for Study Design and Control Group

3.3.1 Rationale for the Study Design

Rituximab has been shown to be non-inferior to cyclophosphamide for patients with AAV in a randomized controlled trial Rituximab in ANCA-Associated Vasculitis (RAVE) trial (Stone et al., 2010). In the RAVE trial, 64% of the subjects in the rituximab group, compared to 53% in the cyclophosphamide group, achieving the primary outcome of complete remission at 24 weeks. In a subgroup analysis, rituximab treatment was superior to cyclophosphamide in PR3-ANCA positive patients, and this difference was statistically significant.

The subset of patients with PR3-AAV, which comprises approximately two thirds of patients evaluated in Western countries, represents the greatest unmet need in AAV. Results from the RAVE trial indicated that PR3-AAV patients had a higher rate of treatment failures and a higher percentage of severe relapses following successful remission induction, thus requiring frequent retreatment with glucocorticoids and other agents exposing patients to cumulative morbidity and organ damage from cumulative glucocorticoid exposure and disease activity. It is hypothesized that obinutuzumab may be superior to rituximab for the treatment of PR3-positive AAV patients based on the improved B-cell elimination potency and longer duration of B-cell depletion than that of rituximab.

This study is a randomized, double-blind, active-controlled trial to explore how obinutuzumab compares to rituximab for remission induction of PR3-AAV. The trial will also test the hypothesis that obinutuzumab treatment at baseline is associated with a longer time to relapse compared with rituximab treatment.

3.3.2 Rationale for the Dose Selection

In the RAVE protocol, rituximab therapy comprised 4 doses of rituximab 375 mg/m^2 per week in conjunction with glucocorticoids starting dose of 1 mg/kg/day and tapering to glucocorticoids free by month 5. This regimen has been modified to include two infusions of 1000 mg per dose 2 weeks apart on day 0 and day 14. The induction and follow up rituximab dose is planned as 1000 mg infusions. The rituximab regimen is selected based on the study by Jones et al. demonstrating that patients administered with 4 infusions of 375 mg/m^2 or 2 infusions of 1000 mg two weeks apart had comparable B cell depletion and similar rates of remission as a function of time in patients with refractory AAV (shown in Figure 2 below) (Jones et al., 2009). In addition, a recent study of comparison of two rituximab regimens for remission induction in ANCA-associated vasculitis showed a similar treatment effect whether rituximab was administered for 2 or 4 infusions. (Renard V. Abstract 2048 at American College of Rheumatology, November 2020).

Reducing the requirement for clinical visits without compromising the effectiveness of the treatment likely results in better treatment compliance.

3.3.3 Rationale for the 16-Week Glucocorticoid Tapering Schedule

A glucocorticoid tapering regimen that gradually reduces the prednisone dose from 60 mg per day on week 1 to 5 mg per day on week 13 to completely discontinues prednisone use by the end of week 16 is specified (section 5.6.2,). A multicenter survey of rituximab therapy for refractory of ANCA+ AAV patients demonstrated that the glucocorticoid taper of 4 months compared to the 5.5 months employed in the RAVE trial would not subject the patients to undue risk and will reduce the overall glucocorticoid use (Jones et al., 2009). The duration of the glucocorticoid taper will be extended to 16 weeks to maintain the goal of reducing the overall steroid use while

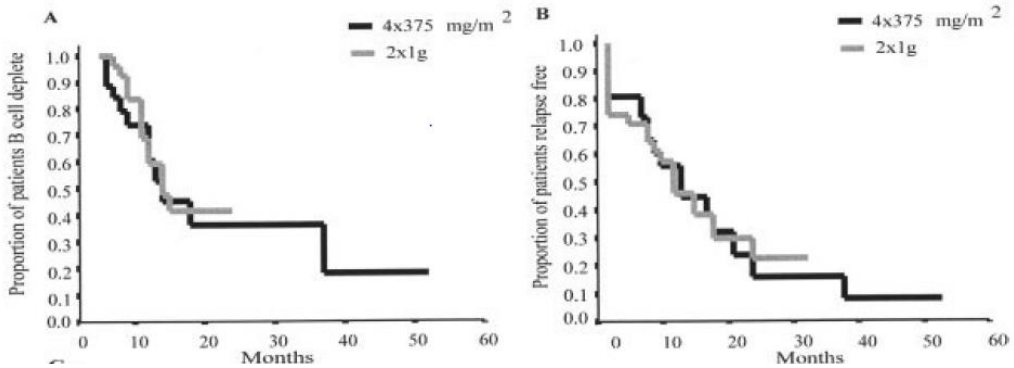


Figure 2 ***(Jones et al. Arthritis & Rheumatism Vol. 60, No. 7, July 2009, pp 2156–2168)***

approximating the standard 4 to 6 months of glucocorticoids tapering schedule. The tapering schedule would be consistent with the 2009 European League Against Rheumatism (EULAR) recommendations for AAV to be between 7.5 mg and 10 mg of prednisolone after 3 months of treatment.

The investigator may increase the glucocorticoid dose if clinically indicated.

3.3.4 Selection of the Primary and the Key Secondary Endpoints

Patients diagnosed with PR3-AAV represent the greatest unmet need in AAV. The achievement of ANCA negativity following treatment is associated with long-term disease control, even though "cure" for PR3-AAV remains elusive. The achievement of sustained complete remission reduces patients' risk from the combined threats of active AAV and complications of treatment, particularly glucocorticoids. (McClure et al., 2019; Specks et al., 2013; van Dam et al., 2020).

3.4 Study Duration and Dates

The remission induction period of the study includes up to 14 days of screening and 6 months of monitoring. The study maintenance period is 1 year after the 6-month induction period. The total duration of the study is approximately 18.5 months for each patient.

4 STUDY POPULATION SELECTION

4.1 Study Population

Thirty (30) patients with severe newly-diagnosed or recurring PR3-AAV are planned.

4.2 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study.

1. Subjects aged 18 or greater.
2. Fulfillment of the definitions of the Second Chapel Hill Consensus Conference for ANCA-associated vasculitis (either granulomatosis with polyangiitis or microscopic polyangiitis).
3. Positivity for ANCA, directed against proteinase-3 (PR3).
4. Severe newly-diagnosed disease or severe relapsing disease. **Severe relapsing disease** is **defined as** at least one major BVAS/WG item or a score ≥ 3 and the investigator deems standard treatment for severe disease is necessary.
5. Minimum BVAS/WG of 3.
6. Relapsing patients must have B cells detectable in the peripheral blood.
7. Patients must have completed COVID-19 vaccination (per current recommended CDC guidelines) at least 4 weeks prior to enrollment. Patients who have recovered from COVID-19 prior to screening with a positive spike protein antibody test result but have not been vaccinated are also eligible.
8. Female subjects of childbearing potential who are not sterile must agree to use an acceptable method of contraception for 18 months after the last dose of infusion medication. Male subjects who are not sterile whose female partners are of childbearing potential must agree to use an acceptable method of contraception for 180 days after the last dose of infusion medication.
    - Females of childbearing potential include any female who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (to be considered postmenopausal, the patient must have had amenorrhea for >12 consecutive months).
    - Acceptable methods of contraception include the use of at least two of the following: 1) intrauterine device; 2) hormonal contraceptives for at least 30 days prior to first dose infusion (oral, injectable, implant or ring); 3) barrier contraceptives (condom or diaphragm) with spermicide; or 4) abstinence.

4.3 Exclusion Criteria

Patients who present any of the following criteria will be excluded from the study.

1. Diagnosis with eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome) as defined by the Chapel Hill Consensus Conference.
2. Positive serum assays for ANCA directed against myeloperoxidase (MPO-ANCA)
3. Non-severe AAV, defined as disease that does not justify treatment with both B cell depletion and a four-month glucocorticoid taper.

4. Any of the co-morbidities:
   - Allergies: a history of severe allergic reactions to human or chimeric monoclonal antibodies or murine protein.
   - Infection (systemic): an active systemic infection at screening visit.
   - Infection (deep space): have been diagnosed as having a deep-space infection, such as osteomyelitis, septic arthritis, or pneumonia complicated by empyema or lung abscesses, within 6 months prior to the screening visit.
   - Infection (blood borne): active hepatitis B or active hepatitis C or a documented history of HIV, hepatitis B, or hepatitis C.
   - Infection (history): History of recurrent significant infection or history of recurrent bacterial infections
   - Liver disease: acute or chronic liver disease that is deemed sufficiently severe to impair their ability to participate in the trial.
   - Renal disease: a history of documented anti-glomerular basement membrane disease (anti-GBM disease).
   - Malignancy: Active or history of malignancy in the last 5 years. Individuals with squamous cell orbasal cell skin carcinomas and individuals with cervical or ductal carcinoma in situ may be enrolled if they have received curative surgical treatment.
   - Active COVID-19 infection.
   - Uncontrolled disease: evidence of glucocorticoid dependent disease (such as asthma, COPD, psoriasis or IBD, etc.) requiring consistently greater than 10 mg of prednisone for disease control which might affect endpoint assessment or,
   - Other uncontrolled diseases, including any uncontrolled psychiatric disorders, drug and alcohol abuse, that could interfere with participation in the trial according to the protocol.
5. Known diagnosis of human anti-chimeric antibodies (HACA) formation.
6. Subjects who are premenopausal and are:
   - Pregnant on the basis of a serum pregnancy test,
   - Breastfeeding, or
   - Do not agree to use effective method(s) of contraception.
7. Use of prohibited medications: They have used any of the prohibited medication listed in Section 5.7.1.
8. Plasma exchange: They have been treated with plasma exchange within the 3 months preceding the screening visit.
9. History of intolerance to rituximab or other chimeric monoclonal antibodies (e.g., infliximab).
10. Recent vaccination: They have had a live vaccine fewer than 4 weeks (28 days) before or during randomization (vaccination with live vaccine through the end of study participation is contraindicated).
11. Daily use of non-steroidal anti-inflammatory drugs (NSAIDs)
12. Exclusion criteria related to laboratory parameters:
    a. Bone marrow suppression as evidenced by a total white count < 4 x10 /l, hemoglobin < 7 gm/dl or platelet count < 100,000/µl

b. Aspartate aminotransferase or alanine aminotransferase or amylase > 2.5 times the upper limit of normal, unless attributed to vasculitis

5 STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 Obinutuzumab

Obinutuzumab is a humanized and glycoengineered Type II anti-CD20 mAb of the IgG1 subclass. The molecular mass of the antibody is approximately 150 kDa. Obinutuzumab is provided as a single 1000 mg dose in a 50 mL glass vials containing 40 mL of 25 mg/mL liquid concentrate. In addition to the antibody, the liquid also contains histidine/histidine-HCl, trehalose, poloxamer 188 and water.

Obinutuzumab dosing solution will be prepared within 24 hours of scheduled dosing at 2°C to 8°C (36°F to 46°F) by diluting 40 mL (1000 mg) of obinutuzumab into a 250 mL 0.9% sodium chloride infusion bag.

5.1.2 Rituximab

Rituximab (RITUXAN) injection is a sterile, preservative-free, clear, colorless solution for intravenous infusion supplied as one 500 mg/50 mL (10 mg/mL) single-dose vial NDC 50242-053-06. Rituximab dosing solution will be prepared within 24 hours of scheduled dosing at 2°C to 8°C (36°F to 46°F) by diluting 1000 mg of rituximab into a 250 mL 0.9% sodium chloride infusion bag.

5.1.3 Infusion Solution

Obinutuzumab or rituximab does not contain antimicrobial preservatives. Therefore, care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation. If not used immediately, the prepared solution may be stored up to 24 hours at 2-8°C.

The infusion must be completed within 48 hours at room temperature (≤ 30°C/86°F) after the final dosing solution is prepared. No incompatibilities between obinutuzumab or rituximab and polyvinyl chloride or polyolefin infusion materials have been observed in concentration ranges from 0.4 mg/mL to 20.0 mg/mL after dilution.

5.2 Treatments Administered

5.2.1 Pre-Medication

Prior to start infusion, premedication with antihistamine (diphenhydramine 50mg) will be prescribed to reduce the potential infusion reactions. All patients will be prescribed with 650 mg to 1000 mg acetaminophen approximately 30 minutes before study drug infusion starts.

5.2.2 Obinutuzumab or Rituximab

Obinutuzumab or rituximab is administered via intravenous infusion at 1000 mg per dose. Patients will receive two doses of obinutuzumab or rituximab administered on day 0 and on day 14 (+/- 2 days).

First infusion: Administer at 50 mg/hr. The rate of the infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.

Subsequent infusions if no adverse events with first infusion: May start at 100 mg/hour and increase at 100 mg/hour every 30 minutes to maximum rate of 400 mg/hour if no adverse events occur.

5.2.3 Handling Potential Infusion Reactions

The handling of potential infusion reaction is outlined in the Investigator's Brochure and summarized below. If a patient experiences a reaction of any grade during infusion, adjust the infusion as the following:

- Grade 4 (life threatening): Stop infusion immediately and permanently discontinue dosing.
- Grade 3 (severe): Interrupt infusion and manage symptoms. Upon resolution of symptoms, consider restarting infusion at no more than half the previous rate (the rate being used at the time that the infusion reaction occurred) and, if patient does not experience any further infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose. Permanently discontinue treatment if patients experience a Grade 3 infusion related symptom at re-challenge.
- Grade 1-2 (mild to moderate): Reduce infusion rate or interrupt infusion and treat symptoms. Upon resolution of symptoms, continue or resume infusion and, if patient does not experience any further infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose.

The following medications may be used for infusion reactions as needed:

Drug	**Dose**	**Indication**
Acetaminophen 325 mg tablet	650 mg PO Q 4 hours prn	Infusion related reactions or temperature greater then 38 degree Celsius (100.4 F)
Diphenhydramine 25 mg/mL	25 mg IVPU Q 4 hours prn	Infusion related reactions; may repeat once if symptoms are not relieved within 15 minutes of initial dose.

Meperidine 25 mg/mL	25 mg IVPU Q 15 min, prn	Rigors, may repeat once (Max dose 50 mg)
Prochlorperazine 10 mg/mL	10 mg IVPU Q 6 hours, prn	Nausea and Vomiting

5.3 Selection and Timing of Dose for Each Patient

Rituximab and obinutuzumab will be dosed according to the same regimens. The two doses of both drugs will be administered approximately 2 weeks apart, on Day 0 at week 1 and on day 14 (±2 days). A window of ± 2 days is permitted to accommodate potential scheduling conflict.

5.4 Patients will be considered treatment failures if the glucocorticoid dose has to be increased either during the prednisone taper or after remission because of a disease relapse or if any other treatment for ANCA-associated vasculitis is prescribed to treat a disease relapse. The patients who experienced treatment failure with detectable B cells (≥5 cells/µl) will be offered open-label obinutuzumab accompanied one to three intravenous methylprednisolone pulses (1000 mg each) starting on or within 10 calendar days of obinutuzumab followed by oral glucocorticoid dosing at the discretion of the investigator (but not to exceed the original specified glucocorticoid tapering regimen) to control the disease. Patients who experience a treatment failure and B cells are still depleted should be treated according to best medical judgment. Patients who respond to the re-treatment and achieve clinical remission will enter the maintenance phase and be evaluated every 3 months until the study completes. Any patient who experiences treatment failure should continue with study follow-up visits per the schedule of assessments through the end of study.Method of Assigning Patients to Treatment Groups

The study will be conducted at 3 investigative sites in the US and will likely involve variable numbers of patients at each site. Enrollment will be on a competitive basis but will not exceed 15 patients (50% of the total) per site. Eligible patients who have completed the screening period and meet all study inclusion/exclusion requirements will be randomized in a 1:1 ratio to receive investigational products. Patients will be assigned to treatment groups in sequential order as they qualify for the study following the randomization procedure provided in Section 5.4.9. Randomization will be stratified according to the baseline renal function (≥ 30 or < 30 mL min^{-1} per 1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equation without the race factor (Levey et al., 2009) (Appendix 4).

5.4.1 Pre-Registration of a Subject

To pre-register a subject, access the Mayo Clinic Research Registration Application at [redacted]. The Research Registration Application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, email the Research Registration Office at [redacted] between the hours of 8:00 am and 4:30pm Central Time (Monday through Friday).

The instructions for the application are available on the Mayo Clinical Office of Clinical Trials web page [redacted] and detail the process for completing and confirming patient pre-registration. Prior to registering/randomizing, this pre-registration process must be completed in its entirety and a Mayo Clinic subject ID number must be available as noted in the instructions.

5.4.1.1 – Verification of Materials

Prior to accepting the pre-registration, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient Pre-Registration Eligibility
- Existence of a signed informed consent form
- Existence of a signed authorization for use and disclosure of protected health information.

5.4.1.2 – Pre-registration Tests/Procedures

Pre-registration tests/procedures must be completed with the guidelines specified on the test schedule.

5.4.2 Documentation of IRB approval

Documentation of IRB approval must be on file in the Research Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with Research Site Management (Fax: [redacted] or email [redacted]). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted, and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Research Registration Office is no longer necessary.

5.4.3 Registration and Randomization of a Subject

To register and randomize a patient, access the Mayo Clinic Research Registration Application at [redacted] The registration/ randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, email Research Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Prior to initiation of protocol treatment, this process must be completed in its entirety and an MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact Research Registration Office at [redacted]. If the patient was fully registered and randomized, the Research Registration Office staff can access the information from the centralized database and confirm the registration.

