## Summary Table of Study Protocol

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| **Title** | Retrospective Cohort Study Evaluating Clinical Outcomes in Patients with Granulomatosis with Polyangiitis (GPA)/microscopic polyangiitis (MPA) Treated with Avacopan |
| **Protocol version identifier** | 20230026 Amendment 1, Version 2.0 |
| **Date of last version of the protocol** | February 19 2024 |
| **EU Post Authorization Study (PAS) Register No** | NA |
| **Active Substance** | TAVNEOS® (avacopan) |
| **Medicinal Product** | NA |
| **Device** | NA |
| **Product Reference** | NA |
| **Procedure Number** | NA |
| **Joint PASS** | NA |

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| **Research Question and Objectives** | Primary objectives<br>• Primary objective 1: To describe the demographics and disease-specific features of patients who are and are not prescribed avacopan for GPA/MPA.<br>• Primary objective 2: Among people prescribed avacopan, to describe the demographics and disease-specific features of patients who do and those who do not initiate avacopan.<br>• Primary objective 3: To describe the outcomes, including disease- and treatment-specific outcomes, of patients who use avacopan.<br>  ○ Proportion achieving remission within 6 months of avacopan initiation with no glucocorticoid (GC) treatment for GPA or MPA within 1 month before Month 6.<br>  ○ Proportion achieving sustained remission at Month 12, defined as remission at Month 6 and remission at Month 12, with no GC treatment for GPA/MPA 1 month before Month 12, and no relapse between Months 6 and 12.<br>Secondary objectives<br>• Secondary objective 1: To investigate baseline factors associated with GC discontinuation and relapse risk in patients who initiate avacopan.<br>• Secondary objective 2: To evaluate the association of GC use patterns with relapse risk and general clinical effectiveness and safety outcomes in patients who initiate avacopan.<br>• Secondary objective 3: To report outcomes in avacopan initiators by duration of avacopan use (≤12 vs >12 months).<br>Exploratory objective<br>• Exploratory objective 1: To examine baseline characteristics and outcomes stratified by presence or absence of severe active GPA/MPA disease status at baseline.<br>• Exploratory objective 2: To evaluate outcomes including disease- and treatment-specific outcomes as well as adverse effects of avacopan initiators through month 24 (for patients treated at MGB).<br>• Exploratory objective 3: To evaluate healthcare resource utilization during follow-up in patients who initiate avacopan. |

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| **Country(ies) of Study** | United States |
| **Author** | PPD |

**Marketing Authorization Holder**

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| **Marketing authorization holder(s)** | Amgen Inc. |
| **MAH Contact** | PPD PhD, MPH<br>PPD<br>One Amgen Center Drive<br>Thousand Oaks, CA<br>91320 |

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

**Proper Version Numbering and Dating**

VERSIONING:

| Protocol Version | Date of Protocol | Page Header Date |
|---|---|---|
| Original Protocol, Version 1.0<br>Protocol Amendment 1, Version 2.0 | February 19, 2024<br>May 18, 2026 | February 19, 2024<br>May 18, 2026 |

**Confidentiality Notice**

## Investigator's Agreement

I have read the attached protocol entitled "Retrospective Cohort Study Evaluating Clinical Outcomes in Patients with GPA/MPA Treated with Avacopan", dated 22 January 2024, and agree to abide by all provisions set forth therein.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my Sub investigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

PPD , MD

Date (DD Month YYYY)

Associate Professor

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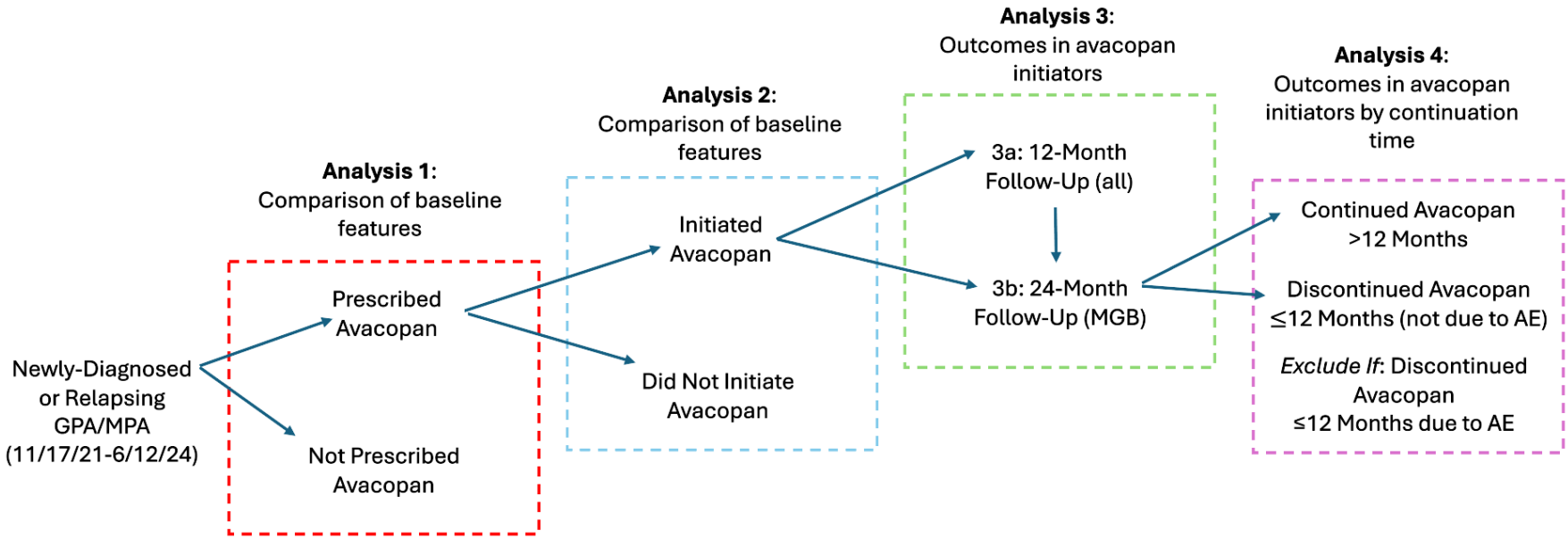
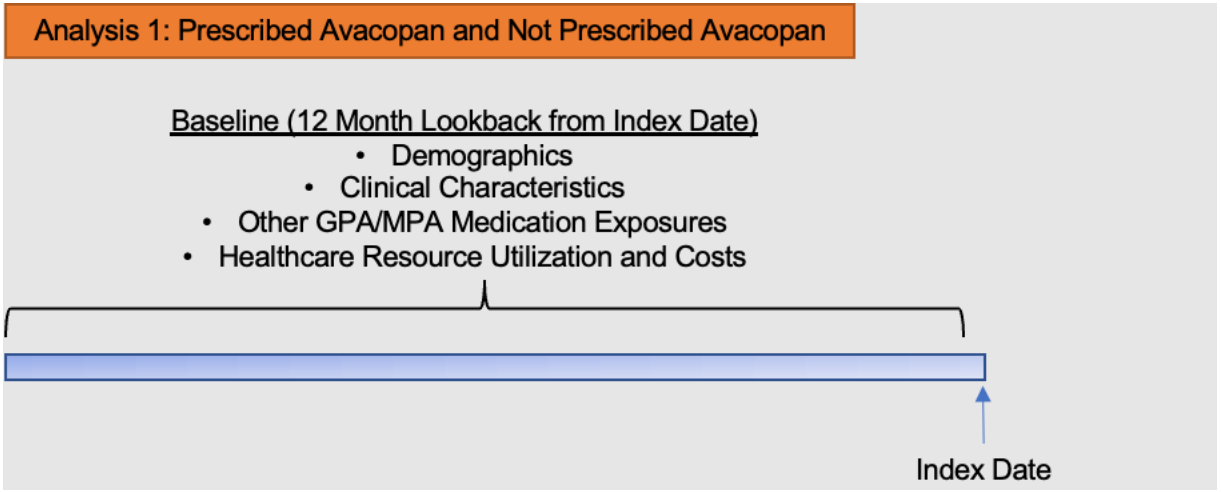
Boston, MA 02114, USA

PPD

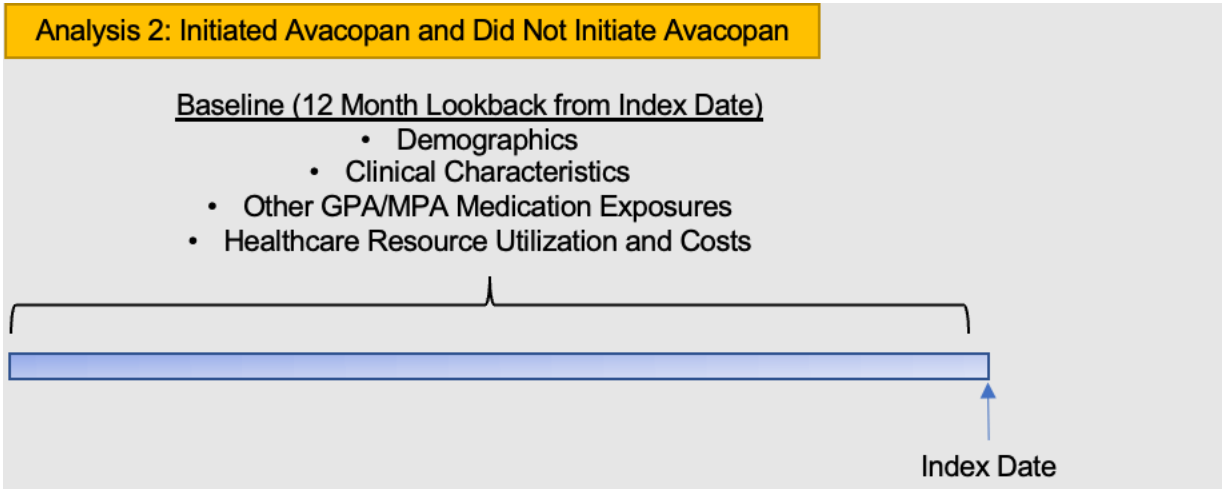
## Study Design Schema




| **Data sources** | **Index dates** |
|---|---|
| Mass General Brigham ANCA-associated vasculitis cohort (Analyses 1, 2, 3a/b, 4)<br><br>Northwestern University (Analyses 1, 2, 3a) | • Analysis 1: Date of avacopan prescription or date of non-avacopan, non-GC treatment prescription (i.e., immunosuppressive drugs specified in Appendix C)<br>• Analysis 2: Date of avacopan prescription (for both avacopan initiators and non-initiators)<br>• Analyses 3 & 4: Date of avacopan initiation |
| Additional details regarding inclusion/exclusion criteria, endpoints, and outcomes are described in Analysis-specific schema | |

