Summary Table of Study Protocol

Title	Retrospective Cohort Study Evaluating Clinical Outcomes in Patients with Granulomatosis with Polyangiitis (GPA)/microscopic polyangiitis (MPA) Treated with Avacopan
Protocol version identifier	20230026, Version 1.0
Date of last version of the protocol	NA
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

Research Question and Objectives	Primary objectives
	• To describe the demographics and disease-specific features of patients who are and are not prescribed avacopan for GPA/MPA.
	• Among people prescribed avacopan, to describe the demographics and disease-specific features of patients who do and those who do not initiate avacopan.
	• To describe the outcomes, including disease- and treatment-specific outcomes, of patients who use avacopan.
	  ○ Proportion achieving discontinuation of glucocorticoids for treatment of GPA or MPA 1 month before Month 6 and disease remission within 6 months of avacopan initiation.
	  ○ 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
	Secondary objectives
	• To investigate baseline factors associated with glucocorticoid discontinuation and relapse risk in patients who initiate avacopan.
	• To evaluate the association of glucocorticoid use patterns with relapse risk in patients who initiate avacopan.
	Exploratory objective
	• To explore the outcomes, including disease- and treatment-specific outcomes, of patients who use avacopan for greater than 12 months.

Country(ies) of Study	United States
Author	PPD

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen Inc.
MAH Contact	PPD PhD, MPH PPD One Amgen Center Drive Thousand Oaks, CA 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	February 19, 2024	February 19, 2024

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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, MSC Date (DD Month YYYY)

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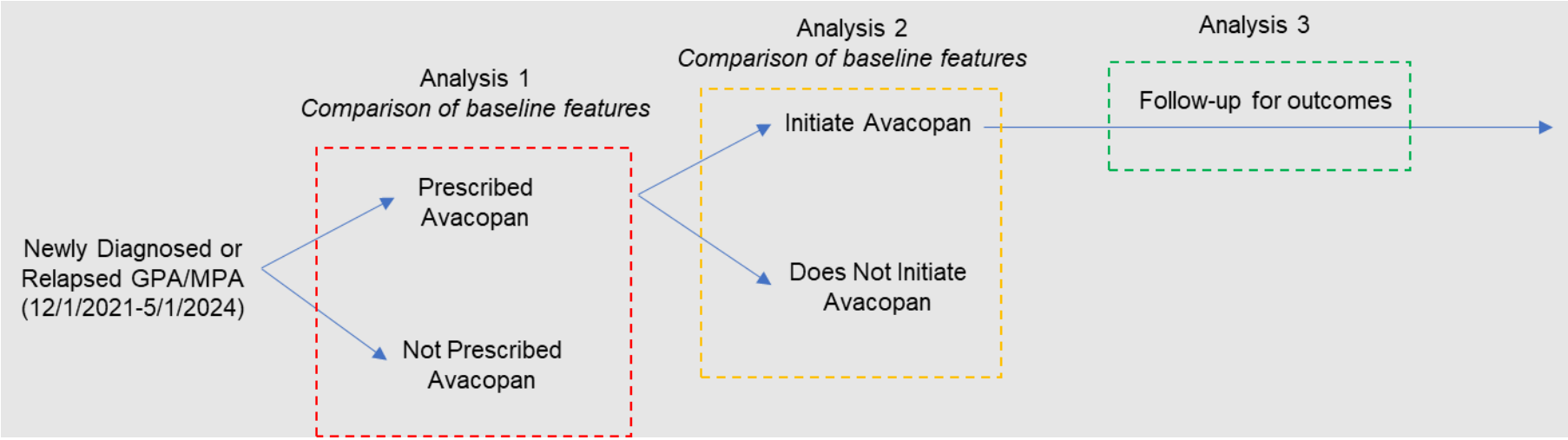
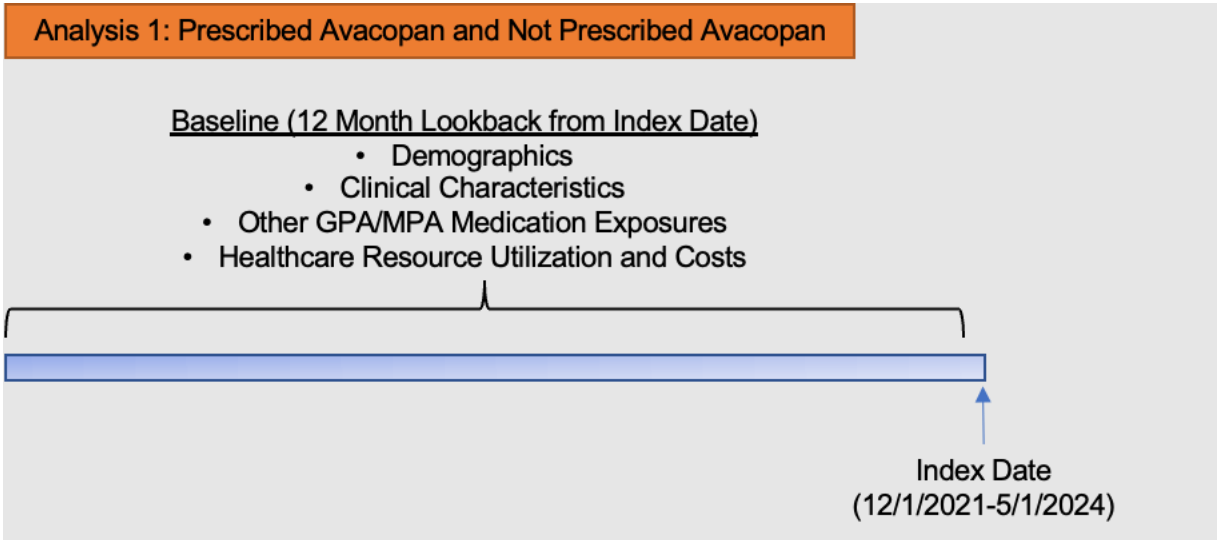
Boston, MA 02114, USA