- Refer to the Research Registration Application training course on the Mayo Clinic Office of Clinical Trials webpage (link above) for instructions on viewing the patient's registration & randomization confirmation.

5.4.4 Correlative Research

An optional correlative research component for biomarker sample testing is part of this study. At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research of Anti-Neutrophil Cytoplasmic Antibody (ANCA-)Associated Vasculitis at Mayo.

- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.

- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

5.4.5 Treatment on Protocol

Treatment on this protocol must commence at an approved designated institution under the supervision of a medically licensed physician. All required baseline symptoms must be documented and graded.

5.4.6 Treatment Start

Treatment cannot begin prior to registration and must begin ≤14 days after registration.

5.4.7 Pretreatment

Pretreatment tests/procedures (See Section 7.2.1) must be completed within the guidelines specified on the test schedule.

5.4.8 Study Drug

Study drug is verified as being available on site. Obinutuzumab and rituximab will be shipped directly to each site from Genentech. (See Section 5.10 for Study drug storage and accountability). Each participating institution will be responsible for monitoring drug supplies and will order additional supplies as needed from Genentech.

5.4.9 Randomization Procedures

After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups (Pocock SH, Simon R. Sequential Treatment Assignment with Balancing for Prognostic Factors in the Controlled Clinical Trial. Biometrics 31(1):103-115, 1975, Mar.)

- Treatment 1: Two infusions of obinutuzumab of 1000 mg each administered 2 weeks apart.

- Treatment 2: Two infusions of rituximab of 1000 mg each administered 2 weeks apart.

After treatment assignment has been ascertained by the registration/randomization application as specified in section 5.4.3, the registration specialist will notify the designated unblinded data manager/nurse/pharmacist at the patient's institution. The name of this contact person is to be entered in the designated space on the eligibility checklist, so the Registration Office personnel have it for each patient at the time of registration. Make sure this contact person will be available at the time of registration so they can take a call from the registration specialist if necessary. This contact person may not be involved in assessing adverse events or any other outcome measure and should not be the same person listed on the Eligibility Checklist Form as the person completing the form. The last page of the Eligibility Checklist Form should provide the sources of communication, either fax or email, and the appropriate contact information. The registration specialist will then communicate the treatment assignment to the designated unblinded contact at the patient's institution.

The unblinded pharmacist will maintain records that indicate the identity of the patient and their corresponding treatment assignment.

5.5 Blinding

During the study conduct, the Sponsor investigator, clinical investigators, clinical site staff, the data coordinating center will be blinded to the patient treatment assignment. On the day of randomization, the research pharmacist who will prepare the dosing solution will obtain the randomization code for the patient based on a communication from the registration specialist (See Section 5.4.9). On the days of dosing, the pharmacist will prepare the dosing solution and label the infusion bag with the patient identification, the randomization number and date and time of the infusion solution preparation.

Situations requiring codes to be broken:

There are two distinct situations in which it is appropriate to break the codes for individual patients enrolled in double-blind trials:

- In the event of an emergency for an individual patient.
- In the event that it would be helpful for the future clinical care of an individual patient after she/he has completed participation in the trial.

If knowledge of the investigational product ingredients is needed on an emergency basis for clinical management of the subject's condition, the investigator will contact the unblinded pharmacist to obtain the treatment assignment. If unblinding occurs for any reason, the time and reason for breaking the blind will be recorded on the case report form (CRF) and the sponsor investigator must be notified within 24 hours.

If, in the judgment of the attending physician, it would be helpful for the future clinical care of the individual patient, the code may be broken after the patient has completed the study. That is, after the patient has been fully evaluated and all evaluation information has been recorded by the attending physician and the patient (if appropriate), the MCCC Registration Office may be emailed to find out which study therapy the patient was receiving.

Unblinded data will be provided to the DSMB by a designated unblinded statistician. Unblinding will be an anticipated step in the evaluation of a suspected unexpected serious adverse reaction (SUSAR). Upon receipt of information supporting a potential SUSAR, the manager responsible for the pharmacovigilance will obtain the individual treatment assignment from the unblinded statistician and communicate it to the Mayo Clinic monitor to complete the submission of an expedited safety report.

5.6 Concomitant Therapy

Concomitant medications are prescription medications, over-the-counter drugs, or dietary supplements that a study participant takes after enrollment in addition to the study drugs defined in the protocol. Concomitant medications may be used by patients for AAV or for other indications.

Concomitant medications administered during the study are to be recorded on the CRF until the end of the study. The medication name, dose, frequency, route of administration, date(s) of administration and reason for administration must be recorded.

5.6.1 Antimicrobial Prophylaxis

Antimicrobial prophylaxis is recommended. The choice and timing of medication is at the investigator's discretion (e.g., Bactrim-1 single strength tablet daily, dapsone-100 mg daily and atovaquone-700 mg twice daily). Specifically, prophylaxis against *Pneumocystis Jirovecii* Pneumonia is strongly recommended for the duration of the participation in the trial.

The medication name, dose, frequency, route of administration, dates of administration and reason for administration must be recorded in the concomitant medication form.

5.6.2 Glucocorticoid Taper

All randomized patients will be prescribed the same glucocorticoid regimen. The glucocorticoid regimen will include one to three pulses of methylprednisolone (1000 mg each) starting on or within 10 calendar days of study day 0 followed by prednisone at a dose of 60 mg per day. The initial treatment with methylprednisolone may start while data for eligibility confirmation are pending. If their first RTX/OBI infusion coincides with one of the methylprednisolone pulses of 1000 mg, then the patient can receive the 1000 mg of methylprednisolone as their pre-RTX/OBI glucocorticoid infusion. If the patients have already completed the three methylprednisolone pulses, they will receive only 60 mg of methylprednisolone before the rituximab or obinutuzumab infusion that day.

The glucocorticoids dose is to be tapered so that by week 17, all patients who have achieved a clinical remission without disease flares will have discontinued glucocorticoids. The recommended tapering of glucocorticoids is outlined in Table 1.

Table 1 Glucocorticoid Tapering Schedule

Taper Week	1	2	3 - 4	5 - 6	7 - 8	9 – 10	11 - 12	13 - 14	15 - 16	17
Prednisone Dose (mg/day)	60	30 - 40	25 - 30	20	15	10	7.5	5	2.5	0

Patients may take their own supply of glucocorticoid. The prednisone equivalents are outlined in Table 2 below:

Table 2 Prednisone Equivalents

Prednisone	**60 mg**
Hydrocortisone	240 mg
Prednisolone	60 mg
Triamcinolone	48 mg
Methylprednisolone	48 mg
Dexamethasone	9 mg
Betamethasone	7.2 mg
Cortisone	300 mg

Short term (up to 5 days) glucocorticoid treatment for the treatment of co-morbid conditions beyond the protocol specified taper may be permitted on a case-by-case basis. Investigators should contact the study medical monitor as soon as possible when this is needed. Patients approved by the medical monitor to receive short term (up to 5 days) glucocorticoids for the treatment of co-morbid conditions will not be considered treatment failures as glucocorticoids are not given due to disease relapse.

5.7 Restrictions

5.7.1 Prior Therapy

Patients with a history of intolerance to rituximab or other chimeric monoclonal antibodies (e.g., infliximab) are not eligible. Patients who have been treated with an anti-CD20 agent before are eligible if their CD19+20+ B lymphocytes have detectable B cells (minimum 5 cells/uL) in the peripheral blood at the time of enrollment. The following medications are prohibited:

- Cyclophosphamide - prohibited within three months prior to baseline (Visit 2)
- IVIg (for the purpose of treating AAV) - prohibited within one month of baseline
- Plasma exchange - prohibited within one month of baseline
- Avacopan is not allowed as adjunct therapy for remission induction or maintenance
- Other biologic disease-modifying anti-rheumatic drugs (DMARDs) must be stopped one month before baseline or for five half-lives, whichever is longer. Examples of DMARDs are listed in Table 3 below.

Table 3 Examples of Biologic DMARDs

Generic Name	Trade Name
Abatacept	Orencia
Adalimumab	Humira
Anakinra	Kineret
Certolizumab	Cimzia
Etanercept	Enbrel
Golimumab	Simponi
Infliximab	Remicade
Rituximab	Rituxan
Tocilizumab	Actemra

Patients taking methotrexate, azathioprine, mycophenolate mofetil, or leflunomide at the time of screening must stop these medications before the baseline visit. Patients taking leflunomide will have to undergo cholestyramine treatment for washout in addition to discontinuation of the drug.

5.7.2 Fluid and Food Intake

There are no restrictions on the intake of fluids or food. Patients who are on anti-hypertensive therapy should hold their medications on the morning of their RTX/OBI infusions but can resume them after the one-hour observation period following the infusion, assuming stable vital signs. At the discretion of the investigator, anti-hypertensive medications can be administered on the morning of the RTX/OBI infusion according to the patient's usual medication schedule before the infusion.

5.7.3 Patient Activity Restrictions

There is no restriction on patient activity.

5.7.4 Immunization

Live vaccines are prohibited within one month (4 weeks) before administration of the investigational treatment and are prohibited until the return of B lymphocytes to normal concentrations following administration of the investigational treatment. Recombinant vaccines can be administered at any time. Patients and investigators must be aware that responses to vaccines of any type may be suboptimal following B cell depletion therapy until such time as B lymphocytes have been repleted to normal concentrations.

Patients must have completed COVID-19 vaccination (including booster per current recommended CDC guidelines) at least 4 weeks (28 days) prior to enrollment. Patients who have recovered from COVID-19 prior to screening with a positive spike protein antibody test result but have not been vaccinated are also eligible.

5.8 Treatment Compliance

The research pharmacy of each clinical site will be provided with the randomization by the designated data manager/nurse/pharmacist at the patient's institution (See Section 5.4.9). The investigator or designated site personnel will notify the study pharmacist that a patient is enrolled and provide a date for the first infusion. The pharmacist will dispense the final investigational products for each subject according to randomization assignment. The date and time of infusion solution preparation will be recorded in the study drug accountability log.

The investigator or designated site personnel will record the infusion start and stop date and time, the amount of administered drug and reasons for infusion interruption or discontinuation in the CRF. As drug is administered during the flush infusion, the flush infusion is included in the administered drug stop date and time.

5.9 Packaging and Labeling

The investigational products, obinutuzumab and rituximab, will be provided to the site pharmacy directly by Genentech. All investigational product supplies are labeled according to the requirements of local laws and regulations.

5.10 Storage and Accountability

The recommended storage condition for obinutuzumab and rituximab is between 2°C and 8°C, protected from light. The products should not be frozen or vigorously shaken.

5.11 Investigational Product Retention at Study Site

The investigational products will be stored in a secure area with limited access. The drug storage facility must comply with the medication storage instructions. The trial staff must record the amount of investigational product dispensed to each subject in the dosing record. The procedures for obtaining drug resupply will be provided in the pharmacy manual. All unused drugs will be destroyed with approved procedures after drug accounting is verified by the sponsor or its designee.

6 STUDY PROCEDURES

Before each patient is enrolled in the clinical study, the investigator will not undertake any investigation not part of standard of care and specifically required for the clinical study until written consent has been obtained. Written informed consent will be obtained according to the regulatory and legal requirements. As part of this procedure, the investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study patient is aware of the potential risks, inconveniences, or adverse events that may occur. The investigator should educate potential patients about the scientific importance of their data and the vital role that their participation has for the outcome of the entire study. The patient must be informed that he/she is free to withdraw from the study at any time. He or she will receive all information that is required by federal regulations and the International Council for Harmonisation (ICH) guidelines.

The informed consent document shall be signed and dated; one copy will be given to the patient, and the investigator will retain a copy as part of the clinical study records. The terms of the consent and when it was obtained must also be documented.

Documentation of informed consent may involve the use or On-Site or Remote Electronic Consent technology. The subject may print or electronically save the form. If the subject prefers not to use Electronic Consent technology, the study team will provide a paper consent form for their signature.

6.1 Screening for I/E Criteria

At the initial screening, the investigator should review the inclusion and exclusion criteria based on the information collected at the screening visit. The investigator should evaluate any change to status affecting conformance to inclusion and exclusion criteria at subsequent visits prior to randomization.

6.2 Medical and Surgical History

The following information will be collected at the screening visit:

6.2.1 Demographics

Year and month of birth, age, sex, and race, and whether a female patient is of childbearing potential will be documented.

6.2.2 Significant Medical and Surgical History

Medical history of AAV is recorded in a specific disease history form. Surgical history related to AAV will be recorded on the AAV disease history form.

6.2.3 Prior Medication History

Use of prescribed or non-prescribed medications, including over the counter drugs, vitamins, herbal preparations, and dietary supplements within the past 30 days prior to screening must be

recorded at study entry. Each medication history will include the agent used, indication for usage, start and stop dates, dose, and frequency. Previous immunosuppressant use for treating AAV will be recorded in the CRF.

6.2.4 AAV Disease History

The following AAV disease related history will be documented:

- The type of AAV (Granulomatosis with polyangiitis or microscopic polyangiitis)
- Biopsy performed to confirm the AAV diagnosis (if so, organ(s) affected)
- Newly diagnosed or relapsing AAV
- Pre-enrollment disease duration (months, years)
- Organs previously affected by AAV, including current presentation
- Organ involvement

6.3 Efficacy Assessments

6.3.1 BVAS/WG Assessment

The BVAS/WG is a method for assessing the activity of vasculitis. The scores range from 0 to 63, with higher scores indicating more active disease when any of the features are new or worse ((Stone et al., 2001). The assessment form includes: 1) 34 separate disease items, categorized into 9 groups; 2) an "other" section; 3) an asterisk by the 15 major items (see below); 4) tick boxes to indicate new/worse or persistent disease; 5) an area to total the scores; 6) a section for the designation of disease status; 7) the physician's global assessment (PGA) of disease activity scale; and 8) a box for administrative use that contains information about the patient identification code and clinical center. Items on the BVAS/WG evaluation form are counted only if they result from active WG, and not from damage from previously active WG or another medical condition. The evaluation form is presented in Appendix 5.

6.3.2 PR3-ANCA Assay

Serum samples are collected at the specified visits for PR3-ANCA assay using a direct enzyme-linked immunosorbent assay (ELISA) (Damoiseaux et al., 2005).

6.3.3 AAV-Patient Reported Outcomes (AAV-PRO)

ANCA-associated vasculitis patient reported outcomes (AAV-PRO) questionnaire is a validated instrument to assess the disease specific states reported by the patients. It is a 29-item questionnaire grouped into 6 domains: organ-specific symptoms (5 items), systemic symptoms (4 items), treatment side effects (5 items), social and emotional impact (6 items), concerns about the future (5 items) and physical function (4 items) (Robson et al., 2018). Each item has 5 ordinal integer response options scored 0 to 4, higher scores representing greater severity or impact as shown in Appendix 6.

6.3.4 VCRC WG/MPA Disease Activity and Transition Assessment

Patient-reported disease severity will be assessed on an 11-point scale (0–10) where the data will be transformed to a scale of 0–100 to allow for comparable data for both cohorts (Tomasson et al., 2012). The data form is presented in Appendix 7.

6.3.5 Biomarker assessments

Biomarker assessments will be conducted to compare the effect of obinutuzumab and rituximab on changes in the peripheral blood cells by flow cytometry. These assessments are intended to profile B cells and other relevant cell populations in PR3-AAV patients before and after obinutuzumab or rituximab administration.

Whole Blood, serum and plasma samples will be collected at specified clinic visits (appendix 1 and appendix 2), and transferred to the analytical laboratory for analyses. Research may involve extraction of DNA and RNA for analysis of non-inherited BCR and TCR sequences and genomic profiling through use of NGS of comprehensive panel of immune cell genes. NGS methods will not include whole genome sequencing (WGS) or whole exome sequencing (WES). Details of the collection procedures and sample handling will be provided in the laboratory manual.

6.3.6 Vital Signs

Vital signs will be measured at the time points indicated in the Schedule of Events and will include seated blood pressure measurements, pulse, and temperature.

Devices designed to measure BP from the finger or wrist may not be used. At each visit, BP measurements will be obtained using a calibrated sphygmomanometer. A single pulse rate measurement should be taken just prior to the BP evaluation in the seated position.

6.3.7 Clinical Laboratory Tests and Parameters

Clinical laboratory tests are listed in Table 4. Patients will be in a seated or supine position during blood collection. Blood samples for hematology and chemistry should be taken using venipuncture techniques and will be sent to the local laboratory for testing. The time points of sampling are indicated in the Table 4 and in Appendix 2 Schedule of Laboratory Testing.

Whole blood will be collected and shipped to a designated laboratory to analyze the effects of obinutuzumab and rituximab on the numbers and activation status of peripheral blood mononuclear cells (PBMC) and their subsets.