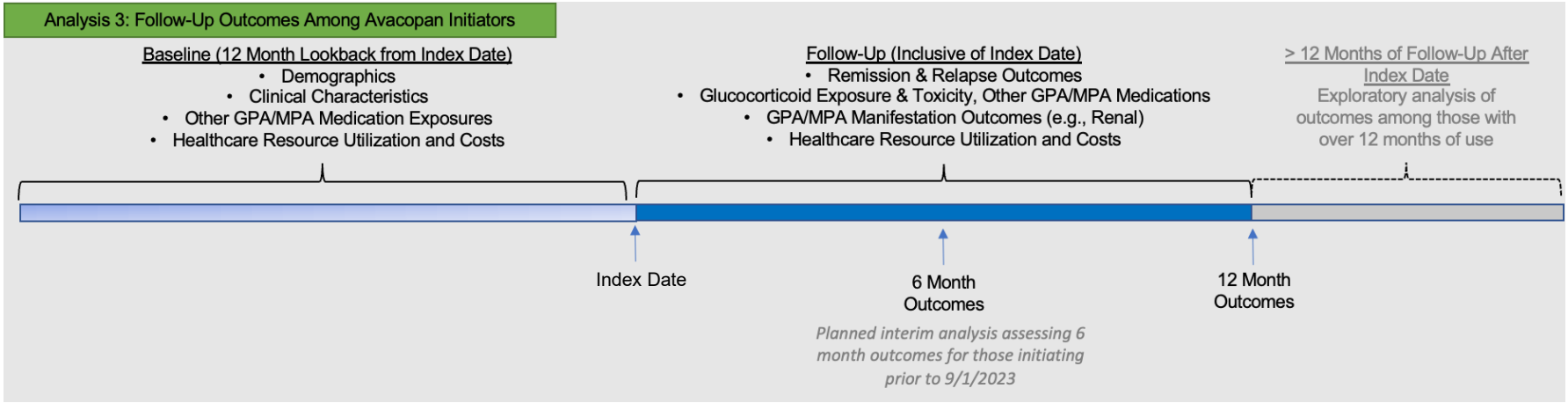



| **Index date**<br>Date of avacopan prescription or date of non-avacopan, non-glucocorticoid treatment prescription | |
|---|---|
| **Inclusion criteria**<br>• Diagnosed with new or relapsing GPA or MPA on or after first date of avacopan prescription at Mass General Brigham or Northwestern University<br>• At least 18 years old on index date<br>**Exclusion criteria**<br>• A diagnosis of EGPA.<br>• GPA/MPA attributed to cocaine/levamisole.<br>• No treatment of GPA/MPA during the baseline or follow-up periods (i.e., not treated for their GPA/MPA).<br>• Interstitial lung disease as the only manifestation of GPA/MPA | **Characteristics to be evaluated**<br>• Demographic features (e.g., age, sex, race/ethnicity)<br>• GPA/MPA features (e.g., BVAS v3, organ involvement, new or relapsing disease)<br>• Comorbidities at index date (e.g., hypertension, hyperlipidemia, Charlson Comorbidity Index)<br>• Healthcare resource utilization up to 12 months prior to index date |




**Index date**
Date of avacopan prescription (for both avacopan initiators and non-initiators)

| **Inclusion criteria** | **Characteristics to be evaluated** |
|---|---|
| • Diagnosed with new or relapsing GPA or MPA on or after November 17, 2021 (NU) or December 1, 2021 (MGB), representing the first date of avacopan use at each respective institution<br>• At least 18 years old on index date<br>• Prescribed avacopan<br>**Exclusion criteria**<br>• A diagnosis of EGPA.<br>• GPA/MPA attributed to cocaine/levamisole.<br>• No treatment of GPA/MPA during the baseline or follow-up periods (i.e., not treated for their GPA/MPA).<br>• Interstitial lung disease as the only manifestation of GPA/MPA | • Demographic features (e.g., age, sex, race/ethnicity)<br>• GPA/MPA features (e.g., BVAS v3, organ involvement, new or relapsing disease)<br>• Comorbidities at index date (e.g., hypertension, hyperlipidemia, Charlson Comorbidity Index)<br>• Healthcare resource utilization up to 12 months prior to index date<br>• Reason for not initiating avacopan |

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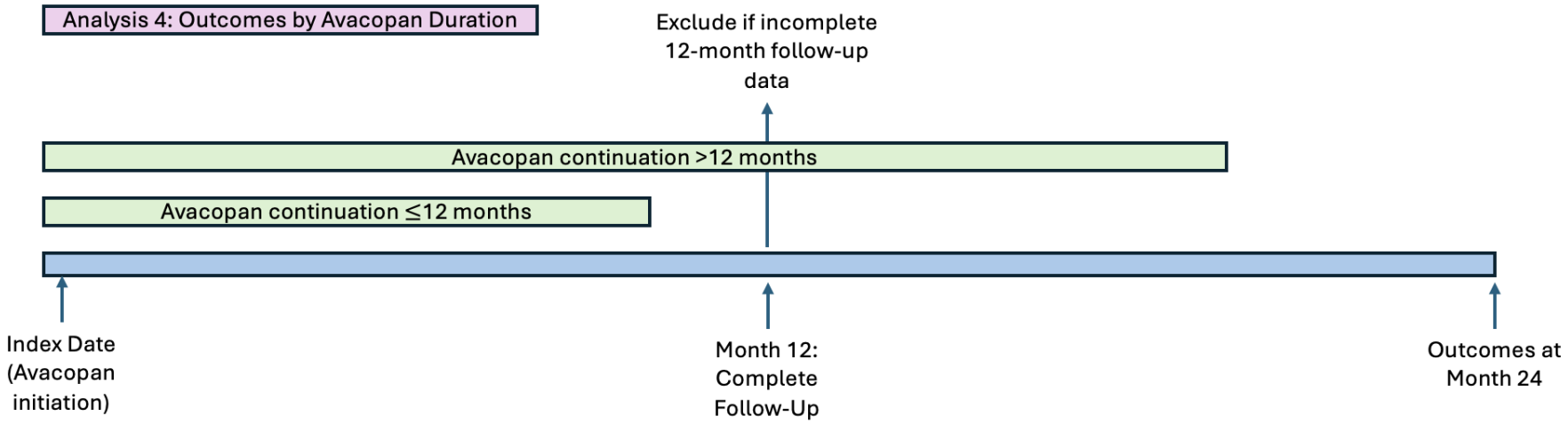
| **Index date**<br>Date of avacopan initiation | **Primary outcomes to be evaluated**<br>• 3a: Proportion achieving remission at month 6 (BVAS=0 at month 6 and no GC for treatment of GPA or MPA 1 month before Month 6)<br>• 3a: Proportion achieving sustained remission at Month 12, defined as remission at Month 6 and remission at Month 12, with no glucocorticoid treatment for GPA/MPA 1 month before Month 12, and no relapse between Months 6 and 12<br>• 3b: Proportion achieving sustained remission at Month 18, defined as BVAS=0 and no GCs in the 1 month prior to months 6, 12, and 18, and no relapse from months 6-18<br>• 3b: Proportion achieving sustained remission at Month 24, defined as BVAS=0 and no GCs in the 1 month prior to months 6, 12, 18, and 24 and no relapse from months 6-24 |
| **Inclusion criteria**<br>• Diagnosed with new or relapsing GPA or MPA on or after November 17, 2021 (NU) or December 1, 2021 (MGB), representing the first date of avacopan use at each respective institution<br>• At least 18 years old on index date<br>• Initiated avacopan | **Additional endpoints to be evaluated through months 12 & 24**<br>• GC exposure, GC toxicity<br>• Disease activity, renal outcomes, ANCA titer changes<br>• Change in comorbidities/biomarkers (e.g., BMI, lipids, A1c)<br>• Healthcare resource utilization (analysis from MGH only) (through month 12 only)<br>• Adverse events attributed to avacopan, infection, relapse, mortality |
| **Exclusion criteria**<br>• A diagnosis of EGPA.<br>• GPA/MPA attributed to cocaine/levamisole.<br>• No treatment of GPA/MPA during the baseline or follow-up periods (i.e., not treated for their GPA/MPA).<br>• Interstitial lung disease as the only manifestation of GPA/MPA | |




| | |
|---|---|
| **Index date**<br>Date of avacopan initiation<br>**Inclusion criteria**<br>• Diagnosed with new or relapsing GPA or MPA on or after November 17, 2021 (NU) or December 1, 2021 (MGB), representing the first date of avacopan use at each respective institution<br>• At least 18 years old on index date<br>• Initiated avacopan<br>• Have complete 12-month follow-up data<br>**Exclusion criteria**<br>• A diagnosis of EGPA.<br>• GPA/MPA attributed to cocaine/levamisole.<br>• No treatment of GPA/MPA during the baseline or follow-up periods (i.e., not treated for their GPA/MPA).<br>• Discontinued avacopan within ≤12 months due to an adverse event<br>• Interstitial lung disease as the only manifestation of GPA/MPA | **Primary outcomes to be evaluated**<br>• Differences in baseline and month 12 (following avacopan initiation) in characteristics between groups (avacopan continuation for ≤12 vs. >12 months), including AAV type, ANCA type, disease status, prescribing provider specialty, concomitant immunosuppression, kidney status (eGFR, dialysis status, UPCR), current and 12-month prior GC exposure<br>• Remission at Months 6, 12, 18, and 24<br>• Sustained remission at Months 12, 18, and 24<br>• Cumulative GC exposure<br>• Glucocorticoid Toxicity Index – Metabolic Domain (GTI-MD)<br>• Renal parameters (estimated glomerular filtration rate [eGFR], proteinuria, hematuria)<br>• Adverse Events |

## 1. Table of Contents

## List of Tables

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## List of Appendices

## 2. List of Abbreviations

ACR: American College of Rheumatology

AIS: Aggregate Improvement Score

ALT: Alanine aminotransferase

ANCA: Anti-neutrophil cytoplasmic antibody

AST: Aspartate aminotransferase

BMI: Body Mass Index

BVAS v3: Birmingham Vasculitis Activity Score version 3

BWH: Brigham and Women's Hospital

CHCC: Chapel Hill Consensus Classification

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

CPK: Creatinine phosphokinase

CT: Computed tomography

CWS: Cumulative Worsening Score

DBP: Diastolic blood pressure

DILI: Drug-induced liver injury

EDW: Electronic Data Warehouse

eGFR: Estimated glomerular filtration rate

ELISA: Enzyme linked immunosorbent assay

ER: Emergency room

EULAR: European Alliance of Associations for Rheumatology

GAD-7: General Anxiety Disorder-7

GC: Glucocorticoid

GPA: Granulomatosis with polyangiitis

GTI-MD: Glucocorticoid Toxicity Index – Metabolic Domain

HCRU: Healthcare Resource Utilization

HDL: High density lipoprotein

HPF: High powered field

ICD: International Statistical Classification of Disease and Related Health Problems

IQR: Interquartile range

LDL: Low density lipoprotein

MGB: Mass General Brigham

MGH: Massachusetts General Hospital

MPA: Microscopic polyangiitis

MPO: Myeloperoxidase

NDI: National Death Index

NU: Northwestern University

PPPM: per patient per month

PR3: Proteinase 3

Q1: Quartile 1

Q3: Quartile 3

RBC: Red blood cell

RPDR: Research Patient Data Registry

SBP: Systolic blood pressure

SD: Standard deviation

TC: Total cholesterol

USRDS: United States Renal Data System

## 3. Responsible Parties

- PPD Principal Investigator, Massachusetts General Hospital
- PPD Principal Investigator, Massachusetts General Hospital
- PPD, Center for Observational Research, Amgen Inc.
- PPD, Center for Observational Research, Amgen Inc.
- PPD, Medical Affairs, Amgen Inc.
- PPD, HEOR, Amgen Inc.

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## 4. Abstract

**Study Title**

Retrospective Cohort Study Evaluating Clinical Outcomes in Patients with Granulomatosis with Polyangiitis (GPA)/microscopic polyangiitis (MPA) Treated with Avacopan

**Study Background and Rationale**

- Avacopan (brand, Tavneos®) is a complement 5a receptor (C5aR) antagonist available as 10 mg oral capsules, with a recommended dosage of 30 mg twice daily with food. Avacopan was studied in a phase 3, active-controlled study (ADVOCATE), which evaluated the safety and efficacy of avacopan to induce and sustain remission without a prednisone taper in patients with newly diagnosed or relapsing anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (GPA or MPA). The two primary endpoints were clinical remission at Month 6, defined as achieving a Birmingham Vasculitis Activity Score version 3 (BVAS v3) of 0 and not taking glucocorticoids (GC) to treat GPA or MPA within 1 month before Month 6, and sustained remission, defined as remission at Months 6 and 12 (BVAS v3 of 0 and not taking GC to treat GPA or MPA within 1 month before Month 12), without relapse between Months 6 and 12.
- Based on evidence from this study that patients receiving avacopan had a significantly higher percentage (66%) of sustained remission of symptoms when compared to an active control group (55%). Avacopan was approved by the US Food and Drug Administration (FDA) in October of 2021 for the treatment of adult patients with severe active GPA or MPA as an add-on to standard therapy including GC. Since its approval, avacopan has been adopted by several international guidelines for the treatment of GPA or MPA as a part of strategies to reduce exposure to GC.
- This retrospective cohort study aims to describe the burden of GPA/MPA, patterns regarding avacopan utilization, and the healthcare utilization and clinical outcomes at 3, 6 and 12 months in avacopan users from the Mass General Brigham (MGB)

GPA/MPA and Northwestern University (NU) registries and at months 18 and 24 in users from MGB.