PPD

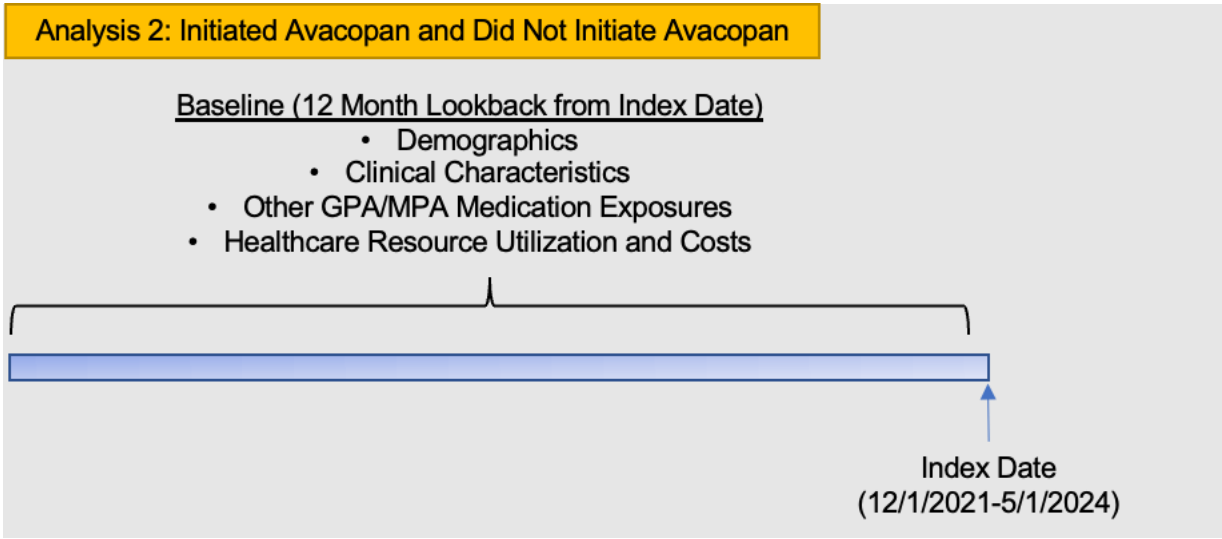
Study Design Schema [Required]