Table 4 List of Laboratory Tests

Category	Test Names
Hematology/ whole blood	hemoglobin, hematocrit, erythrocyte count (red blood cell [RBC] count), thrombocyte count (platelets), leukocyte count (white blood cell [WBC] count) with differential in absolute counts (including neutrophils,

Category	Test Names
	eosinophils, basophils, lymphocytes, and monocytes), erythrocyte sedimentation rate
Serum chemistry/ serum	aspartate aminotransferase (AST); alanine aminotransferase (ALT); total, direct, and indirect bilirubin levels; alkaline phosphatase (ALP); albumin, creatinine; estimated GFR, blood urea nitrogen (BUN); total protein; and glucose (random), c-reactive protein, complete metabolic panel, carbon dioxide (C02)
Hemoglobin A_{1c} / whole blood	Percentage of glycated hemoglobin
Lipid panel/ serum	total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides
Immunology/ serum	ANCA antibody
Immunoglobulin/ serum	Total immunoglobulin, IgG, IgM, IgA, and IgE
Infectious disease testing/ serum	hepatitis B (surface antigen and core antibodies), HCV, and HIV, tuberculosis (TB) testing, COVID-19 by nasal swab ***Infectious disease will be tested at screening (V1) and when clinically indicated. Preferred TB test method is QuantiFERON gold.***
Pregnancy (WCBP only)/ urine Follicle Stimulating Hormone (FSH)/ serum	***Urine pregnancy test (UPT) must be performed at Screening, and at all other trial time points for women of childbearing potential.*** Any woman of age ≥ 55 years with amenorrhea for >1 year, will be considered as having confirmed menopause and FSH or pregnancy testing will not be needed. Postmenopausal females <55 years of age (defined as amenorrhea > 1 year) must have menopause confirmed by elevated follicle-stimulating hormone (FSH) levels at screening. Surgically sterile females do not require any further confirmation of menopause and will not be considered to have reproductive potential.
Urinalysis/ urine	pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, leukocytes, and reflex microscopy
Biomarker samples: Whole blood, RNA, PBMC, serum and plasma	Whole blood samples will be drawn at the visit specified in Appendix 2. Peripheral blood mononuclear cells (PBMC) will be processed and cryopreserved for further biomarker assessments. .

An investigator can perform additional laboratory testing to diagnose or to follow up an adverse event progression or resolution. Clinical safety samples may be analyzed in a local laboratory only if needed within the same day to determine an urgent treatment plan. Subjects will be in a seated or supine position during blood collection.

6.3.8 Electrocardiograms (ECG)

A 12-lead ECG will be obtained at screening to evaluate eligibility criteria. Patients should be lying down (Supine) for at least 5 minutes prior to the safety ECG. Times of the 12-lead ECGs are documented in the Schedule of Events. The Investigator may perform additional ECGs for safety at other times, if deemed necessary.

Safety ECGs will be interpreted, signed, and dated by the Investigator. The ECGs will be classified as normal, not clinically significant (NCS), or having a clinically significant abnormality (CS). In addition, ECG parameters of ventricular rate, PR interval, QRS duration, and QT interval (Fridericia's correction and uncorrected) will be noted on the case report form (CRF).

6.3.9 Adverse Events

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes death, and any other study specific issue of concern.

6.3.9.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with
- ANCA Associated Vasculitis that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

6.3.9.1.1 INTENSITY:

All clinical AEs encountered during the clinical study will be reported on the AE page of the CRF. Intensity of AEs will be graded based on a modified National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 and reported as indicated on the CRF.

For any AEs not found in the CTCAE, a description of intensity grading can be found below:

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate; minimal, local, or noninvasive intervention indicated; limiting age- appropriate instrumental activities of daily living.
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4:	Life-threatening consequences; urgent intervention indicated: by definition also a SAE.
Grade 5:	Death related to AE (Grade 5 is not appropriate for some AEs and therefore is not an option)

Death is an outcome of an adverse event, although in some cases it is noted in severity in CTCAE criteria. Not all CTCAE criteria have an outcome of Grade 5. The cause of death must be listed as the adverse event term in the eCRF and the outcome box of (fatal) on the AE page is also checked.

6.3.9.1.2 INVESTIGATIONAL PRODUCT CAUSALITY:

Investigators should use their knowledge of the study participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to the obinutuzumab or rituximab treatment. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug dosing
- Course of the event, considering especially the effects of dose reduction, discontinuation of trial medication, or reintroduction of the study drug
- Known association of the event with the obinutuzumab or rituximab
- Known association of the event with ANCA-associated AAV under study
- Presence of risk factors in the study participant or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

The clinical investigator must assign an attribution to the AE using the following attribution categories.

Relationship	**Description**
Unrelated to the investigational product	The AE is clearly **NOT** related to the intervention
	The AE is **doubtfully related** to the intervention
	The AE **may be related** to the intervention

Relationship	Description
Related to the investigational product	The AE is **likely related** to the intervention
	The AE is **clearly related** to the intervention

6.3.9.2 Unexpected Adverse Drug Experience

Any adverse drug experience that is not listed in the current labeling for the drug product including events that may be symptomatically and pathophysiologically related to an event listed in the labeling but differ from the event because of greater severity or specificity.

"Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling or investigator's brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

6.3.9.3 Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

6.3.9.4 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be reassessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

e. Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the obinutuzumab or rituximab (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

- **Related**: There is a plausible temporal relationship between the onset of the AE and administration of the obinutuzumab or rituximab, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the obinutuzumab or rituximab or with similar treatments; and/or the AE abates or resolves upon discontinuation of the obinutuzumab or rituximab or dose reduction and, if applicable, reappears upon re- challenge.

- **Not Related**: Evidence exists that the AE has an etiology other than the obinutuzumab or rituximab (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to obinutuzumab or rituximab administration (e.g., cancer diagnosed 2 days after first dose of study drug).

The investigator is responsible for ensuring all SAEs, AE of special interest and unexpected AEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), in accordance with CFR 312.31 (IND Safety Reports) and to Genentech, Inc.

The AE Collection Period begins after obtaining informed consent and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is later. After this period, investigators should only report SAEs that are attributed to study treatment.

Adverse events that are reported after obtaining informed consent will be captured as pre-treatment adverse events. After receipt of the first dose, the adverse events will be captured as Treatment Emergent Adverse events (TEAEs).

The below guidelines should be followed when recording AEs:

Surgical or diagnostic procedures:
For medical or surgical procedures (e.g., colonoscopy, biopsy), the medical condition that led to the procedure is an AE. Elective procedures (e.g., vasectomy), planned hospitalizations, and procedures for treatment of conditions noted in the patient's medical history that have not worsened are not considered AEs.

Chronic disease:
In the case of disease (excluding AAV) that is progressing, if the disease is known when the participant enters the trial, only worsening (increased frequency or intensity of the episodes or attacks) will be documented as an AE. If the disease is detected during the trial, and if repeated episodes enable diagnosis of a chronic disease, the diagnosis will be recorded as the adverse event.

Underlying disease conditions:
Unchanged (stable), chronic conditions, or those related to the underlying disease that are consistent with the disease's natural progression are not AEs and are not to be recorded on the AE page of the CRF. These conditions are considered part of the patient's medical history and must be adequately documented on the appropriate page of the CRF. Day-to-day fluctuations of pre-existing disease should not be recorded as an AE on the AE CRF.

Disease under study:
Unexpected progression, signs, or symptoms of the disease under study are not AEs and are not to be recorded on the AE page of the CRF unless the event meets the definition of an SAE or is not consistent with the typical clinical course of the patient's disease as established by the patient's medical history. **Worsening of the disease under study or other disease-related symptoms should be recorded as an AE only if the event meets the definition of an SAE or is not consistent with the typical clinical course of the disease**

Laboratory abnormalities:
An isolated, out-of-range laboratory result in the absence of any associated, clinical finding may or may not be considered an AE; the Investigator's evaluation should be based on a consideration of the overall clinical context.

An out-of-range laboratory result will be considered clinically significant and recorded as an AE ***when it is part of a clinical abnormality requiring specific medical intervention or follow-up***. The test will be repeated, and the patient will be followed-up until the test value has returned to the normal range or baseline, or the Investigator has determined that the abnormality is chronic or stable. The Investigator will exercise medical judgment in deciding whether out-of-range values are clinically significant and document the assessment in the source records Serious Adverse Event Reporting

6.3.9.5 Definition of Serious Adverse Events

An SAE is any experience (clinical AE or abnormal laboratory test) that suggests a significant hazard, contraindication, side effect, or precaution. An SAE must fulfill at least one of the following criteria at any dose level:

- is fatal (results in the outcome death)*
- is life-threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- is a congenital anomaly/birth defect
- is medically significant or requires intervention to prevent one or other of the outcomes listed above

** Note that the term "sudden death" should only be used when the cause is of a cardiac origin as per standard definition. The terms "death" and "sudden death" are clearly distinct and must not be used interchangeably.*

Any clinical adverse event or abnormal laboratory test value that is serious and which occurs during the course of the study (as defined above), occurring from the enrollment visit (start of study Screening procedures), including long term follow-up must be reported to:

- The Sponsor (or designee) and trial monitor within 24 hours of the Investigator becoming aware of the event (expedited reporting).
- The investigational site's IRB by the Investigator in accordance with their regulations.

6.3.9.6 Initial notification of an SAE

The sponsor must be informed in writing 24 hours from the time the site investigational team first become aware of the event using the SAE report form. Delivery of the SAE form should not be delayed for the purpose of awaiting complete information. Instead, updates should be provided as additional information becomes available.

The SAE form including a written, narrative description of any SAE must be emailed to the Sponsor within 24 hours after awareness of the event.

If paper SAE forms are used, the paper originals of the initial and all follow-up SAE report forms that have been emailed must be retained in the Investigator Site File.

In addition to reporting the SAE via email, the SAE report should be entered into the EDC once the system is available.

As further information regarding the SAE becomes available, such follow-up information should be documented as an update in the EDC system and on a new SAE report form, marked as a follow-up report and emailed to **RSTANCA2021SAFETY@mayo.edu** with the site's CRA in copy.

Starting after informed consent, SAEs must be reported within 24 hours (e.g., SAEs related to invasive Screening procedures such as biopsies, or SAEs related to glucocorticoid treatment during Screening).

Related SAEs ***MUST*** be collected and reported regardless of the time elapsed from the last administration of the study drug, even if the study has been closed.

Unrelated SAEs must be collected and reported during the study and for up to 30 days after the last dose of study medication.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to Investigators at each site and associated IRB when the following conditions occur:

- The event is a SAE
- There is a reasonable possibility that the event is an adverse reaction caused by the administered drug
- The adverse reaction is unexpected, that is to say, not foreseen in the Investigator Brochure
- When all participants at a particular site are off treatment, as defined by the protocol, individual SUSAR reports will be forwarded to the site and its associated IRB on an expedited basis.

Individual SUSARs considered to be a significant safety issue and/or which result in a change to the informed consent form will be reported in an expedited manner to all Investigators and IRBs.

Reporting of any SAEs to applicable regulatory authorities will be the responsibility of the Local Sponsor in compliance with local regulations.

6.3.9.7 Other Safety Findings Requiring Expedited Reporting

Significant safety findings will be reported to the Investigator by the sponsor as obtained from the manufacturer of the study drug products. The site investigator is responsible for reporting to the investigational site's IRB in accordance with their regulations. Reporting to applicable regulatory authorities will be the responsibility of the Sponsor investigator in compliance with local regulations.

6.3.9.8 Pregnancy

Pregnancy in a Female Clinical Trial Participant: If a female subject becomes pregnant while receiving the study drug or within 18 months after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 180 days, a report should be completed and expeditiously submitted to the Investigator and Genentech, Inc. Pregnancies will be followed-up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

The participant should be counseled by a specialist, to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until the outcome of the pregnancy is known. The Investigator should report all pregnancies in clinical trial participants to the Sponsor within 24 hours of becoming aware of them, using the Clinical Trial Pregnancy Reporting Form.

Protocol required procedures after discontinuation of investigational product must be performed on the patient unless contraindicated by pregnancy (*e.g.*, x-ray studies) or the subject withdraws consent. Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the sponsor, on the appropriate Pregnancy Surveillance Form, follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of six months.

6.3.9.9 AEs of Special Interest (AESIs)

AESIs are a subset of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:

  - Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN
  - Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice

- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

Adverse Events of Special Interest for Obinutuzumab

INFUSION RELATED REACTIONS (IRR)

The IRR is defined as any AEs during infusion or within 24 hours of completing the infusion that are considered related to the investigational product by the investigator.

The most frequently observed adverse drug reactions (ADRs) in patients receiving obinutuzumab were IRRs which occurred predominantly during infusion of the first 1000 mg.

DRUG-RELATED NEUTROPENIA

Since neutropenia is often associated with autoimmune disease, only neutropenia attributed to study drug by the investigator are considered AESIs.

DRUG-RELATED THROMBOCYTOPENIA

Thrombocytopenia events assessed as investigational product related by the investigator are considered as AESIs to distinguish these AESIs from thrombocytopenia as a symptom of the autoimmune disease.

WORSENING OF PRE-EXISTING CARDIAC CONDITIONS

In patients with underlying cardiac disease, arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction, and heart failure have occurred when treated with obinutuzumab. These events may occur as part of an IRR and can be fatal. Patients with a history of cardiac disease should be monitored closely. In addition, these patients should be hydrated with caution to prevent a potential fluid overload.

GRADE 3 OR HIGHER INFECTIONS

B-cell depletion may have an impact on the incidence and severity of infections. Due to the pharmacological class of obinutuzumab and the mechanism of action, the Sponsor considers

infections to be an event of special interest. In obinutuzumab and rituximab clinical trials involving non-oncologic patients, the most common infections included urinary tract infection, bronchitis, upper respiratory tract infection, herpes zoster, pharyngitis, influenza, nasopharyngitis, and conjunctivitis.

HEPATITIS B REACTIVATION

HBV reactivation is defined as confirmed presence of HBV DNA > 100 IU/mL in the serum after baseline.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

The diagnosis of PML should be considered in any patient presenting with new-onset or changes to preexisting neurologic manifestations. The symptoms of PML are nonspecific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g., muscular weakness, paralysis, and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs/symptoms regarded as "cortical" (e.g., aphasia or visual-spatial disorientation) may occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture (cerebrospinal fluid testing for John Cunningham Virus [JCV] DNA). The patient should be referred to a neurologist for the evaluation and treatment of PML.

GASTROINTESTINAL PERFORATIONS

Gastrointestinal (GI) perforation may result in peritonitis with a potentially fatal outcome. It generally requires a surgical intervention. GI perforation may affect the upper or lower GI tract. Upper bowl perforation can be either free (when bowel contents spill freely into the abdominal cavity, causing diffuse peritonitis e.g. duodenal or gastric perforation) or contained (when a full-thickness defect is created but free spillage is prevented because contiguous organs wall off the area e.g. duodenal ulcer perforation into the pancreas). Lower bowel perforation (e.g. in patients with acute diverticulitis or appendicitis) results in free intraperitoneal contamination and peritonitis.

6.3.9.10 Other Important Medical Events

HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions with immediate (e.g., anaphylaxis) and delayed onset (e.g., serum sickness), have been reported in patients treated with obinutuzumab. If a hypersensitivity reaction is suspected during or after an infusion (e.g., symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion should be stopped, and treatment permanently discontinued. Hypersensitivity may be clinically difficult to distinguish from infusion related reactions.

6.3.9.11 Follow-up of AEs

Adverse events, especially those related to the study drug should be followed up until they return to baseline status or stabilized. If after follow-up a return to baseline or stabilization cannot be

established and explanation should be recorded, and the ongoing status box noted in the EDC CRF.

6.3.9.12 Follow-up of Post-Treatment SAEs

SAEs that are identified on the last scheduled contact must be recorded on the AE CRF page and reported to the pharmacovigilance group according to the reporting procedures outlined in Section 0. These may include unresolved previously reported SAEs, or new SAEs. The investigator should follow these SAEs until the events are resolved, or the patient is lost to follow-up. Resolution means the patient has returned to the baseline state of health, or stabilization (e.g., the investigator does not expect any further improvement or worsening of the patient's condition). The investigator should continue to report any significant follow-up information to the sponsor until the event has been resolved.

Any new SAEs reported by the patient to the investigator that occur after the last dose of the investigational product should be reported to the pharmacovigilance group. The investigator should follow SAEs identified after the last scheduled contact until the events are resolved, or the patient is lost to follow-up. The investigator should continue to report any significant follow-up information to the sponsor until the event has been resolved. This study requires that patients be actively monitored for SAEs for at least 4 weeks after the last treatment or till the end of the follow-up period, whichever is longer.

If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject [including pregnancy occurring in the partner of a male study subject] who participated in the study, this should be reported as an SAE adequately to Genentech drug Safety during follow-up period.

6.3.9.13 Other Special Situations Reports

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse, or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

6.3.9.14 Product Complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

6.3.9.15 Exchange of Single Case Reports with Genentech

Mayo Clinic will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the Product. The completed MedWatch form must be sent to the Genentech contact specified below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

Fax: [redacted]
Email: [redacted]

All Product Complaints *without* an AE should call via:
PC Hotline Number: [redacted] (M-F: 5 am to 5 pm PST)

Transmission of these reports (initial and follow-up) will include the Safety Reporting Fax Cover Sheet and be sent either electronically or by fax within the timelines specified below:

Serious Adverse Drug Reactions (SADRs)	15 calendar days of the awareness date
Other SAEs	30 calendar days of the awareness date.
Special Situation Reports (Pregnancy) Special Situation Reports (Other)	30 calendar days of the awareness date. 30 calendar days of the awareness date.
Product Complaints	15 calendar days of the awareness date.
AESIs	15 calendar days of the awareness date.