**Study Feasibility and Futility Considerations**

- There are 133 patients identified through January 2024 within the Mass General Brigham system who have been prescribed avacopan and 112 have initiated avacopan. Additionally, since December 1, 2021 (the date of avacopan availability at MGB), there were 60 patients diagnosed with GPA/MPA in the MGB system who were not prescribed avacopan. Among those who have initiated avacopan, there have been 23 relapses. GC exposure has varied but the majority of patients have discontinued GC within 2 months of avacopan initiation. There are only 2 patients in this cohort with missing status regarding avacopan initiation.
- Among 148 avacopan initiators from MGB and NU with 12-month follow-up data, 70 (47.3%) continued avacopan through at least month 12. Among 118 avacopan initiators from MGB with complete 12-month follow-up data, 48 (40.7%) were on avacopan at month 12. The MGB patients with data beyond 12 months will be included in the analysis of outcomes at 18 and 24 months.

**Research Question and Objective(s)**

This study aims to describe the demographic and disease-specific characteristics associated with avacopan prescription and initiation and the outcomes observed among patients who initiate avacopan in a real-world setting between November 17, 2021 and June 12, 2024 (collectively between MGB and NU). Our research questions, study objectives, and endpoints are as follows:

- What are the demographics and disease-specific features of patients who are and are not prescribed avacopan for GPA/MPA?
- What are the demographics and disease-specific features of patients who do and do not initiate avacopan after prescription?
- What are the outcomes, including disease-specific (e.g., disease activity, renal function) and treatment-specific (e.g., glucocorticoid toxicity, infection), among patients who initiate avacopan?
- What are the clinical outcomes (disease, treatment, and kidney-related) among those who receive shorter (≤ 12 months) and longer (>12 months) courses of avacopan therapy?

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| Primary objective 1: To describe the demographics and disease-specific features of patients who are and are not prescribed avacopan for GPA/MPA | Descriptive analysis of baseline demographic and clinical characteristics<br>• Demographic features (e.g., age, sex, race/ethnicity)<br>• GPA/MPA features (e.g., BVAS v3, organ involvement, new or relapsing disease)<br>• Comorbidities at index date (e.g., hypertension, hyperlipidemia, Charlson Comorbidity Index)<br>• Healthcare resource utilization up to 12 months prior to index date |
| Primary objective 2: Among people prescribed avacopan, to describe the demographics and disease-specific features of patients who do and those who do not initiate avacopan | |
| Primary objective 3: Among patients who use avacopan, to describe the outcomes, including disease- and treatment-specific outcomes | • Remission at Month 6<br>• Sustained remission at Month 12<br>• Cumulative GC exposure<br>• Median daily GC dose<br>• GC toxicity<br>• Glucocorticoid Toxicity Index – Metabolic Domain (GTI-MD)<br>• Change in A1c<br>• Change in BMI<br>• Change in lipids<br>• Renal parameters (estimated glomerular filtration rate [eGFR], proteinuria, hematuria)<br>• ANCA titers<br>• Pathology results<br>• Adverse Events |
| **Secondary** | |
| Secondary objective 1: To investigate baseline factors associated with GC discontinuation and relapse risk in patients who initiate avacopan | Descriptive analysis of baseline demographic and clinical characteristics<br>• Demographic features (e.g., age, sex, race/ethnicity)<br>• GPA/MPA features (e.g., BVAS v3, organ involvement, new or relapsing disease)<br>• Comorbidities at index date (e.g., hypertension, hyperlipidemia, Charlson Comorbidity Index)<br>• Healthcare resource utilization up to 12 months prior to index date |

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| Secondary objective 2: To evaluate the association of GC use patterns with relapse risk in patients who initiate avacopan | Relapse, defined as a return (after prior improvement) of vasculitis activity on the basis of at least one major BVAS/WG item, at least three minor BVAS v3 items, or one or two minor BVAS v3 items for at least two consecutive clinical visits (ADVOCATE definition). Relapses will be assessed after Month 1.<br>Patients who had an increase in the BVAS v3 of <3 and the absence of major BVAS/WG items define a minor relapse. All other patients are defined as a major relapse. (Miloslavsky et al. 2015)<br>We will describe general effectiveness (BVAS, remission, relapse), kidney outcomes, and GC toxicity between avacopan initiators who receive an initial GC regimen lasting <2 months vs. ≥2 months. Analyses will adjust for confounders. |
| Secondary objective 3: To report patient characteristics and outcomes in avacopan initiators by duration of avacopan use (by individuals who discontinue within 12 months versus individuals who continue avacopan for >12 months) (for patients treated at MGB) | • Remission at Months 6, 12, 18, and 24<br>• Sustained remission at Months 12, 18, and 24<br>• Cumulative GC exposure<br>• GTI-MD<br>• Renal parameters (estimated glomerular filtration rate [eGFR], proteinuria, hematuria)<br>• Adverse Events |
| **Exploratory** | |
| Exploratory objective 1: To examine baseline characteristics and outcomes stratified by presence or absence of severe active GPA/MPA disease status at baseline | GC exposure, GC toxicities, renal outcomes, remission at Month 6 and sustained remission at Months 12, 18, and 24 |
| Exploratory objective 2: To evaluate outcomes including disease- and treatment-specific outcomes as well as adverse effects of avacopan initiators through month 24 (for patients treated at MGB) | • Remission at Months 6, 12, 18, and 24<br>• Sustained remission at Months 12, 18, and 24<br>• Cumulative GC exposure<br>• GTI-MD<br>• Renal parameters (estimated glomerular filtration rate [eGFR], proteinuria, hematuria)<br>• Adverse Events |

**Hypothesis(es)/Estimation**
This study is primarily descriptive in nature. Hypothesis testing will be used to compare baseline characteristics but not outcomes.

**Study Design/Type**

This is a retrospective cohort study (chart review)

**Study Population or Data Resource**

This study will be conducted at Mass General Brigham, a large healthcare system in eastern Massachusetts and New Hampshire, United States. It includes 2 tertiary care hospitals (Massachusetts General Hospital and Brigham and Women's Hospital) and 12 community hospitals, along with all of the associated primary care and specialty outpatient clinics. Data will be collected from December 2020 (12 months prior to first avacopan prescription at MGB) through May 2026 (up to 24 months of follow-up for all eligible patients at MGB). Data will be collected from the MGB electronic data warehouse (EDW), research patient data registry (RPDR), and by manual chart review of the electronic health record. The study will also include Northwestern University as a second site.

**Summary of GPA/MPA Eligibility Criteria**

Data from the electronic health record will be used to determine diagnosis of GPA or MPA, and will be based on fulfillment of the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) Classification Criteria, or the Chapel Hill Consensus Criteria and/or clinician-documented diagnosis and management as GPA or MPA (see Appendices D and E and Pyo et al. 2023).

Analysis 1 (to address primary objective 1)

1. Diagnosed with new or relapsing GPA or MPA on or after November 17, 2021, the first date of avacopan use at Mass General Brigham or NU
2. At least 18 years old on index date
3. No diagnosis of EGPA
4. No GPA/MPA attributed to cocaine/levamisole
5. No absence of treatment of GPA/MPA during the baseline or follow-up periods (i.e., not treated for their GPA/MPA)
6. No interstitial lung disease as the only manifestation of GPA/MPA

Analysis 2 (to address primary objective 2)

1. Diagnosed with new or relapsing GPA or MPA on or after November 17, 2021, the first date of avacopan use at Mass General Brigham or NU
2. At least 18 years old on index date
3. Prescribed avacopan
4. No diagnosis of EGPA
5. No GPA/MPA attributed to cocaine/levamisole
6. No absence of treatment of GPA/MPA during the baseline or follow-up periods (i.e., not treated for their GPA/MPA)

7. No interstitial lung disease as the only manifestation of GPA/MPA

Analysis 3 (to address primary objective 3, secondary objectives 1 & 2, exploratory objectives 1 & 3 [3a] and exploratory objective 2 [3b])

1. Diagnosed with new or relapsing GPA or MPA on or after November 17, 2021, the first date of avacopan use at Mass General Brigham or NU
2. At least 18 years old on index date
3. Initiated avacopan
4. No diagnosis of EGPA
5. No GPA/MPA attributed to cocaine/levamisole
6. No absence of treatment of GPA/MPA during the baseline or follow-up periods (i.e., not treated for their GPA/MPA)
7. No interstitial lung disease as the only manifestation of GPA/MPA

Analyses 4 (MGB only; to address secondary objective 3)

1. Diagnosed with new or relapsing GPA or MPA on or after December 1, 2021, the first date of avacopan use at Mass General Brigham
2. At least 18 years old on index date
3. Initiated avacopan
4. Have complete 12-month follow-up data
5. Did not discontinue avacopan within ≤12 months due to an adverse event
6. No diagnosis of EGPA
7. No GPA/MPA attributed to cocaine/levamisole
8. No absence of treatment of GPA/MPA during the baseline or follow-up periods (i.e., not treated for their GPA/MPA)
9. No interstitial lung disease as the only manifestation of GPA/MPA

**Follow-up**

Analysis 1: Comparing baseline features among those prescribed and those not prescribed avacopan

Index Date

- Date of avacopan prescription or date of non-avacopan, non-glucocorticoid treatment prescription (Appendix C, immunosuppressive drugs)

Follow-Up Date

- There is no follow-up period, as this analysis is examining baseline factors

Analysis 2: Comparing baseline features among those initiating and those not initiating avacopan after prescription

Index Date

- Date of avacopan prescription (for both avacopan initiators and non-initiators)

Follow-Up Date

- There is no follow-up period, as this analysis is examining baseline factors

Analysis 3:

3a. Month 3, 6, and 12 outcomes among patients who initiate avacopan at MGB or NU

Index Date

- Date of avacopan initiation

3b. Month 18 and 24 outcomes among patients who initiate avacopan at MGB

Index Date

- Date of avacopan initiation

Analysis 4: 24-Month outcomes stratified by duration of avacopan continuation (≤ 12 vs. >12 months) among patients within MGB who initiate avacopan and are alive and not lost to follow-up by month 12

Index Date

- Date of avacopan initiation

**Follow-Up Dates (vary by analysis/outcome)**

Treatment Outcomes

- Date of avacopan discontinuation (for time from initiation to discontinuation)
- Date of glucocorticoid discontinuation and usage patterns, including dosage changes (for time from initiation to discontinuation)
- 6 months after avacopan initiation (for primary outcomes at Month 6)
- 12 months after avacopan initiation (for primary outcomes at Month 12)
- 18 months after avacopan initiation (for primary outcomes at Month 18)
- 24 months after avacopan initiation (for primary outcomes at Month 24)

Clinical Outcomes

- Date of relapse (any relapse and stratified by major or minor relapse; for time from initiation to relapse)
- Date of death (for time from initiation to death)
- Date of end of follow-up (for time from initiation to outcomes of interest)
- Date of loss to follow-up (for time from initiation to outcomes of interest)
- Date of adverse event or other event of interest in specific analyses (for time from initiation to adverse event)

**Variables**

The exposures of interest include:

- Analysis 1: Prescription and non-prescription of avacopan for newly diagnosed or relapsing GPA/MPA
- Analysis 2: Initiation and non-initiation of avacopan among those prescribed avacopan
- Analysis 3: Patients who initiate avacopan
- Analysis 4: ≤12 vs. >12 months of avacopan use among patients who initiate avacopan, have complete 12-month follow-up data, and who did not discontinue avacopan within 12 months due to an adverse event

The outcomes of interest include:

- Analysis 1: Comparing baseline features among those prescribed and those not prescribed avacopan
- Analysis 2: Comparing baseline features of patients initiating and not initiating avacopan among those prescribed avacopan.