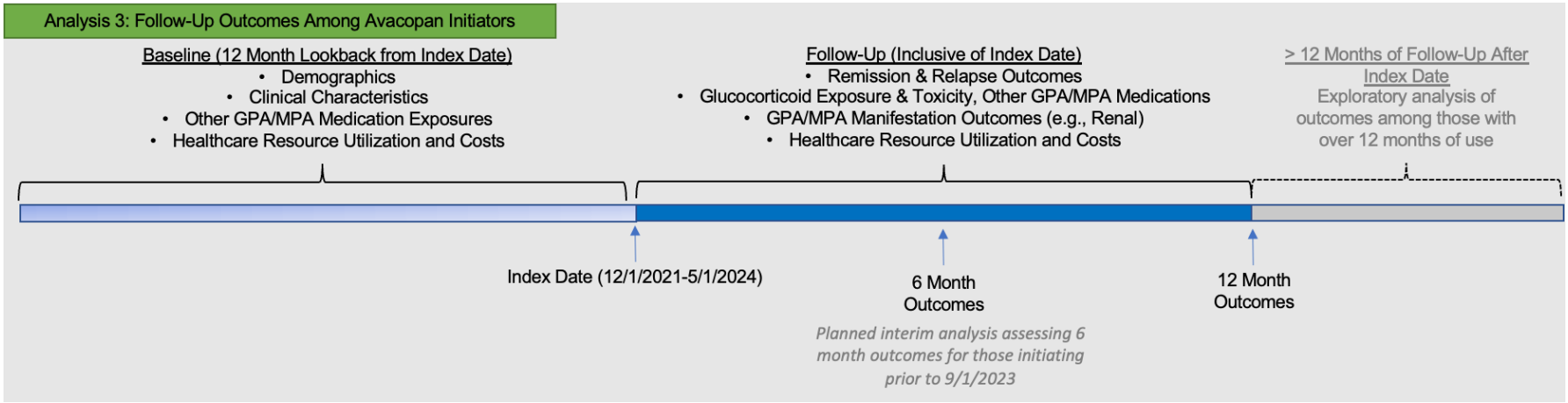
Data source	**Index dates**
Mass General Brigham ANCA-associated vasculitis cohort	• Analysis 1: Date of avacopan prescription or date of non-avacopan, non-glucocorticoid treatment prescription (i.e., immunosuppressive drugs specified in Appendix C) • Analysis 2: Date of avacopan prescription (for both avacopan initiators and non-initiators) • Analysis 3: Date of avacopan initiation
Additional details regarding inclusion/exclusion criteria, endpoints, and outcomes are described in Analysis-specific schema	



Index date Date of avacopan prescription or date of non-avacopan, non-glucocorticoid treatment prescription	
Inclusion criteria • Diagnosed with new or relapsing GPA or MPA on or after December 1, 2021, the first date of avacopan use at Mass General Brigham • At least 18 years old on index date **Exclusion criteria** • A diagnosis of EGPA. • GPA/MPA attributed to cocaine/levamisole. • No treatment of GPA/MPA during the baseline or follow-up periods (i.e., not treated for their GPA/MPA).	**Characteristics to be evaluated** • Demographic features (e.g., age, sex, race/ethnicity) • GPA/MPA features (e.g., BVAS v3, organ involvement, new or relapsing disease) • Comorbidities at index date (e.g., hypertension, hyperlipidemia, Charlson Comorbidity Index) • 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 • Diagnosed with new or relapsing GPA or MPA on or after December 1, 2021, the first date of avacopan use at Mass General Brigham • At least 18 years old on index date • Prescribed avacopan **Exclusion criteria** • A diagnosis of EGPA. • GPA/MPA attributed to cocaine/levamisole. • No treatment of GPA/MPA during the baseline or follow-up periods (i.e., not treated for their GPA/MPA).	**Characteristics to be evaluated** • Demographic features (e.g., age, sex, race/ethnicity) • GPA/MPA features (e.g., BVAS v3, organ involvement, new or relapsing disease) • Comorbidities at index date (e.g., hypertension, hyperlipidemia, Charlson Comorbidity Index) • Healthcare resource utilization up to 12 months prior to index date • Reason for not initiating avacopan