Case Transmission Verification

The parties will verify that all single case reports have been adequately received by Genentech via Mayo Clinic emailing Genentech a Quarterly line-listing documenting single case reports sent by Dr. Specks to Genentech in the preceding time period.

- The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

- If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

- Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by Mayo Clinic to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report (cumulative line-listing) will be sent to Genentech.

Monthly or quarterly line-listings, and cumulative/final CTV should be sent to [redacted]

MEDWATCH 3500A REPORTING GUIDELINES

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description

- Description of event, severity, treatment, and outcome if known

- Supportive laboratory results and diagnostics (Section B.6)

- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up

- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form

- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch3500A (Mandatory Reporting) form is available at https://www.fda.gov/media/69876/download.

Reporting to Regulatory Authorities, Ethics Committees and Investigators

Dr. Specks, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations, unless an IND exemption has been obtained. If this study becomes IND-exempt, Genentech as the Marketing Authorization Holder will be responsible for the reporting of individual case safety reports from the study to the regulatory authority in compliance with applicable regulations.

Dr. Specks, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the study to the European Medicine Agency (EMA) through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

Dr. Specks will be responsible for the expedited reporting of safety reports originating from the Study to the Independent Ethics Committees/ Institutional Review Boards (IEC/IRB) of the Concerned Member States, where applicable.

Dr. Specks as the Sponsor of the Study, will be responsible for the preparation of six-monthly Suspected Unexpected Serious Adverse Reaction (SUSAR) reports and their submission to Investigators, Regulatory Authorities and the Institutional Review Board/Independent Ethics Committee (IRB/IEC), where applicable

Dr. Specks will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

Additional Reporting Requirements for IND Holders:

For Investigator-Initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR §600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of obinutuzumab or rituximab. An unexpected adverse event is one that is not already described in the obinutuzumab or rituximab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of obinutuzumab or rituximab. An unexpected adverse event is one that is not already described in the obinutuzumab or rituximab investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

Fax: [redacted]

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to

Genentech Drug Safety:

Fax: [redacted]

Email: [redacted]

And Dr. Specks will be responsible for the distribution of safety information to Site IRB:

[Mayo Clinic IRB, 200 First Street SW, Rochester, MN 55905 / Fax: [redacted]]

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: [redacted]

Fax: [redacted]

Aggregate Reports

IND Annual Reports

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech

Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: [redacted]

Dr. Specks will forward a copy of the Final Study Report to Genentech upon completion of the Study.

RANDOMIZATION CODES FOR BLINDED CLINICAL TRIALS

The blind will be broken for ADR reports that are Serious and Unexpected, unless otherwise agreed with applicable regulatory authorities.

REPORTING REQUIREMENTS FOR ADVERSE EVENTS ORIGINATING FROM PATIENT REPORTED OUTCOMES

Although sites are not expected to review the PRO data, if physician/study personnel become aware of a potential adverse event during site review of the PRO questionnaire data, he/she will determine whether the criteria for an adverse event have been met and, if so, these must be reported using the Adverse Event and Special Situation Reporting Form.

ADVERSE EVENT REPORTING

Fax MedWatch form immediately to Genentech Safety at:

Fax: [redacted]

Email: [redacted]

Product Complaints Without AE should call via : PC Hotline Number: [redacted] (M-F: 5 AM TO 5 PM PST)

STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

[redacted]

And to Genentech Drug Safety CTV oversight mail box at: [redacted]

QUERIES

Queries related to the overall study design and safety will be answered by Dr. Specks. However, responses to all safety queries from regulatory authorities, Ethics Committees and Institutional Review Board or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. Dr. Specks agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests from Regulatory Authorities and/or IRB/IEC for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

SIGNAL MANAGEMENT AND RISK MANAGEMENT

Genentech is responsible for safety signal management (signal detection and/or evaluation) for their own Product. However, it is agreed that Dr. Specks as Sponsor of the Study, will be primarily responsible for assessment of the benefit-risk balance of the Study.

If Dr. Specks issues a safety communication relevant for Genentech (i.e., a safety issue that notably impacts the benefit-risk balance of the Study and / or triggers any changes to the Study) this will be sent to Roche within five (5) business days of its internal approval.

As needed, Genentech will reasonably assist Dr. Specks with signal and risk management activities related to the Product within the Study.

Genentech will also provide Dr. Specks with any new relevant information that may modify or supplement known data regarding the Product (e.g., relevant Dear Investigator Letter).

COMPLIANCE WITH PHARMACOVIGILANCE AGREEMENT / AUDIT

The Parties shall follow their own procedures for adherence to AE reporting timelines. Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

6.3.10 Concomitant Medication Assessments

A concomitant medication is any medication that the patient has been taking prior to enrollment and that the patient is expected to continue to take for some portion of the trial, as well as any medication other than the investigational product that the patient takes during the course of the trial.

The medications or treatment for controlling the ANCA-AAV must be recorded as concomitant medications in the CRF.

All prescription and over-the-counter medications, including vitamins and herbal supplements, that patients receive during the trial must be documented on the CRF. This documentation should continue until the patients complete the study. All medications should be evaluated to if they are prohibited or not and the appropriate action should be taken.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). A table of concomitant medications based on the anatomic therapeutic chemical classification (ATC) and preferred name will be produced.

6.3.11 Glucocorticoid Toxicity Index (GTI)

The GTI is a validated tool permitting investigators to assess the use of glucocorticoids and its toxicity that is relevant to patients (McDowell et al., 2020). The GTI is designed to measure change in GC toxicity between 2 points in time and includes 2 components, a Composite Index and a Specific List. The full Composite Index includes 9 domains and a total of 31 unique weighted items. Data from the GTI provide two scores:

- The Cumulative Worsening Score (CWS) – The CWS is designed to assess cumulative GC toxicity, regardless of whether the toxicity has lasting effects or is transient. New toxicities that occur are added, but toxicities that appear to resolve on follow-up are not removed. Thus, the CWS serves as a lasting record of and GC toxicity that occurs. The CWS can only increase or remain the same over time.

- The Aggregate Improvement Score (AIS) – The AIS is designed to capture improvement in glucocorticoid toxicity. With the AIS, toxicities can be removed if improvement occurs (and added if worsening occurs). If an item of toxicity is present at baseline or occurs during the trial resolves over the course of follow-up, then that improvement is reflected in a negative AIS for that Item during that interval. The AIS scores improvement in GC toxicity the same as a corresponding worsening of GC toxicity.

6.3.12 Vasculitis Damage Index (VDI)

VDI is a standardized clinical assessment of damage in the systemic vasculitides (Merkel et al., 2011). The VDI consists of 64 items of damage selected by expert consensus as representative of the forms of damage developed by subjects with systemic vasculitis (Appendix 8). The VDI is that it has provided investigators with a method to ensure that items of damage are uniformly collected across centers.

6.4 Removal of Patients from the Trial or Study Drug

6.4.1 Patient Withdrawal

All patients have the right to withdraw consent and discontinue participation without prejudice at any time during the trial. Every effort should be made to comply with the protocol; however, patients will be withdrawn from the trial entirely with no further trial visits if any of the following situation arise:

- Withdrawal of patient's consent or patient's request to discontinue from the trial for any reason.
- The patient is unwilling or unable to comply with the protocol

Patients who are withdrawn from the trial will not be replaced. The reason for the patient's withdrawal from the trial should be recorded on the electronic case report form (eCRF).

6.4.2 Other Special Situations Reports

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

6.4.3 Patient Lost to Follow-up

At the start of the study, the Investigator should try to obtain all relevant contact details for the patient to facilitate contacting the patient, if necessary. In addition, each patient should be encouraged to attend all trial visits for which the patient is scheduled.

If a patient discontinues the study without notifying the investigator, the investigator must make every effort to contact the patient to identify the reason for the patient's withdrawal and to encourage the patient to complete the applicable Early Withdrawal/End of Study visit assessments (Appendix 1, Schedule of Events). If documented attempts to contact the patient fail, and a reason for the patient's discontinuation is undiscoverable, the investigator can declare the patient as "lost to follow-up" at the end of the study. The investigator should document in the corresponding medical record all efforts to contact the patient.

6.5 Early Termination of the Trial

In the event that the trial is terminated early, the sponsor or its designee will complete the following tasks within 7 days:

- Notify all investigational sites, IRB/EC, and DSMB that the trial is terminated
- Discontinue shipment of any new investigational products to the sites, if applicable

The investigators will contact all study patients and schedule the End of Study visit promptly upon the notification that the trial has ended.

The investigator may withdraw a patient from the PRRR study for any of the following reasons:

- A protocol violation occurs,
- A serious or intolerable adverse event occurs,
- A clinically significant change in a laboratory parameter occurs,
- The sponsor or investigator terminates the study, or
- The patient requests to be discontinued from the study.

6.6 Dispensing Study Drug

The study drug for infusion will be prepared by the site pharmacist who has access to the randomization schedule following the procedures in the Pharmacy Manual.

7 STUDY ACTIVITIES

The study activities at each clinic visit listed below are presented in Schedule of Events and Schedule of Laboratory Testing. Detailed study procedures are described in Section 6.

A visit window is allowed for all visits except visit V2. Visit 2 is the first day of dosing and the basis for the visit window.

Table 5 Study Visit Schedule

Visit No.	Visit	Study Day	Visit Window
1	Screening	Varies	Before baseline visit (up to 14 days prior to the baseline visit)
1a	IV steroid #1	G1	Within 10 days of baseline up to day of baseline (V2)
1b	IV steroid #2	G2	Optional, Within 24 hours after IV steroid 1
1c	IV steroid #3	G3	Optional, within 24 hours after IV steroid 2
2	Infusion 1 (Baseline)	0	Within 14 days from screening
3	Infusion 2	14	±2 days of the targeted date
4	Month 1	30	± 2 days of the targeted date
5	Month 2	60	±3 days of the targeted date
6	Month 4	120	±5 days of the targeted date

7	Month 6	180	±10 days of the targeted date
8	Month 9	270	±10 days of the targeted date
9	Month 12	360	±10 days of the targeted date
10	Month 15	450	±10 days of the targeted date
11	Month 18	540	±10 days of the targeted date
99	When disease flares	unscheduled	

7.1 Screening Visit V1 (Up to 14 days Before Day of Randomization)

- Explain the content of the informed consent materials to the patient and collect signed informed consent
- Collect needed information and evaluate conformance to inclusion and exclusion criteria
- Obtain Demographic Information
- Obtain medical history including AAV disease history
- Record pre-treatment medications
- Record current glucocorticoid use
- Measure vital signs, including blood pressures, pulse, and temperature
- Perform a 12-lead ECG measurement
- Complete the BVAS/WG Score
- Complete the VCRC-Disease activity and Transition Assessment by the investigator
- Draw blood for clinical laboratory tests. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean-catch, mid-stream urine sample for urinalysis

7.2 Remission Induction Period (Day 0 to Month 6)

7.2.1 Pre-Treatment of Methylprednisolone

Eligible patients will start the one to three pulses of glucocorticoid of methylprednisolone starting on or within 10 calendar days of study day 0 (1000 mg each, iv infusion). The initial treatment with methylprednisolone may start while data for eligibility confirmation are pending. If their first RTX/OBI infusion coincides with one of the methylprednisolone pulses of 1000 mg, then the patient can receive the 1000 mg of methylprednisolone as their pre-RTX/OBI glucocorticoid infusion. If the patients have already completed the one to three methylprednisolone pulses, they will receive only 60 mg of methylprednisolone before the rituximab or obinutuzumab infusion that day. The pre-RTX/OBI treatment with methylprednisolone may be substituted with the IV pulse for one of the pre-treatment infusions.

7.2.2 Visit 2 (Day 0) Procedures

- Confirm the subject eligibility
- Perform randomization procedures (The randomization procedure may start the day before the scheduled Day 1 visit by the pharmacist. The dosing solution must be prepared within 24 hours of scheduled dosing.)
- Record vital signs, including blood pressures, pulse, and temperature prior to infusion
- Complete the BVAS/WG Score prior to infusion
- Complete the VCRC-Disease activity and Transition Assessment by the investigator
- Review glucocorticoid use prior to infusion
- Complete AAV-PRO by the patients prior to infusion
- Complete GTI assessment prior to infusion
- Complete VDI assessment prior to infusion
- Draw blood for clinical laboratory tests prior to infusion
- Collect samples for mechanistic biomarker assessments prior to infusion
- Collect a clean-catch, mid-stream urine sample for urinalysis prior to infusion
- Assess adverse events prior to, during and after infusion
- Record medications used prior to, during and after infusion
- Administer study drug infusion and observe for 2 hours after infusion is complete

7.2.3 Visit 3 (Day 14 ± 2 days) Procedures

- Record vital signs, including blood pressures, pulse, and temperature prior to infusion
- Complete the BVAS/WG Score prior to infusion
- Complete the VCRC-Disease activity and Transition Assessment by the investigator
- Draw blood for clinical laboratory tests prior to infusion
- Collect a clean-catch, mid-stream urine sample prior to infusion
- Record medications used prior to, during and after infusion
- Review glucocorticoid use prior to infusion
- Assess adverse events prior to, during and after infusion
- Administer study drug infusion and observe for 2 hours after infusion is complete

7.2.4 Visit 4 (1 month after the first infusion) Procedures

- Draw blood for clinical laboratory tests (during clinic visit only)
- Collect a clean-catch, mid-stream urine sample for urinalysis (during clinic visit only)
- Collect samples for mechanistic biomarker assessments
- Complete the BVAS/WG Score

- Complete the VCRC-Disease activity and Transition Assessment by the investigator
- Record medications used
- Review glucocorticoid use
- Assess adverse events

7.2.5 Visit 5 (2 months after the first infusion) Procedures

- Record vital signs, including blood pressures, pulse, and temperature
- Complete the BVAS/WG Score
- Complete the VCRC-Disease activity and Transition Assessment by the investigator
- Draw blood for clinical laboratory tests
- Collect samples for mechanistic biomarker assessments
- Collect a clean-catch, mid-stream urine sample for urinalysis
- Perform VDI assessment
- Record medications used
- Review glucocorticoid use
- Assess adverse events

7.2.6 Visit 6 (Month 4) Procedures

- Record vital signs, including blood pressures, pulse, and temperature
- Complete the BVAS/WG Score
- Complete the VCRC-Disease activity and Transition Assessment by the investigator
- Draw blood for clinical laboratory tests
- Collect samples for mechanistic biomarker assessments
- Collect a clean-catch, mid-stream urine sample for urinalysis
- Record medications used
- Review glucocorticoid use
- Assess adverse events

7.2.7 Visit 7 (Month 6) Procedures

- Record vital signs, including blood pressures, pulse, and temperature
- Perform a 12-lead ECG measurement
- Complete the BVAS/WG Score
- Complete GTI assessment.
- Collect a clean-catch, mid-stream urine sample

- Perform VDI assessment
- Complete AAV-PRO by the patient
- Complete the VCRC-Disease activity and Transition Assessment by the investigator
- Draw blood for clinical laboratory tests
- Collect samples for mechanistic biomarker assessments
- Record medications used
- Assess adverse events

7.3 Maintenance Period

7.3.1 Visits 8, 9 and 10 (Months 9, 12, and 15) Procedures

Study participants will be scheduled to complete a clinic visit every 3 months.

- Record vital signs, including blood pressures, pulse, and temperature
- Complete the BVAS/WG Score
- Complete the VCRC-Disease activity and Transition Assessment by the investigator
- Complete AAV-PRO by the patients at month 12
- Complete GTI assessment
- Perform VDI assessment
- Draw blood for clinical laboratory tests
- Collect samples for mechanistic biomarker assessments
- Collect a clean-catch, mid-stream urine sample for urinalysis
- Record medications used
- Assess adverse events

7.3.2 Visits 11 (Month 18) Procedures

Study participants will be scheduled to complete a final clinic visit.

- Record vital signs, including blood pressures, pulse, and temperature
- Complete the BVAS/WG Score
- Complete the VCRC-Disease activity and Transition Assessment by the investigator
- Complete AAV-PRO by the patient
- Complete GTI assessment
- Perform VDI assessment
- Draw blood for clinical laboratory tests
- Collect samples for mechanistic biomarker assessments
- Perform a 12-lead ECG measurement

- Collect a clean-catch, mid-stream urine sample for urinalysis
- Record medications used
- Assess adverse events
- Complete End of Study record

7.3.3 Visit 99 (Unscheduled Visit) Procedures

- Record vital signs, including blood pressures, pulse, and temperature
- Complete the BVAS/WG Score
- Complete the VCRC-Disease activity and Transition Assessment by the investigator
- Complete AAV-PRO by the patients
- Complete GTI assessment
- Draw blood for clinical laboratory tests
- Collect samples for mechanistic biomarker assessments
- Record medications used
- Assess adverse events

7.4 Early Termination Procedures

Patients who withdraw consent early, procedures outlined for the Month 18 visit (V11) should be completed.