- Features compared in Analysis 1 and 2, include: 1) Demographic features (e.g., age, sex, race/ethnicity); 2) GPA/MPA features (e.g., BVAS v3, organ involvement, new or relapsing disease); 3) comorbidities at index date (e.g., hypertension, hyperlipidemia, Charlson Comorbidity Index); 4) healthcare resource utilization up to 12 months prior to index date; 5) reason for not initiating (Analysis 2 only)

- Analysis 3: Outcomes among those who initiate avacopan, including:
  - 1) Glucocorticoid exposure; 2) remission at Months 6 and 12 (BVAS v3 = 0 and no GC use for GPA/MPA in the 1 month prior); 3) sustained remission at Months 12, 18, and 24; 4) glucocorticoid toxicity; 5) disease activity; 6) renal outcomes; 7) ANCA titer changes; 8) healthcare resource utilization; 9) adverse events attributed to avacopan; 10) infection; 11) relapse (defined as a return (after prior improvement) of vasculitis activity on the basis of at least one major BVAS/WG item, at least three minor BVAS v3 items, or one or two minor BVAS v3 items for at least two consecutive clinical visits); 12) mortality
- Analysis 4: Outcomes among those who initiate avacopan stratified by duration of avacopan use, including: 1) Glucocorticoid exposure; 2) remission at Months 18 and 24 (BVAS v3 = 0 and no GC use for GPA/MPA in the 1 month prior); 3) sustained remission at Month 18 and 24; 4) glucocorticoid toxicity as assessed by the Glucocorticoid Toxicity Index-Metabolic Domains; 5) disease activity; 6) renal outcomes; 7) ANCA titer changes; 8) adverse events attributed to avacopan; 9) infection; 10) relapse (defined as a return (after prior improvement) of vasculitis activity on the basis of at least one major BVAS/WG item, at least three minor BVAS v3 items, or one or two minor BVAS v3 items for at least two consecutive clinical visits) assessed between months 12-24; 11) mortality

Covariates include: 1) Demographic features (e.g., age, sex, race/ethnicity); 2) GPA/MPA features (e.g., BVAS v3, organ involvement, new or relapsing

disease); 3) comorbidities at index date (e.g., hypertension, hyperlipidemia, Charlson Comorbidity Index)

All exposures, outcomes, and covariates are routinely collected via clinically-collected data at Mass General Brigham and Northwestern University, as stored in the electronic health record and/or electronic data warehouse.

**Study Sample Size**

- There are 133 patients identified through January 2024 from within the Mass General Brigham system who have been prescribed avacopan and 112 have initiated avacopan. Additionally, since December 1, 2021, there are 60 patients diagnosed with GPA/MPA in the MGB system who were not prescribed avacopan. Among those who have initiated avacopan, there have been 23 relapses. GC exposure has varied but the majority of patients have discontinued GC s within 2 months of avacopan initiation. There are only 2 patients in this cohort with missing status regarding avacopan initiation.

**Data Analysis**

- The primary and secondary outcomes will be analyzed using a descriptive approach. Summary statistics for continuous variables, including the number of patients, mean, standard deviation (SD), median, Q1, Q3, minimum and maximum, will be calculated after excluding missing/unknown values. For categorical variables, the frequency and percentage will be provided, and a category of “missing/unknown” will be included. Cumulative incidence will be used to describe the occurrence of key outcomes, including GC toxicities, infections, and relapse. Given the variable follow-up time, healthcare resource utilization (HCRU) will be presented as per patient per month (PPPM) metrics. Time to event outcomes (e.g., time to discontinuation of GC) will be calculated using Kaplan-Meier analysis and median follow-up time (interquartile range [IQR]) will be reported.

- Among avacopan users, we will consider analyses evaluating time to events (e.g., glucocorticoid discontinuation, relapse) with adjustment for covariates. We will consider Cox proportional hazard regression models or other methods for time to event analyses and incorporate covariates, considering the number of observed outcomes. Restricted mean survival time will be used to describe time free from glucocorticoid exposure during follow-up.

- Among avacopan users, exploratory analysis of the association of initial glucocorticoid taper duration with the risk of outcomes including BVAS=0 at months 6 and 12 and relapse risk will be assessed using multivariable adjusted analyses. Cluster analysis will be used to explore patterns of glucocorticoid prescribing for patients using avacopan. Cox proportional hazards models will be used to evaluate factors associated with the risk of relapse and factors associated with glucocorticoid discontinuation.

## 5. Amendments and Updates

| Amendment or Update Number | Date | Section of Study Protocol | Amendment or Update | Reason |
|---|---|---|---|---|
| 1 | 18May2026 | Summary Table of Study Protocol; Study Design Schema; Sections 4, 6.2, 6.3, 7, 8.1, 8.2.1-8.2.3, 8.4, 8.5, 8.6, 8.7.1, 8.9, 9.1, 10 | Added Northwestern University as a second study site and updated the protocol for a 2-site study design. | Improve generalizability and sample size. |
| | | Summary Table of Study Protocol; Sections 7.2, 7.3, 8.7.2 | Refined objectives and analyses, including safety/effectiveness, 24-month outcomes, duration-of-use analyses, and stratified/exploratory analyses. | Align objectives and analyses with the amended study design and extended follow-up. |
| | | Study Design Schema; Sections 8.1, 8.2.1-8.2.6, 8.3.1, 8.3.2, 8.7.1, 8.7.2 | Updated eligibility criteria, index dates, follow-up periods, and analytic framework, including addition of Analysis 4. | Reflect the revised multicenter design and expanded 24-month analysis plan. |
| | | Sections 8.4, 8.6, 8.9.2, 8.9.4, 9.1 | Updated data sources, data handling, limitations, missing data considerations, and IRB language for inclusion of NU. | Support study conduct under the 2-site design. |
| | | Summary Table of Study Protocol; Sections 4, 7.3, 8.3.2, 8.7.2 | Removed selected patient-reported outcomes, including RAPID-3, mHAQ, PHQ-8, GAD-7, and PROMIS. | Patient-reported outcomes are available in the EHR for only a substantial minority of eligible individuals. |
| | | Sections 4, 6.2, 7.3, 8.3.2, 8.7.2 | Removed healthcare cost analyses while | Healthcare resource utilization collected to date will be |

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| | retaining healthcare resource utilization analyses. | incorporated, but costing is outside the scope of this project. |
| Sections 4, 8.3.2, 8.7.2, 8.9.4 | Removed collection of non-metabolic glucocorticoid toxicities and focused glucocorticoid toxicity assessment on metabolic outcomes and GTI-MD. | Focus on metabolic glucocorticoid toxicity and limited ability to retrospectively ascertain non-metabolic toxicities by chart review alone. |
| Sections 4, 6.4, 8.7.2 | Clarified that the study remains primarily descriptive, while selected secondary/exploratory analyses may use hypothesis testing or model-based estimation where appropriate. | Clarify interpretation of statistical analyses given sample size, observational design, and descriptive objectives. |
| Study Design Schema; Sections 4, 8.2.1, 8.3.2, 8.7.1 | Extended follow-up for MGB avacopan initiators to include Months 18 and 24 and updated relevant endpoints accordingly. | Enable assessment of longer-term outcomes among patients with available follow-up. |
| Throughout | Administrative changes. | Corrected typographical errors, punctuation, grammar, abbreviations, terminology, and formatting. |

# 6. Rationale and Background

## 6.1 Diseases and Therapeutic Area

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a heterogeneous group of rare, severe, and systemic autoimmune conditions characterized by necrotizing inflammation of small sized to medium-sized blood vessels (Al-Hussain et al. 2017). The most common clinical syndromes included in this group are granulomatosis with polyangiitis (GPA; formerly Wegener granulomatosis) and microscopic polyangiitis (MPA) (Qasim and Patel 2022). In patients with AAV, two types of ANCA, defined by their autoantigen target, are detected in the majority: leukocyte proteinase 3 (PR3) and myeloperoxidase (MPO) (Cornec et al. 2016). Those with GPA are predominantly PR3-ANCA-positive. GPA is characterized by involvement of the upper and lower respiratory tracts and kidney. In contrast, those with MPA are nearly

always MPO-ANCA positive. MPA is characterized by a lack of granulomatous formation and almost ubiquitous kidney involvement (Cornec et al. 2016; Qasim and Patel 2022). The diagnosis of AAV is established by a combination of history, physical exam, laboratory testing, and, frequently, pathologic correlation (Qasim and Patel 2022).

A 20-year population-based study conducted in Rochester, Minnesota from 1996 through 2015 estimated the annual incidence rate for GPA as 1.3 (95% CI: 0.8-1.8) per 100,000 individuals, for MPA as 1.6 (95%CI: 1.0–2.2) per 100,000 individuals (Berti et al. 2017). The same study estimated prevalence proportions of 21.8 (95%CI: 12.9–30.8) per 100,000 individuals for GPA, 18.4 (95%CI: 10.1–26.7) per 100,000 for MPA.

A study by Wallace et al. using an electronic health record (EHR)-enabled registry, maintained by the American College of Rheumatology (ACR), captured 1,462 US patients seen between 2015 and 2017 at 126 practice sites and 398 unique providers (Wallace et al. 2021). This study reported a mean age of 59.8 years, 59% female, 56% white, with GPA as the most common syndrome (75% GPA; 16% MPA, 10% EGPA).

There is no cure for GPA/MPA. Treatment guidelines, including those released by the ACR in July of 2021, have traditionally recommended daily GC and other immunosuppressive medications as part of a strategy to induce remission (Chung et al. 2021). The Wallace study reported GC use for management in 86% of patients between 2015-2017 and use of the steroid-sparing agents rituximab, methotrexate, and mycophenolate mofetil observed in 45%, 33%, and 18% of patients, respectively (Wallace et al. 2021). While induction therapy with immunosuppressive therapies (with or without GCs), followed by maintenance treatment has been demonstrated to reduce GPA/MPA-related mortality, there remains a need for treatment strategies that could avoid or reduce GC toxicity, treat refractory GPA/MPA, and improve long-term outcomes (Gabilan et al. 2022).

Patients with GPA/MPA experience a high burden of damage as a result of the disease and its treatment (Robson et al. 2015). This is also observed in the burden of multimorbidity that has been reported in patients with GPA/MPA. Common comorbidities in patients with GPA/MPA include infection, chronic kidney disease, chronic lung disease, chronic pain (e.g., neuropathy), and neurologic deficits (e.g., foot drop). Leading causes of death in GPA/MPA include infections and cardiovascular events which are driven by multiple factors (Wallace et al. 2020), including glucocorticoid exposure, chronic immunosuppression, and chronic inflammatory states.

Rituximab is typically used to maintain remission in GPA/MPA and has been found to be superior to azathioprine, including among patients with a history of relapse (Guillevin et al. 2014; Smith et al. 2023). However, long-term use of B cell depletion can have substantial consequences, including blunted responses to vaccines, severe infection (e.g., COVID-19), and atypical chronic lung infections.

Disease activity in GPA/MPA can be measured using the Birmingham Vasculitis Activity Score version 3 (BVAS v3). The BVAS v3 is a well-accepted instrument completed by clinicians and investigators based on symptoms, exam findings, laboratory result, as well as pathology and imaging findings (Mukhtyar et al. 2009). This provides a systematic approach for quantifying disease activity due to GPA/MPA at a given time point. The BVAS/WG is an adapted version of the BVAS v3 instrument designed specifically for patients with GPA/MPA. In both the BVAS v3 and BVAS/WG, major items of disease activity are distinguished from minor items. Items in both instruments are weighted and a total score is calculated.

Avacopan (brand, TAVNEOS®) is a complement 5a receptor (C5aR) antagonist available as 10 mg oral capsules, with a recommended dosage of 30 mg twice daily with food. Based on evidence from the ADVOCATE Phase 3 trial that patients receiving avacopan had a significantly higher percentage (66%) of sustained remission of symptoms when compared to an active control group (55%), avacopan was approved by the US Food and Drug Administration (FDA) in October of 2021 for the treatment of adult patients with severe active GPA or MPA as an add-on to standard therapy including GC.

There are limited data describing the real-world experience using avacopan for the treatment of GPA or MPA. Two large real-world studies presented at the 2023 ACR Convergence meeting reported some of the early experience. In one study that included 56 patients initiating avacopan in an academic healthcare system, the median time to discontinuing steroid was approximately 56 days and avacopan was discontinued by 34% of patients for varied reasons, including completion of the intended course or adverse events (Srivatsan et al. 2023). 18% of patients experienced any disease flare, defined as an increase in disease activity requiring treatment. The second analysis included 80 patients who initiated avacopan from multiple academic medical centers (Sattui et al. 2023). By week 26, 92% of patients had discontinued GCs. Avacopan was discontinued in 31% of patients for either completion of treatment or adverse events. Disease relapse, using a different definition than the prior study, was observed in 6% of patients.