Index date Date of avacopan initiation	**Primary outcomes to be evaluated** • Proportion achieving discontinuation of glucocorticoids for treatment of GPA or MPA 1 month before Month 6 and disease remission within 6 months of avacopan initiation. • 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
Inclusion criteria • Diagnosed with new or relapsing GPA or MPA on or after December 1, 2021, the first date of avacopan use at Mass General Brigham • At least 18 years old on index date • Prescribed avacopan	**Additional endpoints to be evaluated** • Glucocorticoid exposure, glucocorticoid toxicity • Disease activity, renal outcomes, ANCA titer changes • Change in comorbidities/biomarkers (e.g., BMI, lipids, A1c) • Healthcare resource utilization (analysis from MGH only) • Patient reported outcome measures • Adverse events attributed to avacopan, infection, relapse, mortality
Exclusion criteria • A diagnosis of EGPA. • GPA/MPA attributed to cocaine/levamisole. • No treatment of GPA/MPA during the baseline or follow-up periods (i.e., not treated for their GPA/MPA).	

1. Table of Contents

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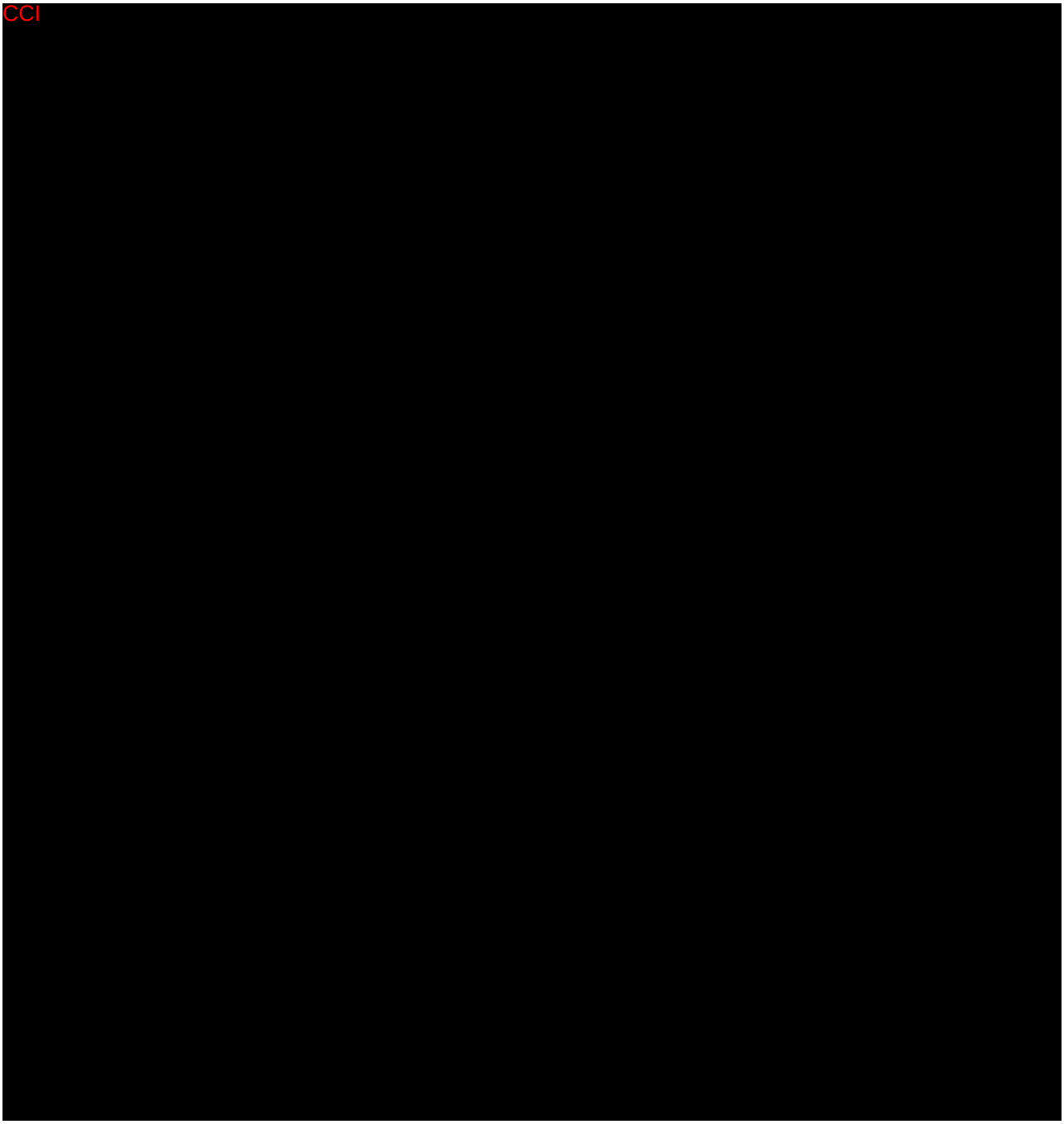