7.5 Study Activities for Treatment Failure Patients

8 PATIENTS WILL BE CONSIDERED TREATMENT FAILURES IF THE GLUCOCORTICOID DOSE HAS TO BE INCREASED EITHER DURING THE PREDNISONE TAPER OR AFTER REMISSION BECAUSE OF A DISEASE RELAPSE OR IF ANY OTHER TREATMENT FOR ANCA-ASSOCIATED VASCULITIS IS PRESCRIBED TO TREAT A DISEASE RELAPSE. THE PATIENTS WHO EXPERIENCED TREATMENT FAILURE WITH DETECTABLE B CELLS (≥5 CELLS/ML) WILL BE OFFERED OPEN-LABEL OBINUTUZUMAB ACCOMPANIED ONE TO THREE INTRAVENOUS METHYLPREDNISOLONE PULSES (1000 MG EACH) STARTING ON OR WITHIN 10 CALENDAR DAYS OF OBINUTUZUMAB FOLLOWED BY ORAL GLUCOCORTICOID DOSING AT THE DISCRETION OF THE INVESTIGATOR (BUT NOT TO EXCEED THE ORIGINAL SPECIFIED GLUCOCORTICOID TAPERING REGIMEN) TO CONTROL THE DISEASE. PATIENTS WHO EXPERIENCE A TREATMENT FAILURE AND B CELLS ARE STILL DEPLETED SHOULD BE TREATED ACCORDING TO BEST MEDICAL JUDGMENT. PATIENTS WHO RESPOND TO THE RE-TREATMENT AND ACHIEVE CLINICAL REMISSION WILL ENTER THE MAINTENANCE PHASE AND BE EVALUATED EVERY 3 MONTHS UNTIL THE STUDY COMPLETES. ANY PATIENT WHO EXPERIENCES TREATMENT FAILURE SHOULD CONTINUE WITH STUDY FOLLOW-UP VISITS PER THE SCHEDULE OF ASSESSMENTS THROUGH THE END OF STUDY.QUALITY CONTROL AND ASSURANCE

The clinical research facility will be monitored by the study monitor to ensure correct performance of the study procedures and to ensure that the study is conducted according to the protocol and relevant regulatory requirements. CRF entries will be verified with the source documentation.

Quality control principles will be applied throughout the performance of this study by following the Standard Operating Procedures (SOPs) of the contract research organization (CRO) and the Principal Investigator. Review procedures will be implemented at the CRO for all documents that are generated in relation to the study.

The laboratory testing will be performed by a CLIA certified central laboratory to ensure the laboratory values are determined consistently.

The overall procedures for quality assurance of clinical trial data, including data collection and management, will be described in the Data Management Plan.

Accurate and reliable data collection will be assured by verification and crosscheck of the eCRF against the Investigator's records by the trial monitor (source document verification), and the maintenance of drug accountability by the Investigator.

Data for this trial will be recorded in the trial electronic case report forms (eCRFs) using Medidata RAVE. The data will be entered by the trial center from the source documents into the eCRF or will be loaded from other files.

A comprehensive validation check program will verify the data and discrepancy reports will be generated accordingly for resolution by the Investigator. All discrepant data will be resolved in the EDC database and data entered in the database will be independently compared with the original Investigator's records.

For classification purposes, preferred terms will be assigned to the original terms recorded on the eCRF, using MedDRA for AEs, diseases and surgical and medical procedures, and the WHO drug dictionary for drug and herbal treatments.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

The following sections provide a summary of the planned analysis of the trial, but a full statistical analysis plan (SAP) will be developed as a separate document and will become the final plan prior to primary efficacy 6-month endpoint analysis. All statistical analyses will be performed using SAS Version 9.4 or higher.

Data summaries will use descriptive statistics (number of subjects [N], mean, standard deviation [SD], median, quartiles, minimum, and maximum) for continuous variables, and frequency and percentage of subjects in each category for categorical and ordinal variables. If there are missing values, the number missing will be presented, but without a percentage.

Unless otherwise specified, all tests will be two-tailed using a 0.05 level of significance. All confidence intervals (CIs) will be two-sided 95% confidence intervals.

9.2 Determination of Sample Size

PRRR is an exploratory proof-of-concept study to evaluate the potential utility of obinutuzumab for the treatment of PR3-ANCA associated vasculitis. We anticipate the proportion of patients in the obinutuzumab group that will achieve complete remission and ANCA negativity is 0.55 and the proportion of patients in the rituximab group that will achieve complete remission and ANCA negativity is 0.30; the planned sample size of 30 patients in two equal size groups is not powered to test the hypothesis that obinutuzumab is superior to rituximab. No sensitivity analyses (e.g., to account for missing data) and no adjustment for multiple comparisons will be conducted. Nominal p-values will be used to examine any trends in the endpoint.

9.3 Analysis Populations

9.3.1 Intention-to-treat Analysis Set:

All subjects who are randomized regardless of treatment adherence or availability of follow up data will be included in the intention-to-treat analysis set (ITT). All analyses of the ITT will be based on each subject's assigned treatment. The ITT will be the secondary analysis set used for the efficacy endpoint analyses where specified.

9.3.2 Modified Intention-to-Treat Analysis Set

All subjects who are included in the intention-to-treat analysis set (ITT), have received any amount of the study drug will be included in the modified intention-to-treat (mITT) analysis set. The mITT will be the primary analysis set used for the efficacy endpoint analyses.

9.3.3 Safety Analysis Set

All subjects who are randomized and have received any amount of the study drug will be included in the Safety Analysis Set. Safety analyses will be based on the medication that was actually dispensed to each patient. This is the primary analysis set for safety.

9.4 Demographics and Baseline Characteristics

Patients must meet all inclusion criteria and none of the exclusion criteria in order to participate in the study. Demographic characteristics include age, gender, race, ethnicity, and study center. Summary descriptive statistics will include counts and percentages for discrete variables and estimation of means, standard deviations, medians, quartiles, minimum and maximum for continuous metrics. These analyses will be carried out for the ITT, mITT and safety analysis sets.

9.5 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the proportion of patients achieving complete remission and ANCA negativity at month 6. Complete remission is defined as:

- BVAS/WG of 0; and
- No requirement for glucocorticoids for treatment of PR3-ANCA associated vasculitis beyond the prescribed 16-week prednisone taper.

Patients must achieve a complete remission as defined above and be ANCA-negative at month 6 in order to meet the primary efficacy endpoint.

The primary efficacy analysis is to compare the proportion of patients assigned to the obinutuzumab group who meet the primary efficacy endpoint criteria at month 6 to the proportion of patients assigned to the rituximab group who meet the primary efficacy endpoint criteria at month 6.

Descriptive statistics (number and percent of subjects meet the primary efficacy endpoint criteria) will be reported by treatment group.

The following null (H_0) and alternative (H_a) hypotheses will be tested using Fisher's Exact test the mITT analysis set:

$$H_0: \pi \text{ obinutuzumab} - \pi \text{ rituximab} = 0$$
$$H_a: \pi \text{ obinutuzumab} - \pi \text{ rituximab} \neq 0$$

π obinutuzumab: proportion of patients assigned to the obinutuzumab group who achieve complete remission and ANCA negativity in 6 months

π rituximab: proportion of patients assigned to the rituximab group who achieve complete remission and ANCA negativity in 6 months

The above null hypothesis will be tested using Fisher's Exact test. Two-sided Newcombe-corrected 95% confidence intervals of the risk difference between treatments with respect to the primary efficacy endpoint success rate will also be presented. It is not expected that the null hypothesis will be rejected at a two-sided 0.05 level of significance given the proof-of-concept nature of the study and given the small sample size; trends seen between treatment groups in the primary endpoint rate will be used to define future studies.

The above analyses on the primary efficacy endpoint success rate will be performed when all subjects have completed 6 months of follow-up (or would have completed 6 months of follow-up) had they not withdrawn.

9.6 Primary Safety Endpoints

Safety data includes adverse events (AEs), vital signs, ECG results and clinical lab results including serum chemistry, hematology, and urinalysis. Observed data will be described as counts and percentages for discrete variables and estimation of means, standard deviations, medians, inter-quartile range, minimum and maximum for continuous metrics. All patients who are randomized and dispensed double-blind study medication will be included in the safety analysis. Data collected from subjects who were enrolled but not randomized will be presented separately. All safety data will be presented in by-subject listings and included in the clinical trial report.

Adverse events will be mapped to preferred term and body system using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The number and percentage of patients reporting treatment emergent adverse events will be presented overall, by MedDRA System Organ Class (SOC) and by MedDRA Preferred Term (PT) within each SOC. A treatment emergent adverse event is an event that begins or worsens in severity at or after the start of randomized treatment. This analysis will be repeated for serious treatment emergent adverse events, for treatment emergent adverse events of special interest, (see list provided below) and for treatment emergent adverse events at least possibly related to study drug. In addition, the number and percent of patients with treatment emergent adverse events will be presented by severity for each SOC and PT. Patients experiencing more than one treatment emergent adverse event within a given SOC and PT will be assigned to most severe category experienced.

Adverse event listings will be provided for the following subsets:

- All treatment emergent AEs
- All TEAEs at least possibly related to the investigational product
- Serious TEAEs
- TEAEs leading to dosing discontinuation or study withdrawal
- GTI scores (Cumulative Worsening Scores and Aggregate Improvement Scores (McDowell et al., 2020)

The adverse events of special interest include:

- Infusion related reactions (IRR)
- Neutropenia
- Thrombocytopenia
- Worsening of pre-existing cardiac conditions
- Infections (infections include all PTs in the SOC of Infections and Infestations)
- Hepatitis B reactivation
- Progressive multifocal leukoencephalopathy (PML)

9.7 Secondary Endpoints

No sensitivity analyses and adjustment for multiple comparisons will be conducted for the secondary endpoints. Nominal p-values will be used to examine any trends in these endpoints. The analyses will be carried out on the ITT and mITT populations, with no imputation for missing data. The secondary endpoints are:

- To compare the proportion of subjects who achieve sustained complete remission at months 6, 12 and 18 (BVAS/WG = 0 without glucocorticoids) by administration of obinutuzumab or rituximab. These comparisons will be carried out using Fisher's Exact test.

- To compare the time to treatment failure through month 18 by administration of obinutuzumab or rituximab; patients will be considered treatment failures if the glucocorticoid dose has to be increased because of a disease relapse either during the prednisone taper or after the remission is achieved. A disease relapse is defined as an increase in the BVAS/WG of 1 point or more accompanied by a decision on the part of the investigator to increase treatment for PR3-AAV. Time-to-treatment failure will be compared between treatments using the log-rank test; Kaplan-Meier plots of time to treatment failure through 18 months will be generated for each randomized treatment group; patients not experiencing treatment failure will be censored at last known follow-up for these analyses.

9.8 Other Assessments or Analyses

The exploratory objectives are to compare:

- the number of relapses, defined as an increase in the BVAS/WG by at least one point accompanied by an increase in the intensity of treatment;
- the Glucocorticoid Toxicity Index (GTI) scores (Cumulative Worsening Score and Aggregate Improvement Score) over time;
- the cumulative glucocorticoid dose;
- the number of severe relapses, defined as the occurrence of life- or organ-threatening disease manifestation(s) or marked by an increase in the BVAS/WG of ≥ 3 and the investigator deems re-treatment is required;
- the changes from baseline in Vasculitis Damage Index (VDI) over time;
- the time to clinical remission;

- the changes in estimated glomerular filtration rate (eGFR);
- the proportion of patients achieving and maintaining complete peripheral blood B cell depletion (CD19+) at each study visit using high-sensitivity flow cytometry (HSFC);
- the kinetics of ANCA:
- Time to ANCA negativity
- Time to ANCA recurrence;
- the kinetic of recurrence of PR3-specific (autoantigen-specific) B cells after B cell depletion
- the changes from baseline on AAV patient reported outcome (AAV-PRO) assessment over time
- VCRC WG/MPA disease activity and transition assessment over time

The mechanistic study results will be analyzed and reported separately.

9.9 Interim Analysis

The primary endpoint analysis will occur after all patients have completed the month 6 study visit. This technically represents an interim analysis and will be handled as described in detail in section 3.1.3.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

The Sponsor investigator is:

Ulrich Specks, MD
Division of Pulmonary and Critical Care Medicine
[redacted]
Mayo Clinic College of Medicine and Science

The Mayo Clinic will function as the data coordinating center. The Mayo Clinic will be responsible for the clinical operation and management of vendors that will perform protocol specified functions. Genentech will provide the investigational products and funding to support the clinical conduct.

The information on serious adverse events experienced by study participants will be reported to the IRB/EC, to the Sponsor Investigator and to Genentech, Inc.

Information regarding other key personnel involved in the conduct of the study, including names and contact details of participating clinical investigators, monitors, clinical laboratories, and technical departments and/or institutions, as well as information on members of additional study committees, will be found in the study files of the investigational site.

10.2 Institutional Review Board (IRB) Approval

Protocol amendments must be made only with the prior approval of the Sponsor. The IRB must be informed of all amendments and give approval for all amendments. For studies conducted outside of the US, approval of substantial amendments must be obtained from the relevant Competent Regulatory Authority before implementation. The Investigator must send a copy of the approval letter from the IRB to the Sponsor and/or the Sponsor's designee.

Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial participants, or when the change(s) involves only logistical or administrative aspects of the trial [e.g., change in monitor(s), change of telephone number(s)].

This protocol and any accompanying material provided to the participant (such as participant information sheets or descriptions of the trial used to obtain informed consent), as well as any advertising or compensation given to the participant, will be submitted by the principal Investigator or coordinating Investigator to the relevant institutional IRB responsible for the investigational trial.

An approval letter or certificate (specifying the protocol number and title) from the IRB must be obtained before starting the trial (initiation). The approval letter to the Investigator should specify the date on which the committee met and granted the approval. The Sponsor (or designee) must also obtain relevant competent authority approvals before starting the trial.

The investigator is responsible for keeping the IRB informed of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, at least once a year. The investigator must also keep the IRB informed of any SAEs occurring to patients under their t supervision.

10.3 Ethical Conduct of the Study

The Investigator will ensure that this trial is conducted in full conformance with the ethical principles that have their origin in the "Declaration of Helsinki", and that are consistent with the principles outlined in the current "Guideline for Good Clinical Practice" ICH Tripartite Guideline GCP E6 or with the laws and regulations (e.g., Title 21 Code of Federal Regulations Parts 50, 54, 56, 312, and 314, where appropriate), whichever affords the greater protection to the individual.

An inspection by the regulatory authorities' representatives may occur at any time. The investigator must agree to the inspection of study-related records by the regulatory authority/Sponsor representatives and must allow direct access to source documents to the regulatory authority/sponsor representatives.

The clinical investigators are responsible for complying with the protocol and all appropriate regulations and guidelines governing global clinical research. Additionally, he/she is responsible for ensuring that all participating staff members are adequately trained and competent to perform his/her assigned tasks.

Any deviations from the protocol must be fully explained and documented by the investigator. The circumstances, action taken, and impact of the deviation on the trial must be communicated by the principal investigator to the designated medical monitor. Significant protocol deviations may lead to discontinuation of investigational product at the discretion of the Sponsor. Any subsequent actions will be assessed by the designated medical monitor and documented.

10.4 Patient Information and Consent

Prior to the beginning of the study, the investigator must have received from the IRB the written approval or favorable opinion of the informed-consent form and any other written information to be provided to patients. The written approval of the IRB together with the approved patient information/informed consent forms must be filed in an appropriate electronic or paper study regulation binder. The informed consent form must contain all elements required by authorized regulatory authorities and the ICH GCP guidelines (E6), in addition to any other elements required by local regulations or institutional policy.

Written informed consent must be obtained before any study-specific procedure takes place. Participation in the study and date of informed consent given by the patient should be documented appropriately in the patient's files. A copy of the signed informed consent form must be provided to the patient. If applicable, it will be provided in a certified translation in the language understood by the patient, if not English. Signed consent forms must remain in each patient's study file and must be available for verification by study monitors at any time.

Documentation of informed consent may involve the use or On-Site or Remote Electronic Consent technology. The subject may print or electronically save the form. If the subject prefers not to use Electronic Consent technology, the study team will provide a paper consent form for their signature.

10.5 Patient Confidentiality and Disclosure of Data

The Investigator must ensure that each patient's anonymity is maintained as described below. On the eCRFs or other documents submitted to the Sponsor and/or its designee, patients must only be identified by trial, Patient Identification Number, and demographics, and pertinent restrictions of local regulations. No other personal identifiers will be used, and data will be de-identified in a manner compliant with Privacy Laws and, for US patients, the HIPAA regulations. Documents that are not for submission to the Sponsor and/or its designee (e.g., signed ICFs and Patient Information Sheets) should be kept in strict confidence by the Investigator in compliance with Federal regulations or other applicable laws or International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) Guidelines. The Investigator and institution must permit authorized representatives of the Sponsor and/or its designee, by representatives of the FDA, national and local health authorities, and the IRB direct access to review the patient's original medical records for verification of trial-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are needed for the evaluation of the trial. The Investigator is obligated to inform the patient in the ICF that his/her trial-related records will be reviewed, by the above-named representatives.

Participants will be informed that data will be held on file, by the Sponsor, and that these data may be viewed by staff including the trial monitor and by external auditors on behalf of the Sponsor and appropriate regulatory authorities. Participants will also be informed that a (trial) study report will be prepared and may be submitted to regulatory authorities and for publication. However, participants will be identified in such reports only by Patient Identification Number and demographics, pertinent to restrictions of local regulations. All patient data will be held in strict confidence, as allowed by law.