### 6.2 Rationale

Since its approval, avacopan has been recommended by several international guidelines for the treatment of GPA and MPA as a part of strategies to reduce exposure to GC (Hellmich et al. 2023; Turgeon et al. 2023). Currently, there are no published real-world data describing patient characteristics and treatment patterns among those using avacopan in the real-world setting or describing the real-world effectiveness of avacopan. This study aims to (1) describe the early users of avacopan including patient demographics and clinical characteristics, medication use, comorbidities, treatment patterns, and to (2) assess clinical outcomes and the associated healthcare resource utilization (HCRU) subsequent to avacopan initiation.

### 6.3 Feasibility and Futility Considerations

There are 133 patients identified through January 2024 from within the Mass General Brigham system who have been prescribed avacopan and 112 have initiated avacopan. Additionally, since December 1, 2021, there are 60 patients diagnosed with GPA/MPA in the MGB system who were not prescribed avacopan. Among those who have initiated avacopan, there have been 23 relapses. Glucocorticoid exposure has varied but the majority of patients have discontinued GC within 2 months of avacopan initiation. There are only 2 patients in this cohort with missing status regarding avacopan initiation.

### 6.4 Statistical Inference (Estimation or Hypothesis[es])

This study is primarily descriptive in nature. Descriptive statistics will be used to summarize baseline characteristics, treatment patterns, and clinical outcomes among the study populations defined for each analysis. Hypothesis testing may be used to compare baseline characteristics between relevant exposure groups, including avacopan users and non-users, avacopan initiators and non-initiators, and groups defined by duration of avacopan or glucocorticoid use, as applicable.

For selected secondary and exploratory outcome analyses, hypothesis testing and/or model-based estimation may be conducted to evaluate associations between exposures or patient characteristics and outcomes of interest, including GC discontinuation, relapse, remission, sustained remission, glucocorticoid exposure or toxicity, renal outcomes, and adverse events. These analyses may include regression-based or time-to-event methods, as appropriate based on the outcome type, follow-up time, and available sample size. Any p-values will be interpreted cautiously and in the context of the descriptive objectives, sample size, potential confounding, and the observational

nature of the study. The study is not designed or powered to formally test confirmatory hypotheses regarding comparative effectiveness or safety outcomes.

## 7. Research Question and Objectives

The current study aims to describe early avacopan users and non-users including patient characteristics, other GPA/MPA-related medication use, and patterns of use among those who do and do not initiate avacopan. Among patients who initiate avacopan, we will also assess renal and extrarenal outcomes due to the disease and its treatment (e.g., glucocorticoid toxicity, infection), avacopan treatment patterns, other GPA/MPA-related medication use, and economic outcomes in two US-based cohorts of patients with GPA/MPA from two separate integrated healthcare systems. Certain analyses will only be conducted at one of the two healthcare systems and outlined where applicable.

### 7.1 Primary Objectives

a. To describe the demographics and disease-specific features of patients who are and are not prescribed avacopan for GPA/MPA.

b. Among people prescribed avacopan, to describe the demographics and disease-specific features of patients who do and those who do not initiate avacopan.

c. To describe the outcomes, including disease- and treatment-specific outcomes, of patients who use avacopan.

### 7.2 Secondary Objectives

a. To investigate baseline factors associated with glucocorticoid discontinuation and relapse risk in patients who initiate avacopan.

b. To evaluate the association of glucocorticoid use patterns with relapse risk and general clinical effectiveness and safety outcomes in patients who initiate avacopan.

c. To report outcomes in avacopan initiators by duration of avacopan use, comparing 12 versus greater than 12 months of use.

### 7.3 Exploratory Objectives

a. To examine baseline characteristics and outcomes stratified by presence or absence of severe active GPA/MPA disease status at baseline.

b. To evaluate outcomes, including disease- and treatment-specific outcomes as well as adverse effects of avacopan initiators through Month 24 for patients treated at MGB.

c. To evaluate healthcare resource utilization during follow-up in patients who initiate avacopan.

## 8. Research Methods

This is a retrospective cohort study conducted using electronic health records, including structured data, unstructured data, and manual chart review.

### 8.1 Study Design

This is a retrospective cohort study to examine the patterns of use of avacopan and outcomes among patients with GPA/MPA who do and do not use avacopan. These patients will be assessed in two ways: 1) Prescribed and not prescribed avacopan; 2) Initiators and non-initiators of avacopan after prescription. Depending on the analysis, the primary outcomes of interest include: 1) the prescription/non-prescription of avacopan; 2) initiation/non-initiation of avacopan; and 3) disease- and treatment-specific outcomes following avacopan initiation for GPA/MPA. Corresponding covariates of interest will vary according to the analysis but will include demographic- and disease-specific features. This study is meant to generate real-world evidence regarding the use of avacopan, for which this design is appropriate.

### 8.2 Setting and Study Population

#### 8.2.1 Study Period

Data will be collected up to 12 months prior to date of GPA/MPA treatment initiation and patients will be followed for up to 12 months from the date of GPA/MPA treatment initiation (at NU) and 24 months (at MGB).

#### 8.2.2 Selection and Number of Sites

The study will be conducted at MGB and NU.

#### 8.2.3 Subject/Patient/Healthcare Professional Eligibility

##### 8.2.3.1 Inclusion Criteria

Data from the electronic health record will be used to determine diagnosis of GPA or MPA, and will be based on fulfillment of the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) Classification Criteria, or the Chapel Hill Consensus Criteria and/or clinician-documented diagnosis and management as GPA or MPA (see Appendices D and E and Pyo et al. 2023).

Patients will be included if they meet all of the following criteria:

**Analysis 1**

1. Diagnosed with new or relapsing GPA or MPA on or after November 17, 2021, the first date of avacopan use at either NU or Mass General Brigham
2. At least 18 years old on index date

**Analysis 2**

1. Diagnosed with new or relapsing GPA or MPA on or after November 17, 2021, the earliest date of avacopan use at either NU or MGB
2. At least 18 years old on index date
3. Prescribed avacopan

**Analysis 3**

1. Diagnosed with new or relapsing GPA or MPA on or after November 17, 2021, the first date of avacopan use at either NU or MGB
2. At least 18 years old on index date
3. Initiated avacopan

**Analysis 4**

1. Diagnosed with new or relapsing GPA or MPA on or after December 1, 2021, the first date of avacopan use at Mass General Brigham
2. Initiated avacopan and have complete 24-month follow-up data available, regardless of duration of avacopan use
3. Did not discontinue avacopan within 12 months due to an adverse event

#### 8.2.3.2 Exclusion Criteria

Patients will be excluded if they meet any of the following criteria:

1. A diagnosis of EGPA.
2. GPA/MPA attributed to cocaine/levamisole.
3. No treatment of GPA/MPA during the baseline or follow-up periods (i.e., not treated for their GPA/MPA with avacopan or the medications in Appendix C).

4. Interstitial lung disease as the only manifestation of GPA/MPA given that many may not meet classification criteria for GPA/MPA and given that lung disease is often primarily fibrotic and less likely to be responsive to therapy

#### 8.2.4 Matching

Not applicable

#### 8.2.5 Baseline Period

Up to 12 months prior to date of avacopan prescription or corresponding initiation of GPA/MPA-specific treatment for patients not prescribed avacopan (i.e., the medications in Appendix C).

#### 8.2.6 Index Date

Patients prescribed avacopan will be indexed based on their first avacopan prescription. Patients not prescribed avacopan will be indexed based on their RTX/CYC.

#### 8.2.7 Study Follow-up

Among patients who initiate avacopan, follow-up will begin from date of treatment initiation until the soonest of: outcome of interest, death, or loss to follow-up.

### 8.3 Variables

#### 8.3.1 Exposure Assessment

People are followed from the date of treatment initiation until an outcome of interest. Dispensing is tracked by the MGB specialty pharmacy, and initiation is well-documented in patients' charts. There are some potential scenarios in which a patient's exposure status may change or recur (e.g., due to discontinuation and/or relapse):

1. Avacopan → avacopan at least 12 months after index date: A patient can experience a relapse after discontinuing avacopan (based on patient's chart) and at least 12 months after their index date (initial avacopan initiation). In this case, the person would be considered as a new exposure. The number of people with > 1 exposure would be reported and these cases will also be analyzed and reported separately in addition to being aggregated with the overall group of avacopan initiators.
2. Avacopan → avacopan within 12 months of index date. A patient can experience a relapse after discontinuing avacopan within 12 months of their index date (initial avacopan initiation). In this case, the person would be considered as a new exposure. The number of people with > 1 exposure would be reported and these cases will also be analyzed and reported separately in addition to being

aggregated with the overall group of avacopan initiators. They would continue to contribute exposure time for their initial exposure up through 12 months of follow-up (intention-to-treat approach). They will also be analyzed using a per-protocol approach beginning with their updated index date (second initiation of avacopan) and their time in the original exposure arm could be censored once avacopan is initiated for their relapse.

3. Avacopan → non-avacopan within 12 months of index date. A patient can experience a relapse after prior treatment with avacopan within 12 months of their index date and initiate a non-avacopan regimen after relapse. This person would only be analyzed in their initial exposure group and captured as a relapse. Patients who relapse while on avacopan will be analyzed and reported as such.
4. Avacopan → non-avacopan at least 12 months after index date. This person would be someone who initiated avacopan and completed 12 months of follow-up. After Month 12, they experience a relapse and initiate a non-avacopan-based regimen. Data will be collected through month 24 among MGB patients who initiated avacopan and have complete 12-month follow-up regardless of duration of avacopan continuation

### 8.3.2 Outcome Assessment

| Outcome | Definition |
|---|---|
| Remission at month 6 (similar to ADVOCATE definition) | BVAS v3 = 0 *and* no receipt of GC for the treatment of GPA or MPA during the 1 month before Month 6 |
| Remission at month 6 on low-dose GCs | BVAS v3 = 0 *permitting* use of GC with a prednisone-equivalent daily dose ≤5mg for the treatment of GPA or MPA during the 1 month before Month 6 |
| Sustained remission at month 12 (similar to ADVOCATE definition) | Remission at Month 6 and remission at Month 12 (BVAS v3 of 0 and no receipt of GC for treatment of GPA/MPA within 1 month of Month 12) and no relapse between Months 6 and 12. |
| Sustained remission at month 12 on low-dose GCs | Remission on low-dose GCs at Month 6 and remission on low-dose GCs at Month 12 (BVAS v3 of 0 and a prednisone-equivalent daily dose ≤5mg for treatment of GPA/MPA within 1 month of Month 12) and no relapse between Months 6 and 12. |
| Sustained remission at month 18 (similar to ADVOCATE definition) | Remission at Months 6, 12, and 18 (BVAS v3 of 0 and no receipt of GC for treatment of |

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| | ANCA-associated vasculitis within 1 month of Month 18) and no relapse between Months 6 and 18. |
| Sustained remission at month 24 (similar to ADVOCATE definition) | Remission at Months 6, 12, 18, and 24 (BVAS v3 of 0 and no receipt of GC for treatment of ANCA-associated vasculitis within 1 month of Month 12) and no relapse between Months 6 and 24. |
| GC discontinuation | Date of last GC dose for the treatment of GPA/MPA. |
| Modified glucocorticoid discontinuation | Patients on long-term glucocorticoid therapy for adrenal insufficiency prior to avacopan initiation will fulfill the definition of glucocorticoid discontinuation on the date they return to their prior baseline glucocorticoid dose if ≤ 7.5mg/day |
| Cumulative GC exposure | Measured in prednisone equivalent doses received up to the time point of interest based on clinical documentation and GC prescriptions.<br>Exposure occurring prior to avacopan initiation or other treatment will be tallied and reported in combination with exposure after avacopan or other treatment initiation and separately.<br>Exposure prior to the index date will be tallied and reported separately for two time periods: exposure in the 3 months prior to index date, and exposure in the 12 months prior to index date.<br>GC administered as pre-treatment for rituximab will be included in the cumulative dosage. |
| Median daily GC dose | Measured in prednisone equivalent doses received up to the time point of interest based on clinical documentation and GC prescriptions |
| Relapse (BVAS-based definition) | Defined as a return (after prior improvement) of vasculitis activity on the basis of at least one major BVAS/WG item, at least three minor BVAS v3 items, or one or two minor BVAS v3 items for at least two consecutive clinical visits (similar to ADVOCATE definition). Relapses will be assessed after Month 1.<br>Patients who had an increase in the BVAS v3 of <3 and the absence of major BVAS/WG items define a minor relapse. |

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| | All other patients are defined as a major relapse. (Miloslavsky et al. 2015) |
| Alternative (treatment-based) relapse definition | Defined as a return of vasculitis (after prior improvement) activity per clinician documentation warranting an increase in GC or other change in immunosuppression. |
| GPA/MPA-specific disease activity | Measured using BVAS v3 |
| Infection | Defined as any infection documented in the electronic health record regardless of treatment. |
| Severe infection | Defined as any infection documented in the electronic health record leading to inpatient hospitalization or requiring at least one dose of intravenous antibiotic or other antimicrobial. |
| GG toxicity | • Change in A1c from baseline to end of study<br>• Change in lipids (TC, LDL, HDL, Triglyceride) from baseline to end of study<br>• Change in BMI from baseline to end of study<br>• Incident diabetes attributable to glucocorticoid use<br>  ○ New diagnosis of diabetes based on A1c ≥ 6.5% or other clinical test<br>• Worsened diabetes attributable to GC use (defined by at least one of the following)<br>  ○ Increased A1c<br>  ○ Newly initiating or higher dose of diabetes treatment (including oral drugs or injectables)<br>• Incident hypertension attributable to GC use (defined by at least one of the following)<br>  ○ SBP ≥ 130 or DBP ≥ 80 on two occasions<br>  ○ Newly initiating medication to treat hypertension<br>• Worsened hypertension in someone with a prior diagnosis of hypertension; attributable to GC use (defined by at least one of the following)<br>  ○ Newly initiating or higher dose of medication to treat hypertension |

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| | • Incident dyslipidemia attributable to GC use (defined by at least one of the following)<br>  ○ Newly initiating medication to treat dyslipidemia<br>• Worsened dyslipidemia in someone with a prior diagnosis of dyslipidemia; attributable to GC use (defined by at least one of the following)<br>  ○ Newly initiating or higher dose of medication to treat dyslipidemia |
| GTI-MD | Change in GTI-MD AIS and GTI-MD CWS scores from baseline calculated using the GTI algorithm using change in lipids, BMI, hemoglobin A1c, and blood pressure at months 3, 6, 12, 18, and 24 |
| Change in A1c | Measured clinically and extracted from the data warehouse or electronic health record. We will collect A1c test results available during the study period. A1c will be reported at 3, 6, 12, 18, and 24 months (as available) of follow-up. Change in A1c will be reported using all available results and reported as % change from baseline. |
| Change in BMI | Measured clinically and extracted from the data warehouse or electronic health record. We will collect all BMI results available during the study period. BMI will be reported at 3, 6, 12, 18, and 24 months (as available) of follow-up. Change in BMI will be reported using all available results and reported as % change from baseline. We will use the height documented closest to the time point of interest for calculating BMI if both weight and height are not available on the same date. BMI is calculated as kg/m2. |
| Change in lipids | Measured clinically and extracted from the data warehouse or electronic health record. Specifically, we will collect total cholesterol, high density lipoprotein, low density lipoprotein, and triglyceride results. We will collect all lipid results available during the study period. Lipids will be reported at 3, 6, 12, 18, and 24 months (as available) of follow-up. Change in lipids will be reported using all available results and reported as % change from baseline. |

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| Renal function | Renal function will be assessed by eGFR (mL/min/1.73m$^2$). We will use eGFR based on creatinine (not cystatin c). eGFR will be calculated without race adjustment using the 2021 CKD-EPI formula. Creatinine/eGFR is measured clinically and extracted from the data warehouse or electronic health record. We will report the absolute and percent change in eGFR as well as the proportion on baseline dialysis who are dialysis-free at relevant timepoints, as well as eGFR < 20 to eGFR ≥30 |
| Proteinuria | Proteinuria will be assessed using spot protein to creatinine ratios. We will collect all proteinuria results available during the study period. Proteinuria (yes/no and degree) will be reported at 3, 6, 12, 18, and 24 months (as available) of follow-up. Change in proteinuria will be reported using all available results and the proportion achieving no proteinuria and/or < 500mg/24 hours will be reported. |
| Hematuria | Hematuria will be assessed by urinalysis. Using urinalysis results measured clinically and extracted from the data warehouse or electronic health record, we will classify hematuria by RBC/hpf as present or absent. |
| ANCA | PR3- and MPO-ANCA will be measured clinically and extracted from the electronic data warehouse or electronic health record. ELISA results will be extracted. We will extract the value of the titer and whether the titer is positive or negative according to the associated reference ranges. We will collect all ANCA ELISA results available during the study period. ANCA results will be reported at 3, 6, 12, 18, and 24 months (as available) of follow-up. We will report the number of people classified as positive and negative at each time point. |
| Pathology results | Results of pathology collected as part of the diagnostic evaluation for GPA/MPA, including renal, pulmonary, sinonasal, skin, or other biopsies through month 12. Reports will be summarized as: 1) diagnostic of ANCA-associated vasculitis; 2) supportive of a diagnosis of ANCA-associated vasculitis; or 3) inconclusive or not diagnostics of ANCA-associated |

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| | vasculitis. Renal biopsy will be reported as focal, crescentic, mixed, and sclerotic, normal, or other. |
| Outpatient visits | Defined as an outpatient visit when professional service was billed for consultation, new, or established care. Visits will be characterized as related to or not related to GPA/MPA based on the use of an ICD-10 billing code associated with vasculitis in a primary or secondary position through month 12. |
| Hospitalization | Defined as admission to an acute-care hospital for an acute condition. Overnight stays for observation as part of an emergency room visit will not be counted. Overnight stays for observation after procedure will not be counted. The number of hospitalizations per person will be tallied and reported as median among those with ≥ 1 hospitalization and median among the entire cohort. Length of hospitalization will be measured as days of hospitalization inclusive of date of admission and discharge. The chief reason for hospitalization will be extracted from the discharge note through month 12. |
| Emergency room (ER) visit | Defined as a visit to an urgent care or emergency room for an acute condition. ER visits that result in an admission will be included in this count through month 12. The chief reason for ER visit will be extracted from the discharge note. |
| Surgeries, procedures, and biopsies | Defined as MPA/GPA- or complication-related surgery, procedure, or biopsy through month 12. Examples would include surgery for sinonasal disease, surgery for lung biopsy, CT-guided lung biopsy, transbronchial lung biopsy, etc. Each dialysis session would not be counted as a procedure. |
| Adverse events | Defined as hepatic events and drug-induced liver injury (DILI), based on reported treatment-emergent adverse events, serious adverse events, treatment-emergent adverse events leading to withdrawal, and measured liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin). Further descriptive analysis of hepatic |

| | |
|---|---|
| | events will include severity, time to onset, resolution or outcome, discontinuation of avacopan, concomitant medications (e.g., immunosuppression, TMP-SMX) and characteristics of individuals experiencing these events.<br>Defined as infections (including fatal infections, serious infections, life-threatening infections, serious opportunistic infections, and hepatitis B reactivation), based on reported treatment emergent adverse events<br>Defined as drug rash based on clinical assessment and/or biopsy findings (if done)<br>Defined as serious hypersensitivity reactions, including angioedema and anaphylaxis, based on reported adverse events and serious adverse events<br>Defined as creatinine phosphokinase (CPK) increases, based on reported treatment-emergent adverse events and measured CPK levels<br>Defined as major cardiovascular events (non-fatal or fatal myocardial infarction or stroke, percutaneous coronary intervention, unstable angina)<br>Defined as general safety topics including malignancy |
| Cause of death | Cause of death will be extracted from death certificate data as the underlying cause of death. If death certificate data are unavailable then the electronic health record will be reviewed and a physician will assign an underlying cause of death. The immediate event leading to cause of death will also be extracted. |
| Maintenance of remission treatment | Treatment used to maintain remission at least 4 months after remission induction (with respect to the earliest start of GC to treat recently newly diagnosed or relapsed GPA/MPA). This can include a maintenance dose of rituximab, azathioprine, methotrexate, mycophenolate mofetil, or other. |

### 8.3.3 Covariate Assessment

| **Covariate** | **Definition** |
|---|---|
| Age | Age (years) at index date |

| | |
|---|---|
| Sex | Male/Female |
| Race | As documented in registration at Mass General Brigham (White, Asian, Black, Hawaiian/Pacific Islander, Native American/Alaskan Native, Unknown, Multiple/Other) |
| Ethnicity | As documented in registration at Mass General Brigham (Hispanic/Latinx or non-Hispanic/Latinx) |
| Insurance | Insurance provider at index date. |
| Median income | Based on Zip-code level census data |
| Treatment delay | Among those with newly diagnosed disease during the study period, the duration of time (days) between first sign/symptom and index date (Analyses 1 and 2). |
| Year of diagnosis | Year of GPA/MPA diagnosis |
| Year of index date | Index date as defined above based on avacopan prescription or initiation |
| Provider type prescribing avacopan | Rheumatology, nephrology, pulmonology, other, multiple |
| Location of treatment initiation (avacopan or non-avacopan) | Inpatient or outpatient |
| GPA/MPA disease status | New diagnosis or relapsing |
| ANCA type | PR3-ANCA+, MPO-ANCA+, dual positive (MPO and PR3), ANCA negative |
| AAV type | GPA, MPA, or undefined GPA/MPA |
| Other immunosuppression/treatment used for remission induction | Rituximab, cyclophosphamide, methotrexate, mycophenolate mofetil, azathioprine, plasma exchange, other |
| Delay in avacopan initiation | Time from avacopan prescription to use of first dose. |
| GC use prior to avacopan initiation | Measured in prednisone equivalent doses received up to the time point of interest based on clinical documentation and GC prescriptions.<br>Exposure occurring prior to avacopan initiation for treatment of the disease activity being treated with avacopan or other therapy will be tallied and reported.<br>Exposure prior to the index date will be tallied and reported separately for two time periods: exposure the 3 months prior to index date, and exposure in the 12 months prior to index date |

| | |
|---|---|
| Disease activity | BVAS v3 |
| Charlson Comorbidity Index | Total score and individual components will be reported. |

#### 8.3.4 Validity and Reliability

Data will be abstracted from electronic health records, which is considered a valid and reliable source of patient health data. BVAS v3 is a validated measure of disease activity in vasculitis (Mukhtyar et al. 2009).

### 8.4 Data Sources

Data sources at MGB will include:

1. Electronic data warehouse/research patient data registry: Collects all clinical data in a centralized data warehouse.
2. Electronic health record: To be reviewed manually by research staff. This includes a section in which outside records can be accessed (Care Everywhere) as well as a collection of outside records that are scanned in for review.
3. Mortality data are collected through chart review as well as probabilistic linkage to the National Death Index as data becomes available (usual delay of ~1-2 years). Mortality data are also collected through a linkage to the Social Security Master Death File.
4. Data on end-stage renal disease are collected through chart review as well as linkage to the United States Renal Data Set, maintained by the National Institutes of Health (NIH). Data are periodically linked as they become available (usual delay of ~1-2 years).

Data sources at NU will include:

1. Electronic data warehouse: Pulls clinical data from the EHR to a centralized data warehouse.
2. Electronic health record: To be reviewed manually by research staff. This includes a section in which outside records can be accessed (Care Everywhere) as well as a collection of outside records that are scanned in for review.