Upon the patient's permission, medical information may be given to the patient's personal physician or other appropriate medical personnel responsible for the patient's welfare.

10.6 Study Monitoring

A representative of the data coordinating center will conduct site visits to inspect study data, patients' medical records, and CRFs in accordance with ICH guidelines, GCP, and the respective national and local government regulations and guidelines.

The clinical investigator will permit authorized representatives of the Sponsor and the respective national or local health authorities, other authorized regulatory authorities, and IRB to inspect facilities and records relevant to this study.

10.7 Data Handling and Record Keeping

10.7.1 Confidentially

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled stud period.

10.7.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are

contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

10.7.3 Case Report Forms

Data will be captured at each participating site by qualified study staff who will perform primary data collection from source-document reviews to electronic case report forms (eCRF) via Medidata Rave, the information technology endorsed by Mayo Clinic's Clinical Trial Management System (CTMS) as described in Appendix/Attachment (please fill in Appendix/Attachment location info within protocol). Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained. Data will be entered for this study utilizing one or a combination of the following methods:

1. Data may be captured electronically, without use of paper.
2. Data may be transcribed from the Electronic Medical Record (EMR-an electronic source that must be available for review) into an EDC system, without use of paper.
3. Data may be captured on paper (considered source documentation) and transcribed into the EDC system, BUT paper documentation must be retained and available for review

10.7.4 Data Management

Study sites will transcribe subject source data into eCRFs using Medidata Rave. The Medidata Rave system is compliant with 21 CFR (Code of Federal Regulations) Part 11 FDA (Food and Drug Administration) requirements. Edit checks, electronic queries, and audit trails are built into the system to ensure accurate and complete data collection and security. Data will be transmitted via the internet from investigational sites to a central hosting site, utilizing state-of-the-art encryption mechanisms to ensure security and confidentiality.

10.7.5 Data Processing

All data is entered into electronic case report forms (eCRF's) through the Medidata Rave system. Case report forms are automatically rolled out based on a predetermined, visit based schedule to improve study staff workflow and data quality. Data is exported nightly to a secure FTP for analysis and reporting.

10.7.6 Data Security and Confidentiality

The Medidata Rave database access model is role based and fully auditable at the study, form, and field levels. Data is de-identified whenever possible and the ability to update data is limited to necessary staff. Access is managed by the Mayo Clinic Research Service Center, under a

controlled and monitored access request system. Metadata's platform specifically supports Electronic Record and Electronic Signature (ER/ES) requirements, including US 21 CFR part 11.

10.7.7 Data Quality Assurance/Data Clarification Process

Each eCRF contains edit checks and custom functions to ensure the highest possible data quality. Only necessary eCRF's are available for data entry to reduce the possibility of erroneous entry.

10.7.8 Data Clarification Process

The edit checks and custom functions on the eCRF's trigger queries requesting the attention of appropriate study staff. The fields are marked in pink to allow study staff to quickly identify the data fields that require attention or actions. Additionally, secure email notifications are sent for adverse event tracking and monitoring. The data collected in the source documents for this trial will be entered into the trial EDC eCRF. An audit trail will maintain a record of initial entries and changes made; time and date of entry; and name of person making entry or change. For each participant enrolled, an eCRF must be completed and electronically signed by the investigator or authorized delegate from the trial staff. If a participant withdraws from the trial, the reason must be noted in the eCRF. If a participant is withdrawn from the trial because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

The Investigator should ensure the accuracy, completeness and timeliness of the data reported to the Sponsor in the CRFs and in all required reports.

10.8 Retention and Availability of Records

The Investigator is required to retain the trial records and reports until at least 2-years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2-years have elapsed since the formal discontinuation of clinical development of the investigational product. If no marketing application is to be filed, or an application is not approved for the drug, the Investigator will retain the study (trial) records for 15 years after shipment and delivery of the drug for investigational use is discontinued and the Sponsor has so notified the FDA, per 21 CFR 312.57. Study (trial) records should, however, be retained longer if required by the applicable national and/or local regulatory requirements.

The Investigator must make study (trial) data accessible to the monitor, other authorized representatives of the Sponsor, and regulatory agency inspectors upon request. A file for each patient must be maintained that includes the signed ICF and the Investigator's copies of all source documentation related to that patient. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was transcribed.

10.9 Independent Data Safety Monitoring Board (DSMB)

The DSMB is an independent group consisting of qualified clinicians and at least one statistician. The DSMB will review the safety data, from the study. The DSMB will operate under a charter and will convene for safety review meetings at the interval.

10.10 Protocol Violations/Deviations

Protocol violations include deviations from the inclusion and exclusion criteria, concomitant medication restrictions, and any other protocol requirement that results in a significant added risk to the patient or has an impact on the quality of the data collected or the outcome of the study. A deviation occurs when there is non-adherence to study procedures or schedules, as specified by the protocol, which does not involve inclusion/exclusion criteria or the primary endpoint and which does not place the patient at any added risk or affect the data quality or study outcome. Examples of deviations may include common out-of-window visits, a missed procedure, etc. Protocol violations will be reported in the final clinical study report, whereas protocol deviations may be mentioned but are not required to be reported.

It is important to conduct the study according to the protocol. Protocol deviation waivers will not be prospectively granted by the sponsor. If minor protocol deviations occur, the clinical investigator must decide the most appropriate way to proceed with study activities and should consult the study representative for assistance. If major protocol deviations occur, the sponsor's Medical Monitor must be notified immediately so that a decision about whether to keep the patient in the study can be made.

Only when an emergency occurs that requires a departure from the protocol for an individual patient can there be a departure without the Sponsor's pre-approval. The nature and reasons for the protocol deviation/violations will be recorded in the patient's CRF, and the investigator must notify the Sponsor.

Protocol deviations/violations will be reported in the final study report.

10.11 Access to Source Documentation

Authorized sponsor representatives will conduct site visits to inspect study data, patients' medical records, and CRFs in accordance with ICH guidelines, GCPs, and the respective local and national government regulations and guidelines.

The investigator will permit authorized representatives of the sponsor and the respective national or local health authorities, other authorized regulatory authorities, and IRB to inspect facilities and records relevant to this study.

Each center will be visited at regular intervals by a monitor to ensure compliance with the study protocol, GCP, and legal aspects. This will include on-site checking of the CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters.

All CRF data will be entered into a clinical database. Following the correction of any errors, the clinical database will be locked.

10.12 Retention of Data

The study file and all source data should be retained until notification is given by the sponsor for destruction.

If the investigator withdraws from the trial and relinquishes his/her responsibility for the maintenance and retention of records, he/she must notify the sponsor in writing so that arrangements can be made to properly store the trial materials.

10.13 Financial Disclosure

Clinical investigator/ sub-investigator must provide financial information and promptly update this information if any relevant changes occur during the course of the investigation and for one year following completion of the study. "The course of the study" refers to the time from the date the clinical investigator entered into an agreement with the Sponsor to conduct the study until the completion of the study. Completion of the study means that all study patients have been enrolled and follow-up of study data on all patients has been completed in accordance with the clinical protocol.

A financial disclosure form (FDF) will be provided to the clinical investigator and all sub-investigators who are directly involved in the treatment or evaluation of research patients prior to the site initiation visit. Clinical investigators are required to provide an updated FDF if there are changes in disclosable financial interests, arrangements or payments. Types of disclosable financial interests are provided on the FDF. Copies of the FDF will be included in the study Trial Master File.

Upon the patient's permission, medical information may be given to the patient's personal physician or other appropriate medical personnel responsible for the patient's welfare.

10.14 Audits and Inspections

In accordance with ICH, GCP and the Sponsor and/or its designee audit plans, this trial may be selected for audit. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories) and review of trial-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH, GCP, and applicable regulatory requirements. The Investigator/ institution should make available for direct access all requested trial-related records (ICH GCP 4.9.7) to appropriately qualified personnel from the Sponsor or its designees, or to health authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents (i.e., completed CRFs, Investigator site files, and any source documents should be stored in a protected secure location [ICH GCP 4.9.4]).

If for any reason the study trial records are moved to another location, the Investigator should notify the Sponsor of the new location.

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Appendix 1 Schedule of Events

(A) Procedures During the Remission Induction Period

Study Procedures	**Screening**		**Remission Induction Period**					
Visit	**V1[1]**	**V1 a-c**	**V2**	**V3**	**Month 1/V4**	**Month 2/V5**	**Month 4/V6**	**Month 6/V7**
Visit Day	**-14 - 0**		**0**	**14**	**30**	**60**	**120**	**180**
Visit Window				**±2**	**±2**	**±3**	**±5**	**±10**
Informed consent	X							
Inclusion/exclusion	X		X					
Demography	X							
Medical hist. including AAV history and prior medication	X							
Randomization			X					
Study drug administration[2]			X	X				
Glucocorticoid use[3]	X	X	X	X	X	X	X	
Vital signs	X		X	X	X	X	X	X
Physical Examination	X		X	X	X	X	X	X
ECG	X							X
AE assessment		X	X	X	X	X	X	X
Concomitant medication		X	X	X	X	X	X	X
BVAS/ WG Score/ Remission/Relapse evaluation	X			X	X	X	X	X
AAV-PRO			X					X
VCRC WG/MPO Disease Activity & Transition Assessment	X			X	X	X	X	X
GTI assessment			X					X
VDI			X			X		X
Clinical Laboratory Test Collection	X[4]			X	X	X	X	X
Blood sample for HSFC and/or TBNK[5]	X		X		X	X	X	X
Serum for ANCA Antibody[5]	X							X
Blood for PBMC[5]	X		X			X	X	X
Serum for biomarkers[5]			X		X	X	X	X
PAXgene RNA[5]			X		X			X
Whole Blood EDTA tube for			X		X			X

Study Procedures	**Screening**		**Remission Induction Period**					
Visit	**V1[1]**	**V1 a-c**	**V2**	**V3**	**Month 1/V4**	**Month 2/V5**	**Month 4/V6**	**Month 6/V7**
Visit Day	**-14 - 0**		**0**	**14**	**30**	**60**	**120**	**180**
Visit Window				**±2**	**±2**	**±3**	**±5**	**±10**
molecular B cell enumeration								
Plasma for biomarkers[5]			X	X	X	X	X	X

[1] Any required screening assessments conducted as part of standard of care within 14 days of Day 0 may be used as a part of screening.

[2] For subjects who meet treatment failure criteria, dosing with obinutuzumab and glucocorticoids should be administered as soon as possible. The clinic visits will follow the same schedule as the first day of dosing (V2)

[3] Glucocorticoid regimen must be recorded for the first 16 weeks and in subsequent visits if glucocorticoid use is needed.

[4] ANCA test to be performed at local lab for assessment of study eligibility.

[5] Samples will be drawn before administration of study drug on dosing days.

(B) Procedures During the Maintenance Period

Study Procedures	**Follow-Up Period**				
Visit	Month 9 V8	Month 12 V9	Month 15 V10	Month 18 V11	Unscheduled V99[1]
Visit Day	**D270**	**D360**	**D450**	**D540**	**N/A**
Visit Window	**±10**	**±10**	**±10**	**±10**	
Informed consent					
Inclusion/exclusion					
Demography					
Medical history including AAV history and prior medication					
Randomization					
Study drug administration					
Glucocorticoid use[2]					
Vital signs	X	X	X	X	X
Physical Examination	X	X	X	X	X
ECG				X	
AE assessment	X	X	X	X	X
Concomitant medication	X	X	X	X	X
BVAS/ WG Score/ Remission/Relapse evaluation	X	X	X	X	X
AAV-PRO		X		X	X
VCRC WG/MPO Disease Activity & Transition Assessment	X	X	X	X	X
GTI assessment	X	X	X	X	X
VDI	X	X	X	X	
Clinical Laboratory Test Collection	X	X	X	X	X
Blood sample for HSFC and/or TBNK[3]	X	X	X	X	X
Serum for ANCA Antibody[3]	X	X	X	X	X
Blood sample for PBMC[3]	X	X	X	X	X
Serum for biomarkers[3]	X	X	X	X	X
PAXgene RNA[3]		X		X	
Whole Blood EDTA Tube for molecular B cell enumeration		X		X	
Plasma for biomarkers[3]	X	X	X	X	X

[1] Subjects who experience signs or symptoms that indicate disease recurring should make an unscheduled visit so appropriate evaluation and treatment can be initiated. If the visit fits the window of a pre-scheduled visit, only one visit is to be completed and the data should be captured in the pre-scheduled visit case report forms.

[2] Glucocorticoid regimen must be recorded for the first 16 weeks and in subsequent visits if glucocorticoid use is needed.

[3] Samples will be drawn before administration of study drug on dosing days.

Appendix 2 Schedule of Laboratory Testing

Study Procedures	Screening	Remission Induction Period						Maintenance Period				
Visit	**V1[1]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**11**	**V99**
Visit Day	**D-14 – D0**	**D0**	**D14**	**D30**	**D60**	**D120**	**D180**	**D270**	**D360**	**D450**	**D540**	**Unscheduled**
Hematology[2]	X	X	X	X		X	X	X	X	X	X	X
Serum chemistry[3]	X	X	X	X		X	X	X	X	X	X	X
HbA_{1c} & lipids[4]		X				X	X		X		X	
ANCA negativity[5]	X						X	X	X	X	X	X
Immunoglobulins[6]		X					X				X	
CD19[7]	X	X					X					X
Infectious disease testing[8,9]	X											
Pregnancy (WCBP only); FSH[10]	X	X	X	X								
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for flow cytometry (TBNK)[11]	X	X			X	X	X	X	X	X	X	X
Blood sample for HSFC[11]		X		X		X	X	X	X	X	X	
Serum for biomarkers[11]		X		X	X	X	X	X	X	X	X	X
Blood sample for PBMCs[11,12]	X	X			X		X				X	
PAXgene RNA[11]		X		X			X		X		X	
Whole Blood EDTA tube for molecular B cell enumeration		X		X			X		X		X	
Plasma for biomarkers[11]		X	X	X	X	X	X	X	X	X	X	X

[1] Any required screening assessments conducted as part of standard of care within 14 days of Day 0 may be used as a part of screening.

[2] Hematology tests include: hemoglobin, hematocrit, erythrocyte count (red blood cell [RBC] count), thrombocyte count (platelets), leukocyte count (white blood cell [WBC] count) with differential in absolute counts (including neutrophils, eosinophils, basophils, lymphocytes, and monocytes, erythrocyte sedimentation rate (ESR).

[3] Serum chemistry tests include: comprehensive metabolic profile including aspartate aminotransferase (AST); alanine aminotransferase (ALT); total, direct, and indirect bilirubin levels; alkaline phosphatase (ALP); albumin, creatinine; estimated GFR, blood urea nitrogen (BUN) carbon dioxide (C02, and glucose (random)); total protein; C-Reactive Protein.

[4] Hemoglobin A1c and Lipids: total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides should be drawn on Baseline, Month 4, 6, 12 and 18 only.

[5] PR3 ANCA antibody will be determined centrally at the Mayo clinical laboratory; MPO ANCA and PR3 ANCA antibodies will be measured by local laboratory at screening visit only to determine eligibility.

[6] Total immunoglobulin, IgG, IgM, IgA, and IgE will be measured.

[7] Whole blood flow cytometry will be performed to determine CD19+ B cells in relapsing patients only.

[8] Infectious disease tests include: hepatitis B (surface antigen and core antibodies), HCV, and HIV, tuberculosis (TB) testing, COVID-19 by nasal swab. Infectious disease will be tested at screening (V1) and when clinically indicated.

[9] Preferred tuberculosis (TB) testing method is QuantiFERON-TB Gold (QFT). If patient has a negative purified-protein derivative tuberculin skin test (PPD TST) result from a test performed with 1 year of day 0, QFT does not need to be performed at screening.

[10] Postmenopausal females < 55 years of age (defined as amenorrhea >1 year) must have menopause confirmed by elevated follicle-stimulating hormone (FSH) levels at screening.

[11] Samples will be drawn before administration of study drug on dosing days.

[12] PBMC will be processed and cryopreserved for the biomarkers.

Table 6 Laboratory Sample Handling

Sample	Tests	Blood Vol. (mL)	Testing / Storage Lab	Storage/ Temp (ºC)
Routine Safety Lab Testing				
Whole blood	Hematology	2	Local	N/A
Whole blood	HbA_{1c}	2	Local	N/A
Whole blood	Flow cytometry CD19	3	Local	N/A
Serum	Comprehensive metabolic panel & Liver enzymes	2	Local	N/A
Serum (fasted)	Lipid panel	3	Local	N/A
Serum	ANCA antibody (screening)	2	Local	N/A
Serum	Immunoglobulins	5	Local	
Serum/Nasal swab	Infectious diseases	3	Local	
Urine (WOCBP)	Pregnancy	N/A	In clinic	N/A
Serum (WOCBP)	FSH menopause confirmation	2	Local	N/A
Urine	Urinalysis	N/A	Local	N/A
Research Testing For Outcome Assessment				
Serum	ANCA antibody	3	Mayo	-80
Mechanistic Study Biomarkers				
Whole blood	Blood sample for HSFC and/or TBNK	5	LabCorp	N/A
PBMC	Sample for biomarkers	50	Mayo	-80
Serum	Sample for biomarkers	5	LabCorp	-80
Serum	Sample for biomarkers	10	Mayo	-80
Plasma	Sample for biomarkers	6	Mayo	-80
Paxgene RNA	Sample for biomarkers	5	Mayo	-80
Whole Blood EDTA tube for molecular B cell enumeration	Sample for biomarkers	5	LabCorp	-80

Abbreviation: PBMC: peripheral blood mononuclear cells; WOCBP: women of childbearing potential.