**Research Patient Data Registry (RPDR) and Electronic Data Warehouse (EDW):**

The EDW is the back-end of RPDR. All data from EDW are compiled in RPDR with some exceptions. For that reason, we largely rely on EDW for our data collection steps but RPDR is useful for extracting laboratory data. We will be using data that have

already been collected on historical patient visits from various administrative, billing, and clinical data sources. The EDW gathers clinical data from several hospital systems at Mass General Brigham Healthcare. (Enterprise Master Patient Index - EMPI, Hospital Decision Support System - EPSI (formerly TSI), Physician Billing System - IDX and EPIC, Longitudinal Medical Record - LMR, Corporate Provider Master - CPM, Clinical Data Repository - CDR, and MGB Personalized Medicine - MGBPM) and stores the data in one central data warehouse. Researchers are able to query this data by using an online query tool. The detailed medical records are returned to researchers in an encrypted Microsoft Access file and text (.txt) files. Detailed medical records may include the following types of data: Transfusion, Cardiology, Contact Information, Demographics, Diagnoses, Discharge Notes, Endoscopy, Laboratory Tests, Allergy, LMR Health Maintenance, LMR Medications, LMR Notes, LMR Problems, LMR Vital Signs, Medications, Microbiology, Operative Notes, Pathology Reports, Procedures, Providers, Pulmonary, PROMS, Radiology Reports, Radiology Tests and Transfusion, Visit Notes. Furthermore, images from hospital image repositories can be returned and viewed online.

**Mass General Brigham:**

MGB HealthCare System is a not-for-profit, integrated health care system in Boston, Massachusetts founded by Brigham and Women's Hospital (BWH) and Massachusetts General Hospital (MGH) – two of the nation's leading academic medical centers. MGB includes community and specialty hospitals, a physician network, community health centers, home care and other health related services. MGB institutions maintain a total research budget of more than $1.4 billion, and MGH and BWH are the largest private hospital recipients of National Institutes of Health funding in the nation. MGB is the largest health system in Massachusetts and cares for 6 million patients throughout its network, with ~2 million patients seen annually at MGH, BWH and affiliated healthcare centers. The composition of the covered lives in terms of race, gender and age is reflective of eastern Massachusetts. MGB is an innovative integrated healthcare network that includes multiple major hospitals with more than 7,000 physicians attending to four million outpatient visits and 160,000 admissions per year. Since 2015, MGB has used Epic as its electronic health record across the healthcare system, facilitating easy chart review.

**National Death Index (NDI):**

As the most complete source of death information in the United States, the NDI currently holds the following: All death records from 1979-latest for all 50 states, the District of Columbia, New York City, Puerto Rico, and U.S. Virgin Islands; Records from select years for Guam, American Samoa, and the Northern Marianas. Requests for death certificate information are sent annually to the National Death Index for all patients in the MGB AAV cohort whose vital status is unknown (e.g., loss to follow-up) or for whom a cause of death is unknown.

**United States Renal Data Set (USRDS):**

The USRDS is national registry of kidney failure patients, representing an estimated 94% of patients who receive dialysis or kidney transplantation. Patients who refuse replacement therapy, die prior to enrollment, or receive transient dialysis for acute renal failure are prohibited from enrollment. Nephrologists are required by law to submit a report to the USRDS within 45 days of a patient starting a new kidney failure treatment.

Analyses of patient data linked to NDI and USRDS will be limited to patients from MGB.

### 8.5 Study Size

This is a descriptive analysis using secondary data and no *a priori* hypotheses will be tested in this study. Therefore, sample size calculation and power analysis are not applicable. Section 6.3 presents the estimated patient size.

### 8.6 Data Management

De-identified data from NU will be directly entered into the MGB REDCap database, a HIPAA-compliant web-based platform used to store data. Data entry (both NU and MGB) will be reviewed monthly to query extreme or implausible data values, implausible dates, missing data, or conflicting data.

#### 8.6.1 Obtaining Data Files

Not applicable

#### 8.6.2 Linking Data Files

Data files between MGB, the NDI, and USRDS are routinely linked by patient identifiers. The NDI matching process is probabilistic and the USRDS matching is exact by first/last name, date of birth, sex, and social security number (if available). Analyses using linked data will be limited to MGB.

#### 8.6.3 Review and Verification of Data Quality

Not applicable

## 8.7 Data Analysis

Data analysis will be performed by the team at Massachusetts General Hospital.

### 8.7.1 Planned Analyses

#### 8.7.1.1 Interim Analysis/Analyses

An interim analysis will be performed in May 2024 for preparation of an abstract to be submitted to the ACR Convergence 2024 meeting. This interim analysis will include patients identified through September 1, 2023. Their baseline characteristics and 6 month outcomes (specifically glucocorticoid exposure, remission at Month 6) will be reported. An additional interim analysis will be performed in December 2024 for preparation of an abstract to be submitted to EULAR 2025. An analysis with both MGB and NU data will be submitted to EULAR 2026, and an analysis of the preliminary 24-month MGB data will be submitted to ACR 2026.

#### 8.7.1.2 Primary Analysis

There are four primary analyses. Analysis 1 will describe the baseline characteristics of patients by avacopan prescription status (yes/no), as well as the baseline characteristics of patients prescribed avacopan by initiation status (yes/no). This analysis is limited to the cohort of patients identified beginning in November 2021 at either NU or MGB (eligible for avacopan based on first use). Analyses 2 and 3a will examine the 6- and 12-month outcomes among initiators of avacopan, respectively. Analysis 3b will examine 24-month outcomes among avacopan initiators. Analysis 1 will be performed at least six months after the study start date when the final cohort of avacopan initiators is identified and baseline data are collected. Analyses 2 and 3 will begin once at least 6 months after the last avacopan patient is identified during the inclusion period and at least 6 months of follow-up data are collected. Analysis 4 will describe 24-month outcomes based on duration of avacopan use.

#### 8.7.1.3 Final Analysis

The final analysis for the first manuscript will be performed when the final patient included (last person who initiated avacopan within 6 months of study start) has reached the 12-month end point. A second manuscript will consist of 24-month follow-up data and analyses of different outcomes based on the duration of avacopan use as described above.

### 8.7.2 Planned Method of Analysis

The primary outcomes will be analyzed using a descriptive approach. Summary statistics for continuous variables, including the number of patients, mean, standard deviation

(SD), median, Q1, Q3, minimum and maximum, will be calculated after excluding missing/unknown values. For categorical variables, the frequency and percentage will be provided, and a category of “missing/unknown” will be included. Differences in baseline characteristics of exposure groups of interest in Analyses 1 (Primary objective 1) (e.g., prescribed avacopan and not prescribed avacopan) and 2 (Primary objective 2) (e.g., initiated vs. did not initiate avacopan) among those who initiated avacopan included in Analysis 3 will be presented using descriptive statistics (i.e., parametric and non-parametric methods as appropriate). Analysis 3 and its stratified and secondary analyses will address Primary objective 3, Secondary objectives 1 and 2, and Exploratory objectives 1-3. Adjusted analyses may be performed depending on the sample size, using logistic regression, as appropriate to evaluate independent associations between baseline factors and groups of interest in Analyses 1 and 2. For instance, to evaluate the association of renal involvement with prescription of avacopan, one may consider adjustment for potential demographic factors that could be confounders of this relationship. Cumulative incidence will be used to describe the occurrence of key outcomes, including GC toxicities, infections, and relapse. Given the variable follow-up time, HCRU will be presented as PPPM metrics. Time to event outcomes (e.g., time to discontinuation of GC) will be calculated using Kaplan-Meier analysis and median (IQR) will be reported. Restricted mean survival time will be used to describe time free from GC exposure during follow-up.

A secondary analysis of the association of GC exposure with the risk of relapse will be assessed using multivariable adjusted analyses. Cox proportional hazards models will be used to evaluate factors associated with the risk of relapse and factors associated with GC discontinuation.

Analysis 4 (addressing Secondary objective 3) will consist of a descriptive, secondary analysis of effectiveness (e.g., BVAS, remission, sustained remission, relapse) and safety outcomes (e.g., adverse events, GC toxicity) over 24 months, as well as stratified analyses of outcomes among patients who continued avacopan for pre-specified time points (e.g., ≤12 vs >12 months and ≤18 vs >18 months), pending sample sizes. We will also evaluate the association of both baseline and time-varying factors with avacopan usage >12 months. Details of these analyses will be finalized pending identification of relevant sample sizes.

#### 8.7.2.1 General Considerations

The planned analyses are primarily descriptive in nature.

Descriptive statistics will be used to summarize baseline characteristics, treatment patterns, and clinical outcomes among the study populations defined for each analysis. Hypothesis testing may be used to compare baseline characteristics between relevant exposure groups, including avacopan users and non-users, avacopan initiators and non-initiators, and groups defined by duration of avacopan or glucocorticoid use, as applicable.

For selected secondary and exploratory outcome analyses, hypothesis testing and/or model-based estimation may be conducted to evaluate associations between exposures or patient characteristics and outcomes of interest, including GC discontinuation, relapse, remission, sustained remission, glucocorticoid exposure or toxicity, renal outcomes, and adverse events. These analyses may include regression-based or time-to-event methods, as appropriate based on the outcome type, follow-up time, and available sample size. Any p-values will be interpreted cautiously and in the context of the descriptive objectives, sample size, potential confounding, and the observational nature of the study. The study is not designed or powered to formally test confirmatory hypotheses regarding comparative effectiveness or safety outcomes. Given the rarity of GPA/MPA and the relatively low number of patients in our study, we acknowledge that some clinically meaningful differences in baseline characteristics may not reach statistical significance.

#### 8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

The frequency of missing data will be summarized for each covariate and outcome and reported. Data will not be imputed.

#### 8.7.2.3 Descriptive Analysis

##### 8.7.2.3.1 Description of Study Enrollment

Not applicable.

##### 8.7.2.3.2 Description of Subject/Patient Characteristics

The first primary analysis will report the baseline characteristics of the population. These characteristics are described in section 8.3.3.

#### 8.7.2.4 Analysis of the Primary, Secondary, and Exploratory Endpoint(s)

The analysis comparing patients who are and are not prescribed avacopan and those who do and do not initiate avacopan will only be descriptive. These analyses will describe baseline features (e.g., demographic- and disease-specific features) by the exposures of interest. Depending on the covariate, the distribution of values between

exposure arms will be compared using appropriate parametric or non-parametric summary measures.

When evaluating outcomes of patients who use avacopan to treat GPA/MPA, we will use descriptive statistics to characterize outcomes. Follow-up time will be determined from the index date until end of follow-up and the rate of outcomes of interest will be reported. We will evaluate the cumulative incidence of the categorical outcomes of interest. We will evaluate the time to events (e.g., relapse, GC discontinuation) using Kaplan-Meier curves. Changes in continuous values over time will be summarized using % change from baseline as well as by the mean/median values at select time points among patients followed to those time points. We will also categorize these values into clinically meaningful subgroups to characterize these differences.

The number of HCRU events will be summed for each patient and divided by patient follow-up time in days and multiplied by 30 (to report on a per patient per month [PPPM] basis) and averaged across the cohort, and as annualized estimates.

In exploratory analyses, we will use Cox proportional hazards models to assess the association of baseline factors with the risk of relapse and the likelihood of GC discontinuation at selected time points among patients who initiate avacopan. Depending on the sample size, we will consider an emulated target trial framework with clone-censor-weight approaches to evaluate the association of time to GC discontinuation with outcomes of interest (e.g., relapse). We will consider cluster analysis methods to describe the different GC patterns of use among patients treated with avacopan.

#### 8.7.2.5 Sensitivity Analysis

None

##### 8.7.2.5.1 Subgroup Analysis

We will examine GC exposure, GC toxicities, and renal outcomes for subgroups created by the stratifying variables identified in Section 8.7.2.5.2.

##### 8.7.2.5.2 Stratified Analysis

We will examine GC exposure, GC toxicities, and renal outcomes across strata in the bulleted list below. We will also examine the outcomes of remission at Month 6 and sustained remission at Month 12 (as well as sustained remission at Months 18 and 24 when pertinent) by the same strata.

- Renal and non-renal disease (renal involvement defined by items in the BVAS v3)
- Early and late initiator of avacopan (above/below median time to avacopan initiation from the start of GPA/MPA induction therapy)
- MPO- and PR3-ANCA+ GPA/MPA
- New diagnosis and relapsing of GPA/MPA
- Age < 65 years or ≥ 65 years
- Presence or absence of severe active GPA/MPA disease (defined as the presence of any BVAS kidney or neurologic involvement, gangrene, scleritis, retinal exudates or hemorrhage, sensorineural hearing loss, mesenteric ischemia, diffuse alveolar hemorrhage, respiratory failure, sinonasal disease with bony and/or cartilage damage, subglottic stenosis, cutaneous ulceration, retro-orbital disease, or active GPA/MPA in ≥3 organ systems) at baseline
- Results will be stratified by study site for comparability and assessed whether a pooled analysis is appropriate
- Duration of continuation of avacopan (≤12 vs >12 months)
- Adverse events among people on conventional synthetic DMARDs
- Adverse events among people on rituximab/cyclophosphamide combination

#### 8.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

We will conduct sensitivity analyses to evaluate the potential impact of missingness on our study outcomes.