Appendix 3 Chapel Hill Consensus Conference

DIAGNOSTIC CRITERIA

Widely accepted diagnostic criteria—as opposed to classification criteria or definitions—have not yet been developed for Wegener's Granulomatosis (WG) and microscopic polyangiitis (MPA). In 1994, the Chapel Hill International Consensus Conference developed definitions for these vasculitides and some of their mimickers.[1] These definitions, along with the American College of Rheumatology (ACR) Criteria for the classification of vasculitides,[2] are useful in formulating the diagnostic criteria that will be applied to determine a participant's eligibility for this clinical trial.

Chapel Hill Consensus Conference Definitions for Microscopic Polyangiitis

- Necrotizing vasculitis with few or no immune deposits affects small vessels (i.e., capillaries, venules, or arterioles).
- Necrotizing arteritis involving small and medium-sized arteries may be present.
- Necrotizing glomerulonephritis is very common.
- Pulmonary capillaritis often occurs.

ACR Criteria for the Classification of Wegener's Granulomatosis

Among a group of patients with various forms of systemic vasculitis, the presence of at least two of these four criteria is associated with a sensitivity of 88.2% and a specificity of 92.0% for WG.

- Nasal or oral inflammation: painful or painless oral ulcers or purulent or bloody nasal discharge
- Abnormal chest radiograph: nodules, fixed infiltrates, or cavities
- Urinary sediment: microhematuria or red cell casts
- Granulomatous inflammation on biopsy: granulomatous inflammation within the wall of an artery or in the perivascular area

ACR Criteria for the Classification of Churg-Strauss Syndrome

Although we wish to exclude Churg-Strauss syndrome (CSS) from this trial, we will use the following ACR criteria for the classification of this disorder:

Among a group of patients with various forms of systemic vasculitis, the presence of at least four of these six criteria is associated with a sensitivity of 85.0% and a specificity of 99.7% for CSS.

- Asthma: wheezing or high-pitched rales
- Eosinophilia: >10% of white blood cell differential

[1]Jennette JC et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum*. 1994; 37:187–192.
[2] Fries JF et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Summary. *Arthritis Rheum*. 1990; 33:1135–1136.

- Mononeuropathy or polyneuropathy: mononeuropathy, multiple mononeuropathies, or polyneuropathy attributable to vasculitis
- Pulmonary infiltrates, nonfixed: migratory or transitory pulmonary infiltrates
- Paranasal sinus abnormality: acute or chronic paranasal sinus pain, tenderness, or radiographic opacification
- Extravascular eosinophils: biopsy, including artery, arteriole, or venule showing accumulations of eosinophils in extravascular areas

Appendix 4 CKD-EPI Creatinine Equation

CKD-Epi equation is developed in 2009 by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and is the recommended method for estimating GFR in adults (Levey et al., 2009). It is designed for use with laboratory creatinine values that are standardized to the isotope dilution mass spectrometry (IDMS) and estimates GFR from serum creatinine, age, sex, and race. The CKD-Epi equation uses a 2-slope "spline" to model the relationship between estimated GFR and serum creatinine, and a different relationship for age, sex and race.

For the PRRR study, the race will not be factored in to estimate the GFR. The CKD-Epi equation expressed eGFR as a single equation is shown below:

$$eGFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]}$$

eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2
S_{Cr} (standardized serum creatinine) = mg/dL
$\kappa = 0.7$ (females) or 0.9 (males)
$\alpha = -0.329$ (females) or -0.411 (males)
min = indicates the minimum of S_{Cr}/κ or 1
max = indicates the maximum of S_{Cr}/κ or 1
age = years

Appendix 5 BVAS/WG

The BVAS for Wegener's granulomatosis (BVAS/WG) is a modification of BVAS specifically designed for use in studies of granulomatosis with polyangiitis (Wegener's) (Stone et al., 2001)

BVAS for Wegener's Granulomatosis Evaluation Form

Tick box (☐ or ○) only if abnormality is ascribable to the presence of active Wegener's Granulomatosis (chronic damage should be scored separately in the Vasculitis Damage Index, VDI.)

☐ Tick box only if the abnormality is **persistent disease activity** since the last assessment and not worse within the **previous 28 days.**

○ Tick box only if the abnormality is **newly present or worse** within the **previous 28 days.**

△ If no items are present in any section, tick "none".

Major items are in bold and marked with *

All WG-related clinical features need to be documented on this form if they are related to active disease. Use "OTHER" category as needed.

1. Clinic ID: ____
2. Patient ID: ____
3. Patient name code: ____
4. Date form completed: __ __ - __ __ __ - __ __ (day - month - year)
5. Visit ID: ____

	Persistent	New/Worse	None
6. GENERAL			△1
a. arthralgia/arthritis	☐1	○2	
b. fever (≥38.0 °C)	☐1	○2	
7. CUTANEOUS			△1
a. purpura	☐1	○2	
b. skin ulcer	☐1	○2	
c. * **gangrene**	☐1	○2	
8. MUCOUS MEMBRANES/EYES			△1
a. mouth ulcers	☐1	○2	
b. conjunctivitis/episcleritis	☐1	○2	
c. retro-orbital mass/proptosis	☐1	○2	
d. uveitis	☐1	○2	
e. * **scleritis**	☐1	○2	
f. * **retinal exudates/hemorrhage**	☐1	○2	
9. EAR, NOSE & THROAT			△1
a. bloody nasal discharge/nasal crusting/ulcer	☐1	○2	
b. sinus involvement	☐1	○2	
c. swollen salivary gland	☐1	○2	
d. subglottic inflammation	☐1	○2	
e. conductive deafness	☐1	○2	
f. * **sensorineural deafness**	☐1	○2	
10. CARDIOVASCULAR			△1
a. pericarditis	☐1	○2	
11. GASTROINTESTINAL			△1
a. * **mesenteric ischemia**	☐1	○2	
12. PULMONARY			△1
a. pleurisy	☐1	○2	
b. nodules or cavities	☐1	○2	
c. other infiltrate secondary to WG	☐1	○2	
d. endobronchial involvement	☐1	○2	
e. * **alveolar hemorrhage**	☐1	○2	
f. * **respiratory failure**	☐1	○2	

	Persistent	New/Worse	None
13. RENAL			△1
a. hematuria (no RBC casts) (≥1+ or ≥10 RBC/hpf)	☐1	○2	
b. * **RBC casts**	☐1	○2	
c. * **rise in creatinine >30% *or* fall in creatinine clearance >25%**		○2	
***Note:** If both hematuria and RBC casts are present, score only the RBC casts (the major item).*			
14. NERVOUS SYSTEM			△1
a. * **meningitis**	☐1	○2	
b. * **cord lesion**		○2	
c. * **stroke**		○2	
d. * **cranial nerve palsy**		○2	
e. * **sensory peripheral neuropathy**		○2	
f. * **motor mononeuritis multiplex**		○2	
15. OTHER (describe all items and * items deemed major)			△1
_____	☐1	○2	
_____	☐1	○2	
_____	☐1	○2	
_____	☐1	○2	

16. TOTAL NUMBER OF ITEMS:

a.	b.	c.	d.
____	____	____	____
Major New/Worse	Minor New/Worse	Major Persistent	Minor Persistent

DETERMINING DISEASE STATUS:

Severe Disease/Flare: ≥1 new/worse Major item.
Limited Disease/Flare: ≥1 new/worse Minor item.
Persistent Disease: Continued (but not new/worse) activity.
Remission: No active disease, including either new/worse or persistent items.

17. CURRENT DISEASE STATUS *(check only one)*:

Severe Disease/Flare (1)
Limited Disease/Flare (2)
Persistent Disease (3)
Remission (4)

18. PHYSICIAN'S GLOBAL ASSESSMENT (PGA)

Mark line to indicate the amount of WG disease activity (not including longstanding damage) within the **previous 28 days:**

Remission |——————————————————————| **Maximum activity**
0 10

19. Value in item #18: ___ mm *(distance from 0 to tick mark in millimeters)*

20. DATE FORM REVIEWED: __ __ - __ __ __ - __ __ (day - month - year)
21. STUDY PHYSICIAN ID: __ __
22. STUDY PHYSICIAN SIGNATURE: _____
23. CLINIC COORDINATOR ID: __ __
24. CLINIC COORDINATOR SIGNATURE: _____

Figure 1. Evaluation form for the Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG). RBC = red blood cell; hpf = high-power field.

- Disease manifestations are to be scored only when they are attributable to active vasculitis. If there is reasonable evidence a manifestation is likely attributable to another etiology (e.g., infection, other co-morbidity), it should not be scored.
- Persistent disease scoring should be used for all manifestations due to active (but not new or worsened) vasculitis.
- Specialist opinion, or the results of laboratory or imaging investigations may be required for some items.
- The items of serum creatinine in section 8. “Renal” should be scored only on the first visit.
- There are several items, i.e. Nodules or cavities that are not compatible with persistent disease and can only be scored under new/worse scoring.
- When the BVAS/WG is assessed for the first time in that patient or any of the features have started or deteriorated in the past month, please use the new/worse scoring.
- Bold printed and starred items are given 3 points, whereas all other items are assigned 1 point.
- Features persisting for >3 months represent damage rather than disease activity and should be scored on a Vasculitis Damage Index (VDI) form and not on a BVAS/WG form.

Appendix 6 AV-PRO Assessment

AAV-PRO Questionnaire

Symptoms

Due to having vasculitis or its treatment, please rate your experience of the following problems, in general, during the past 4 weeks.

Please ✓ only one box for each statement.

		None	Very mild	Mild	Moderate	Severe
1.	Chest problems (such as wheezing, 'chest tightness', coughing, or shortness of breath)	☐	☐	☐	☐	☐
2.	Problems with your ears (such as pain, difficulty hearing, a sense of pressure, or blockage)	☐	☐	☐	☐	☐
3.	Problems with your eyes (such as pain, blurred or poor vision, or sensitivity to light)	☐	☐	☐	☐	☐
4.	Problems with your nose or sinuses (such as pain, a sense of pressure, nosebleeds, blockage, runny nose, or crusting)	☐	☐	☐	☐	☐
5.	Problems with your mouth or throat (such as dryness, mouth sores, hoarseness, sore throat, or difficulty eating/swallowing)	☐	☐	☐	☐	☐
6.	Problems with your joints (such as aches and pains or swelling)	☐	☐	☐	☐	☐
7.	Pain, cramps or weakness affecting your muscles	☐	☐	☐	☐	☐
8.	Problems with your skin (such as swelling, blotches, a rash, bruising, or lumps)	☐	☐	☐	☐	☐
9.	Tiredness or fatigue	☐	☐	☐	☐	☐
10.	Feeling uncomfortably hot, cold, or feverish	☐	☐	☐	☐	☐
11.	Indigestion, heartburn, nausea, or sickness (vomiting)	☐	☐	☐	☐	☐

Difficulties with everyday life

Due to having vasculitis or its treatment, how difficult have you found the following activities, in general, during the past 4 weeks?

Please ✓ only one box for each statement.

	No difficulty	A little difficult	Moderately difficult	Extremely difficult	I could not do this
12. Walking around shops for at least an hour	☐	☐	☐	☐	☐
13. Walking up a flight of stairs	☐	☐	☐	☐	☐
14. Doing the physical activities that you wanted to (such as walking, sports, or fitness classes)	☐	☐	☐	☐	☐
15. Washing and drying yourself, or getting dressed, without help from another person	☐	☐	☐	☐	☐
16. Getting enough good sleep	☐	☐	☐	☐	☐

Social and emotional impact

Due to having vasculitis or its treatment, how often have the following applied to you, in general, during the past 4 weeks?

Please ✓ only one box for each statement.

	None of the time	Rarely	Sometimes	Often	All of the time
17. I have felt concerned about my weight (weight gain or weight loss)	☐	☐	☐	☐	☐
18. I have felt upset or frustrated because I have been unable to work or do my everyday tasks	☐	☐	☐	☐	☐

Social and emotional impact *(continued)*

Due to having vasculitis or its treatment, how often have the following applied to you, in general, during the past 4 weeks?

Please ✓ only one box for each statement.

	None of the time	Rarely	Sometimes	Often	All of the time
19. I have worried about what will happen to me in the future	☐	☐	☐	☐	☐
20. I have been anxious, worried or stressed	☐	☐	☐	☐	☐
21. I have had difficulty concentrating or being focussed	☐	☐	☐	☐	☐
22. I have felt down or depressed	☐	☐	☐	☐	☐
23. I have worried about being dependent on other people	☐	☐	☐	☐	☐
24. I have had difficulty making long-term plans (for example, plans involving work, close relationships, or family)	☐	☐	☐	☐	☐
25. I have worried about travelling a long distance from home	☐	☐	☐	☐	☐
26. I have felt embarrassed or self-conscious due to my appearance or symptoms	☐	☐	☐	☐	☐
27. I have felt that I have let other people down (for example, because you couldn't provide help, or had to cancel an arrangement)	☐	☐	☐	☐	☐
28. I have felt that my life is now focussed on coping with my condition	☐	☐	☐	☐	☐
29. I have worried about the long-term effects of treatment	☐	☐	☐	☐	☐

Appendix 7 VCRC WG/MPA Disease Activity and Transition Assessment

Screening

Participant ID _____

Instructions: Rate each item for:
i) activity since last study visit (maximum 28 days)-use full range of choices, as appropriate;
ii) change since last study assessment and then complete 2 sections on lower right.
I=improved; S=same (no change); W=worse

For baseline visits, comparison is to prior clinical visit and/or investigator's assessment of disease course.

	ACTIVITY None					Most Severe		CHANGE I	S	W
General	N/A	0	1	2	3	4	5			
Arthritis/arthralgias										
Fever										
Cutaneous	N/A	0	1	2	3	4	5			
Purpura										
Skin ulcer										
Gangrene										
Mucous Membrane/ Eyes	N/A	0	1	2	3	4	5			
Oral ulcers										
Conjunctivitis/ episcleritis										
Retro-orbital mass/ proptosis										
Uveitis										
Scleritis										
Retinal exudates/ hemorrhage										
Ear, Nose & Throat	N/A	0	1	2	3	4	5			
Bloody nasal discharge										
Sinus involvement										
Swollen salivary gland										
Subglottic inflammation										
Conductive deafness										
Sensorineural deafness										
Cardiovascular	N/A	0	1	2	3	4	5			
Pericarditis										
Gastrointestinal	N/A	0	1	2	3	4	5			
Mesenteric ischemia										
Pulmonary	N/A	0	1	2	3	4	5			
Pleurisy										
Nodules or cavities										
Other infiltrate secondary to WG										
Endobronchial involvement										
Alveolar hemorrhage										
Respiratory failure										

	ACTIVITY None					Most Severe		CHANGE I	S	W
Renal	N/A	0	1	2	3	4	5			
Hematuria (no casts)										
RBC casts										
Rise in creat >30% or fall in cr cl >25%										
Nervous System	N/A	0	1	2	3	4	5			
Meningitis										
Cord lesion										
Stroke										
Cranial neuropathy										
Sensory periph neuropathy										
Motor mononeuritis multiplex										
Other Items (carry forward from prior)	N/A	0	1	2	3	4	5			
Weight loss										
Fatigue/Malaise										
Skin nodules										

Overall change from previous study assessment?

Improved	Stable	Worse

Overall change from baseline study assessment?