- First, we will conduct an analysis limited to people who receive their primary care within the MGB system.
- Second, we will conduct an analysis limited to patients who are “loyal” customers of the MGB system based on their interactions with the system prior to the index date (Lin 2020).

#### 8.7.2.5.4 Other Sensitivity Analysis

Not applicable

### 8.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

Adverse events of special interest

- Rash (hypersensitivity reactions)
- Hepatic function test elevations
- Infections

### 8.8 Quality Control

All data manually extracted from the electronic health record are directly entered in REDCap. Data collected from the electronic data warehouse and research patient data registry are stored as .txt files and then imported into SAS and stored as SAS datasets for analysis. REDCap data are imported into SAS as SAS datasets for analysis. All data are stored behind the MGB firewall on a shared folder that is restricted to people with permission and requires a username and password to access. All study staff are trained in human subjects research and in data extraction to ensure consistency.

### 8.9 Limitations of the Research Methods

Mass General Brigham (MGB) is a large healthcare system in eastern Massachusetts which has a large catchment area including eastern Massachusetts, New Hampshire, Maine, Rhode Island, and Northern Connecticut. Northwestern University's healthcare system (Northwestern Medicine) is composed of 11 hospitals primarily serving the northeastern Illinois region, specifically the Chicago area and surrounding counties. This area includes 9 counties with a population exceeding 8.6 million. As a system that includes two quaternary hospitals, patients from around the United States and world also receive their care at MGB. Despite the large catchment areas for these 2 healthcare systems, the generalizability of observations regarding access to avacopan and outcomes may be influenced by the types of patients with GPA/MPA served at MGB and NU, which are predominantly White. In this study, we are leveraging the entirety of MGB and NU, which includes major flagship hospitals at both institutions as well as outpatient primary care and specialty care practices. As such, patients prescribed avacopan by rheumatologists, nephrologists, and other provider types will be identified. While this improves generalizability, MGB and NU are also recognized as leaders in vasculitis care which could bias the patient population towards one with more severe disease. However, since many patients receive their primary and specialty care within the respective MGB and NU systems and then develop GPA/MPA, we will also capture many patients who would otherwise present in the community setting. When comparing patients who were prescribed avacopan to patients treated for GPA/MPA prior to the FDA approval, certain differences in clinical practice and other secular trends might

influence practice. We have tried to limit this impact by designing the study period to begin after FDA approval of avacopan. Additionally, we can consider sensitivity analyses related to time. Because this is not a study based on administrative claims data, some patients may receive care outside of the MGB and NU systems. We will try to capture diagnoses and medication prescriptions (e.g., GC and immunosuppressive therapy for GPA/MPA) from outside the MGB system using manual chart review of Care Everywhere (links MGB's Epic healthcare record to that of other systems around the country which use Epic) and scanned documentation. Similarly, we will try to capture diagnoses and medication prescriptions from outside the NU healthcare system using Care Everywhere. Because patients with GPA/MPA are followed very closely by their vasculitis providers, we feel that careful chart review will ensure adequate capture of relevant outcomes being assessed in this study. We will report the number of patients with missing covariates and outcomes and consider sensitivity analyses to further evaluate the potential impact of missing data.

### 8.9.1 Internal Validity of Study Design

Patients prescribed avacopan are systematically identified from across the MGB and NU healthcare systems since it is only approved for use in patients with GPA/MPA. For patients who are not prescribed avacopan, we rely on a previously developed algorithm to identify GPA/MPA cases. While avacopan prescriptions should capture nearly everyone prescribed avacopan, the algorithm to identify other GPA/MPA cases may not capture patients with as high a level of sensitivity. As such, it may capture a subset of patients who could differ from avacopan recipients. We will evaluate these differences at baseline and consider adjustment for relevant confounders if such analyses are pursued. When comparing groups, we will comprehensively measure confounders at baseline and consider methods to adjust for differences in analyses comparing groups. We are including patients who fulfill one of three GPA/MPA diagnostic criteria: ACR/EULAR Classification Criteria for GPA or MPA; Chapel Hill Consensus Classification (CHCC) for GPA or MPA; or clinician-diagnosis and management of GPA or MPA. This may introduce some heterogeneity in the observed findings. We will conduct subgroup analyses among those who fulfill each of these criteria to investigate the potential impact that using these three criteria might have.

#### 8.9.1.1 Measurement Error(s)/Misclassification(s)

It is possible that exposure to certain variables of interest may be difficult to assess in some people. For instance, specific daily amounts of glucocorticoid use by a patient at

home may vary from what is reported in the chart. However, we do not expect such differences to be large given the close management of this condition by the patient's clinicians and we will comprehensively assess prescription data, instructions, as well as patient communication messages to evaluate the exposure to glucocorticoid therapy during the study period. Disease activity is assessed retrospectively using BVAS v3. This is based on a physician's assessment on chart review of another clinician's documentation, along with laboratory, imaging, and/or pathology data. It may be that the documentation in the chart is incomplete and the BVAS v3 score estimates may be lower than in reality. We will report this as a limitation in our study but expect that comprehensive chart review will limit the impact of this error.

#### 8.9.1.2 Information Bias

As above, there may be information bias because of the retrospective nature of this study, which relies on clinical documentation to assess some outcomes. This potential bias will be acknowledged and comprehensive methods to systematically review each medical record, including review of clinical notes, outside records, and patient messages, should minimize the impact of this error.

#### 8.9.1.3 Selection Bias

As above, many patients who receive care at MGB and NU for GPA/MPA may differ from those receiving care in the community setting or elsewhere in the US and around the world. This may bias our cohort towards a population with more severe disease. However, as discussed above, MGB and NU serve as community healthcare providers to many patients in the New England and Midwestern areas. We can consider subgroup analyses where we evaluate patients who received longitudinal care within MGB or NU prior to their GPA/MPA diagnosis.

#### 8.9.1.4 Confounding

The primary purpose of this study is a descriptive study of use of and outcomes of avacopan in patients with GPA/MPA. As such, the outcomes being reported are descriptive in nature.

### 8.9.2 External Validity of Study Design

As above, there may be limits to the generalizability of our findings given this is a study being conducted in a healthcare system in New England, USA. The addition of the NU site increases generalizability toward those receiving healthcare from a large healthcare system in the Midwestern region of the US.

### 8.9.3 Analysis Limitations

Some patients will receive care outside of the healthcare systems selected for this study. This could influence the measurement of certain outcomes and could influence analyses. We will consider the potential impact of these limitations in our analyses and consider subgroup analyses where we limit analyses to patients with certain threshold of healthcare utilization prior to their GPA/MPA diagnosis. Patients in this study may be lost to follow-up or experience competing risks depending on the outcome of interest. We will consider variable length of follow-up in our analyses of relevant outcomes. We will also consider methods for accounting for competing risks depending on their frequencies.

### 8.9.4 Limitations Due to Missing Data and/or Incomplete Data

Most missing data will not be imputed and will be reported as a separate category as "missing/unknown." There are no major concerns regarding missingness from the exposure of interest given that patients are being identified based on their prescription data. It would be unlikely that a patient is prescribed avacopan outside of MGB or NU, and it is not available in linked records, scanned documentation, or clinical documentation. As discussed above, it is possible that some data at baseline or during follow-up are missing because patients may receive care outside of MGB or NU. This will be addressed by comprehensive and systematic medical record review, including of records from other healthcare systems.

The one exception to this is that laboratory (hemoglobin A1c and low density lipoprotein) and vital (blood pressure and weight) data will be imputed for calculation of the GTI-Metabolic Domains as missing data do not allow for calculation of scores. Data will be imputed primarily by last observation carried forwards or backwards. For weight, LDL, or hemoglobin A1c, missing values with 2 adjacent values (e.g., a missing 3 month value when a baseline and 6 month value are available) will be imputed to be in the midpoint of the two available values.

We will conduct sensitivity analyses to evaluate the potential impact of missingness on our study outcomes. First, we will conduct an analysis limited to people who receive their primary care within the MGB or NU systems. Second, we will conduct an analysis limited to patients who are "loyal" customers of the MGB or NU systems based on their interactions with the system prior to the index date (Lin 2020).

## 9. Protection of Human Subjects

This is an IRB-approved study that is permitted to collect protected health information for the purposes of accessing charts, calculating time to events, and assessing exposures, covariates, and outcomes. The database used to store all data is HIPAA compliant. All data being reported/shared are aggregated and deidentified. This has been approved by both the MGB and NU IRBs.

### 9.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The Mass General Brigham IRB has approved this study as secondary use of previously collected data (Protocol # 2023P001281). The study has also been approved by the Northwestern University IRB. Future IRB amendments with protocol updates will be addressed on a case-by-case basis if needed.

If CCF participates in this study, they will submit this protocol to their IRB.

### 9.2 Patient Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

For serious adverse events reported to Amgen, subjects are deidentified.

## 10. Collection, Recording, and Reporting of Safety Information and Product Complaints

This study is analyzing secondary data from EHR medical charts (MGH and NU) and no safety data will be collected.

## 11. Administrative and Legal Obligations

### 11.1 Protocol Amendments and Study Termination

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement.

## 12. Plans for Disseminating and Communicating Study Results

The results of this study will be submitted for publication, including a planned research abstract submission and a manuscript submission to a clinical audience targeted journal, to be determined in future.

### 12.1 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for

the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

## 13. References

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# 14. Appendices

## Appendix A. List of Stand-alone Documents

None

## Appendix B. Glucocorticoid Equivalent Dose

| Glucocorticoids (oral) | Equivalent dose (mg) |
|---|---|
| Cortisol | 20.0 |
| Cortisone | 25.0 |
| Prednisone | 5.0 |
| Prednisolone | 5.0 |
| Triamcinolone | 4.0 |
| Methylprednisolone | 4.0 |
| Dexamethasone | 0.75 |
| Hydrocortisone | 20.0 |

## Appendix C. Other GPA/MPA-related Medications

| | |
|---|---|
| **Immunosuppressive drugs** | • Rituxan (rituximab) |
| | • Riabni (rituximab-arrx) |
| | • Ruxience (rituximab-pvvr) |
| | • Truxima (rituximab-abbs) |
| | • Mycophenolate mofetil |
| | • Methotrexate |
| | • Azathioprine |
| | • Cyclophosphamide |
| **Systemic glucocorticoids** | • Dexamethasone |
| | • Prednisone |
| | • Prednisolone |
| | • Methylprednisolone |
| | • Hydrocortisone |

## Appendix D. ACR/EULAR Classification Criteria for GPA/MPA*

| | GPA | MPA |
|---|---|---|
| **Clinical Criteria** | | |
| Nasal passage involvement | +3 | -3 |
| Cartilaginous involvement | +2 | |
| Conductive or sensorineural hearing loss | +1 | |
| **Laboratory Criteria** | | |
| PR3-ANCA+ | +5 | -1 |
| MPO-ANCA+ | -1 | +6 |
| Serum eosinophil ≥ 1,000/uL | -4 | -4 |
| **Histologic Criteria** | | |
| Granuloma, granulomatous inflammation, or giant cells | +2 | |
| Pauci-immune glomerulonephritis | +1 | +3 |
| **Radiology Criteria** | | |
| Pulmonary nodules, mass, or cavitation on chest imaging | +2 | |
| Fibrosing or ILD on chest imaging | | +3 |
| Nasal or paranasal sinusitis or mastoiditis on imaging | +1 | |
| Cut-off score for classification | ≥5 | ≥5 |

*A diagnosis of small- or medium-vessel vasculitis must be made and other medical conditions mimicking vasculitis excluded before applying these classification criteria.

## Appendix E. Chapel Hill Consensus Conference Nomenclature on Vasculitis

| GPA | MPA |
|---|---|
| Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (e.g., capillaries, venules, arterioles, arteries and veins). Necrotizing glomerulonephritis is common. | Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent. |