Improved	Stable	Worse

Appendix 8 Vasculitis Damage Index

VASCULITIS DAMAGE INDEX (VDI)

This is for recording organ damage that has occurred in patients *since the onset of vasculitis*
Patients often have co-morbidity before they develop vasculitis, **which must not be scored**
Record features of active disease using the Birmingham Vasculitis Activity Score (BVAS)
A new patient 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

	No	Yes
1. Musculoskeletal		
None	☐	
Significant muscle atrophy or weakness		○
Deforming/erosive arthritis		○
Osteoporosis/vertebral collapse		○
Avascular necrosis		○
Osteomyelitis		○
2. Skin/Mucous membranes		
None	☐	
Alopecia		○
Cutaneous ulcers		○
Mouth ulcers		○
3. Ocular		
None	☐	
Cataract		○
Retinal change		○
Optic atrophy		○
Visual impairment/diplopia		○
Blindness in one eye		○
Blindness in second eye		○
Orbital wall destruction		○
4. ENT		
None	☐	
Hearing loss		○
Nasal blockage/chronic discharge/crusting		○
Nasal bridge collapse/septal perforation		○
Chronic sinusitis/radiological damage		○
Subglottic stenosis (no surgery)		○
Subglottic stenosis (with surgey)		○
5. Pulmonary		
None	☐	
Pulmonary hypertention		○
Pulmonary fibrosis		○
Pulmonary infarction		○
Pleural fibrosis		○
Chronic asthma		○
Chronic breathlessness		○
Impaired lung function		○
6. Cardiovascular		
None	☐	
Angina angioplasty		○
Myocardial infarction		○
Subsequent myocardial infarction		○
Cardiomyopathy		○
Valvular disease		○
Pericarditis ≥ 3 mths or pericardectomy		○
Diastolic BP ≥ 95 or requiring antihypertensives		○

Name	
Trial Number	
Date	
Centre	

	No	Yes
7. Peripheral vascular disease		
None	☐	
Absent pulses in one limb		○
2nd episode of absent pulses in one limb		○
Major vessel stenosis		○
Claudication >3 mths		○
Minor tissue loss		○
Major tissue loss		○
Subsequent major tissue loss		○
Complicated venous thrombosis		○
8. Gastrointestinal		
None	☐	
Gut infarction/resection		○
Mesenteric insufficiency/pancreatitis		○
Chronic peritonitis		○
Oesophageal stricture/surgery		○
9. Renal		
None	☐	
Estimated/measured GFR ≤ 50%		○
Proteinuria ≥ 0.5g/24hr		○
End stage renal disease		○
10. Neuropsychiatric		
None	☐	
Cognitive impairment		○
Major psychosis		○
Seizures		○
Cerebrovascular accident		○
2nd cerebrovascular accident		○
Cranial nerve lesion		○
Peripheral neuropathy		○
Transverse myelitis		○
11. Other		
None	☐	
Gonadal failure		○
Marrow failure		○
Diabetes		○
Chemical cystitis		○
Malignancy		○
Other		○

Total VDI Score. Record the number of positive items (1 point for each). The VDI score can either increase or remain the same over time. Remember to carry forward any previous items of damage. ☐

VDI Modified from Exley AR, Bacon PA, Luqmani et al (1997) Development and initial validation of the VDI ... Arthritis Rheum 40: 371-380

Appendix 9 Glucocorticoid Toxicity Index

(Excerpt from "Quantification of Glucocorticoid-Associated Morbidity in Severe Asthma Using the Glucocorticoid Toxicity Index", 2020 Elsevier Inc.)

Development of the GTI

The original version of the GTI (GTI 1.0) underwent preliminary validation by a multispecialty group of 19 physician experts.[E1] These experts represented 10 medical subspecialties: pulmonary medicine, rheumatology, pediatric rheumatology, nephrology, neurology, ophthalmology, dermatology, infectious disease, maternal-fetal medicine, and psychiatry. The investigator group, which included 10 researchers from the United States and 9 from Europe, Canada, or Australia, employed group consensus methods and multicriteria decision analysis (MCDA).[E2]

A full explanation of how the items required to give a complete quantification of glucocorticoid (GC)-related toxicity were determined is outlined in the paper by Miloslavsky et al.[E1] In brief, items to be included in the GTI scoring were determined on the following principles: (1) they occur commonly in GC- exposed patients (5% of such patients); (2) they are independent of other items in the GTI; (3) they are more likely to result from GC exposure than from the underlying disease; (4) they are likely to change over a short period of time (i.e., to either improve or worsen over a period of at least 3 months); and (5) they can be measured simply and noninvasively. A small number of the measured variables may be outside the usual clinical measurements for a given disease, but these are easy to collect and important for assessing GC toxicity as part of routine care.

The GTI assigns relative weights that have been determined systematically to each toxicity item in the Composite Index. These weights were developed through MCDA[E2] using pairwise "forced-choice" methods within the 1000Minds platform; all possible combinations of Composite Index items were ranked in order of toxicity severity. A point system reflecting the relative weight of each item in terms of toxicity was thereby derived.

Scoring the GTI

The fundamental principle with regard to the scoring approach is that an improvement in GC toxicity is given the same absolute weight as a worsening of GC toxicity of the same (but opposite) magnitude. This approach generated 2 scores from the Composite Index data called: (1) the Aggregate Improvement Score and (2) the Cumulative Worsening Score.

Aggregate Improvement Score

When starting a new treatment, the AIS is important in establishing that the new therapy is effective at diminishing any GC toxicity over time. With the AIS, toxicities are removed if they improve or resolve completely over longitudinal follow-up. Toxicities can also be added to the AIS over time if new or worsened GC toxicities occur. With the AIS, improvement in GC toxicity has the same absolute value as does worsening to the same degree in the opposite direction.

Cumulative Worsening Score

On the other hand, documentation of cumulative GC toxicity that occurs over the course of the trial or introduction of a new treatment is important, even if some toxicities are transient. The CWS is designed to assess the summative GC toxicity, regardless of whether the toxicity has lasting effects or resolves with time. New toxicities that occur are added to the CWS total, but toxicities that resolve on follow-up are not removed. The CWS serves as a lasting record of any GC toxicity that has occurred and can only increase or remain the same over time.

The GTI: Composite Index and Specific List

The GTI is designed to measure change in GC toxicity between 2 points in time and includes 2 components, a Composite Index and a Specific List. The full Composite Index includes 9 domains and a total of 31 unique weighted items (see below). The Composite Index captures information about common GC-induced morbidities that distinguish high GC users from low GC users. The domains of toxicity represented in the Composite Index are well recognized by both clinicians and patients as being important: BMI, glucose tolerance, blood pressure, lipids, GC- induced myopathy, bone mineral density, skin toxicity, neuro- psychiatric effects and infections. Important to the GTI's purpose of recording change in GC toxicity, the domains of the Composite Index all represent elements of GC toxicity that are expected to either worsen or improve with variations in GC doses over time.

The Specific List was created as the second component of the GTI because not all GC toxicities are either sufficiently common or easily measurable for inclusion in the Composite Index. Nevertheless, even relatively uncommon or difficult-to-measure toxicities are important to record because such morbidities contribute substantially to the overall burden of GC use. The Specific List permits a more complete accounting of cumulative GC toxicity than that afforded by the Composite Index alone. Examples of toxicities included in the Specific List are osteonecrosis and posterior subcapsular cataracts, reflecting GC- induced damage that is irreversible. Because items in the Specific List occur rarely, often reflect cumulative GC toxicity, and frequently have a disproportionate impact on patients' quality of life, weights are not assigned to Specific List items.

The Specific List includes 11 domains (9 of which are also shared by the Composite Index) and 23 unique items (see below). Together, the Composite Index and the Specific List aspire to capture the full sweep of GC toxicity that is relevant to patients.

Weights

The GTI assigns systematically determined relative weights to each toxicity item in the Composite Index. These weights were developed through MCDA.[E2] Using pairwise "forced-choice" methods within the 1000Minds platform, all possible combinations of Composite Index items were ranked in order of toxicity severity. A point system reflecting the relative weight of each item in terms of toxicity was thereby derived. The MCDA method is more systematic than group consensus methods such as Delphi exercises, in which investigators are asked to order all possible toxicities or assign relative weights. The MCDA method also carries a lower cognitive burden for investigators involved in a consensus exercise, because investigators are required to compare only 2 items at a time. This MCDA approach has been employed now in multiple studies developing classification criteria for immune-mediated diseases.[E3-E6]

Table E1. Approach to calculating the baseline GTI Score: toxicities assigned weighted score: toxicities assigned weighted scores from the Composite Index to establish a baseline GTI score

Toxicity Domain		Points
Body Mass Index	BMI < 27	0
	BMI ≥ 27 or < 30	21
	BMI ≥ 30	36
Glucose Metabolism	HgbA1c < 5.7	0
	HgbA1c <5.7 but on medication	32
	HgbA1c ≥ 5.7	32
	HgbA1c ≥ 5.7 but on medication	44
	Diabetic retinopathy, nephropathy, or neuropathy (count only one)	44
Blood Pressure	Normotensive: systolic ≤ 120 and diastolic ≤ 85 no medications	0
	Systolic ≤ 120 and diastolic ≤ 85 but on medications	19
	Systolic > 120 or diastolic > 85 on no medications	19
	Systolic > 120 or diastolic >85 and on medications	44
	Hypertensive emergency or PRES (count only one)	44
Lipid metabolism	LDL ≤ target	0
	LDL ≤ target but on medications	10
	LDL > target on no medications	10
	LDL > target on treatment	30
Bone/tendon	Normal BMD or no known history of osteoporosis	0
	Osteoporosis	29
	Insufficiency fracture secondary to osteoporosis	29
	Osteonecrosis	29
	Tendon rupture while on corticosteroid	29
Glucocorticoid myopathy	No myopathy	0
	Minor glucocorticoid myopathy	9
	Moderate glucocorticoid myopathy	63
	Sever glucocorticoid myopathy	63
Skin	No skin toxicity	0
	Minor skin toxicity (1 or more than 1 minor skin item)	8
	Moderate skin toxicity (1 or more than 1 moderate skin item)	26
	Severe Skin toxicity (1 or more than 1 severe skin toxicity)	26
	Select only 1 (minor, moderate or severe)	

Neuropsychiatric	No neuropsychiatric toxicity	0
	Minor (1 or more than 1 minor NP item: Insomnia, mania, depression, cognitive)	11
	Moderate (1 or more than 1 moderate NP item: insomnia, mania, depression, cognitive)	74
	Severe (1 or more than 1 severe NP item: insomnia, mania, depression, cognitive)	74
	Psychosis	74
	Glucocorticoid-induced violence	74
	Select only 1 (minor, moderate or severe)	
Infection	No GTI-relevant infections within the prebaseline GTI interval of the study	0
	Oral or vaginal candidiasis or noncomplicated zoster (<grade 3) within the prebaseline GTI interval of the study	19
	Grade 3 or 4 infection within the pre-baseline GTI interval of the study	93
Ocular	Increased IOP	33
	Posterior subcapsular cataract	33
	Central Serous retinopathy	33
Gastrointestinal	GI perf absence of NSAIDS	33
	PUD without *Helicobacter pylori*	33
Endocrine	Adrenal insufficiency	33

BMD, bone mineral density; GI, gastrointestinal; GTI, Glucocorticoid Toxicity Index; HgbA1c, glycated haemoglobin; IOP, intraocular pressure; LDL, low density lipoprotein; NP, neuropsychiatric; NSAID, nonsteroidal anti-inflammatory drug; PRES, posterior reversible encephalopathy syndrome; PUD, peptic ulcer disease.*Minor: Acneiform rash (grades 1-2), easy bruising (grade 1), hirsutism (grade 1), atrophy/striae (grade 1), erosions/ulceration (grade 1). Moderate: Acneiform rash (grades 3), easy bruising (grade 2), hirsutism (grade 2), atrophy/striae (grade 2), erosions/tears/ulceration (grade 2). Severe: Acneiform rash (grade 4), atrophy/striae (grade 3), erosions/tear/laceration (grade 3).

Table E2. GTI Composite Index: domains and weights of the 31 unique items in 9 domains.

Domains		Score
1. Change in Body Weight (BMI)	Decrease by ≥ 5 BMI units	-36
	Decrease by > 2 but < 5 BMI units	-21
	No significant change (± 2 BMI units)	0
	Increase of 2 to < 5 BMI units	21
	Increase of 5 or more BMI units	36
2. Glucose metabolism	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
3. Blood Pressure	Improvement in BP AND decrease in medication	-44
	Improvement in BP OR decrease in medication	-19
	No significant change	0
	Increase in BP OR increase in medication	19
	Increase in BP AND increase in medication	44
4. Hyperlipidemia	Decrease in LDL AND decrease in medication	-30
	Decrease in LDL OR decrease in medication	-10
	No significant change	0
	Increase in LDL OR increase in medication	10
	Increase in LDL AND increase in medication	30
5. Bone health (BMD)	Increase in BMD (gain of more than 0.5)	-29
	No significant change in BMD (± 0.5)	0
	Decrease in BMD (loss of more than 0.5)	29

6. Corticosteroid myopathy	Moderate weakness to none	-63
	Moderate-to-mild weakness	-54
	Mild weakness to none	-9
	No significant change	0
	None-to-mild weakness (without functional limitation)	9
	Mild-to-moderate weakness	54
	None-to-moderate weakness (With functional limitation)	63
7. Skin corticosteroid-related toxicity	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
8. Neuropsychiatric – corticosteroid-related symptoms	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
9. Infection	No infection	0

	Oral of vaginal candidiasis or uncomplicated zoster (<grade 3)	19
	Grade 3, 4 or 5 infection	93

BMD, bone mineral density; *GTI*, Glucocorticoid Toxicity Index; *HgbA1c*, glycated haemoglobin; *LDL*, low density lipoprotein; *NP*, neuropsychiatric.

Table E3. GTI specific list: 11 domains (9 of which are shared by the Composite Index and 23 unique Items

Description	At Baseline or Before	New since baseline
Body Mass Index (BMI)		
• An absolute increase in BMI of more than 8 units (and 24.9 kg/m²		
Blood Pressure		
• Hypertensive emergency		
• PRES (Posterior reversible encephalopathy syndrome		
Endocrine		
• Symptomatic adrenal insufficiency		
Bone Health		
• Osteonecrosis of one joint		
• Osteonecrosis of more than one joint		
• Bone mineral density decrease >6%		
• Insufficiency fracture		
• Insufficiency fracture in more than one bone		
Muscle and Tendon		
• Severe glucocorticoid myopathy		
• Tendon rupture		
• More than 1 tendon rupture		
Eye		
• Central Serous Retinopathy		
• New-onset or worsened elevation of intraocular pressure requiring treatment or change in treatment		
• Posterior subcapsular cataracts (or history of same)		
Infection		
• Grade 4 infection		

• Grade 5 infection		
Glucose tolerance		
• Diabetic nephropathy		
• Diabetic neuropathy		
• Diabetic retinopathy		
Gastrointestinal Tract		
• Gastrointestinal perforation (occurring in the absence of regular nonsteroidal anti-inflammatory drug use)		
• Peptic Ulcer disease confirmed by endoscopy (excluding *Helicobacter pylori*)		
Skin		
• Sever skin toxicity		
Neuropsychiatric		
• Psychosis, defined as hallucinations, delusions, or disorganized thought process (occurring in the absence of mania, delirium, or depression).		
• Glucocorticoid-induced violence toward self or others		
Other Glucocorticoid toxicities		

GTI, Glucocorticoid Toxicity Index.

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Appendix 10 Clinical Trial Management Systems (CTMS)

CTMS is the Mayo Clinic Research Committee-endorsed institutional resource for clinical data management. CTMS is a robust institutional effort initiated in 2010 to address emerging changes within the data and statistical coordinating centers affiliated with NCI-funded cooperative groups. In 2010, NCI selected Medidata Rave® [redacted]) as the required data collection tool for all cooperative studies. To capitalize on Mayo Clinic and the NCI's investment in Medidata Rave®, Mayo Clinic formalized a three-tier data management infrastructure with the Medidata Rave® product as the premier system.

Medidata Rave® is a product for multi-center clinical trials conducted under 21 CFR Part 11 requirements. This web-based system provides ease of use coupled with an integrated randomization module (Medidata Balance™), custom reporting, robust data validation routines, and straightforward integration with SAS. •

Electronic Data Capture: Medidata Rave® allows for data collection in multisite studies. During the course of the data entry into Medidata Rave®, the system provides real-time within-case report form (CRF) and inter-CRF data consistency verification. Medidata Rave® is flexible in nature so that all data can be entered even if "required" fields and or other consistency checks requirements are not satisfied. The system uses an internal "flagging" or "query" system to distinguish the valid from the invalid data thereby ensuring compliance with the FDA guidance document "Computerized Systems Used in Clinical Trials." All data discrepancy issues are tracked and audited by the system to ensure the highest quality data is available for analysis and study reporting.

Contained within the CTMS initiative at Mayo Clinic is a diverse set of administrative and technical personnel to support the development and implementation of clinical trials in Medidata Rave®. While the time necessary to program Rave's electronic case report forms (eCRFs) has been directly budgeted, the CTMS initiative supports protocol independent activities such as software/server maintenance, data standards, institutional system integrations, SAS data, and training of study personnel through institutional resources.

The dedicated VPN connection between Mayo Clinic and Medidata provides the conduit for data connectivity. Clinical trial data hosted in Medidata is accessible when needed for SAS using the SAS On Demand Connection, in combination with Mayo Clinic's SAS Pipeline program, which creates a common and direct combination of the metadata (labels, formats, etc.) and data (raw values) into SAS datasets on a scheduled (nightly) basis. This process removes the need to separately label and format the entire clinical trial database separately in SAS

Appendix 11 Principal Investigator Signatures

Study Title: A Randomized, Double-Blind, Active Comparator-Controlled Study to Evaluate the Effect of Obinutuzumab versus Rituximab in PR3-

	Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis
Study Number:	21-012197
Final Date:	Version 3.0 17OCT2023

This clinical study protocol was subject to critical review and has been approved by the sponsor.

Signed:_____ Date:_____
Ulrich Specks, M.D.
Division of Pulmonary and Critical Care Medicine
[redacted]
Mayo Clinic College of Medicine and Science

Signed:_____ Date:_____
[redacted], M.D., M.P.H.
Principal Investigator
Professor of Medicine
Harvard Medical School
Massachusetts General Hospital

Appendix 12 Clinical Investigator's Signature

Study Title:	A Randomized, Double-Blind, Active Comparator-Controlled Study to Evaluate the Effect of Obinutuzumab versus Rituximab in PR3-Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis
Study Number:	21-012197
Final Date:	Version 3.0 17OCT2023

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____
Clinical Investigator