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2. List of Abbreviations

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

CCF: Cleveland Clinic Foundation

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

mHAQ: Modified Health Assessment Questionnaire

MPA: Microscopic polyangiitis

MPO: Myeloperoxidase

NDI: National Death Index

PHQ-8: Patient Health Questionnaire-8

PPPM: per patient per month

PR3: Proteinase 3

PROM: Patient Reported Outcome Measure

PROMIS: Patient Reported Outcomes Measurement Information System

Q1: Quartile 1

Q3: Quartile 3

RAPID3: Routine Assessment of Patient Index Data 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, Center for Observational Research, Amgen Inc.
- PPD, Medical Affairs, Amgen Inc.
- PPD, HEOR, Amgen Inc.
- PPD HEOR, Amgen Inc.
- PPD, Medical Affairs, Amgen Inc.
- PPD, Medical Affairs, Amgen Inc.
- PPD, Medical Affairs, Amgen Inc.

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 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 glucocorticoids 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 glucocorticoids (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 1, 3, 6 and 12 months in avacopan users from the Mass General Brigham (MGB) GPA/MPA registry and potentially from the Cleveland Clinic Foundation (CCF) (negotiations are ongoing).

Study 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 (the date of avacopan availability at MGB), 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 glucocorticoids within 2 months of avacopan initiation. There are only 2 patients in this cohort with missing status regarding avacopan initiation.

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 December 1, 2021 and May 1, 2024. 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?

Objectives	Endpoints

Primary	
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 • Demographic features (e.g., age, sex, race/ethnicity) • GPA/MPA features (e.g., BVAS v3, organ involvement, new or relapsing disease) • Comorbidities at index date (e.g., hypertension, hyperlipidemia, Charlson Comorbidity Index) • Healthcare resource utilization up to 12 months prior to index date
Among people prescribed avacopan, to describe the demographics and disease-specific features of patients who do and those who do not initiate avacopan	
Among patients who use avacopan, to describe the outcomes, including disease- and treatment-specific outcomes	• Complete remission at Month 6 • Complete remission at Month 12 • Proportion who achieve discontinuation of glucocorticoids for treatment of GPA or MPA 1 month before Month 6 and disease remission (based on a BVAS v3 of 0) within 6 months of avacopan initiation, as defined in ADVOCATE • Proportion who achieve sustained remission at Month 12. • Cumulative glucocorticoid exposure • Median daily glucocorticoid dose • Glucocorticoid toxicity • Glucocorticoid Toxicity Index – Metabolic Domain (GTI-MD) • Change in A1c • Change in BMI • Change in lipids • Renal parameters (estimated glomerular filtration rate [eGFR], proteinuria, hematuria) • ANCA titers • Pathology results • Adverse Events • Patient reported outcome measures (RAPID-3, mHAQ, PHQ-8, GAD-7, and PROMIS)
Secondary	
To investigate baseline factors associated with glucocorticoid discontinuation and relapse risk in patients who initiate avacopan	Descriptive analysis of baseline demographic and clinical characteristics • Demographic features (e.g., age, sex, race/ethnicity)

	• GPA/MPA features (e.g., BVAS v3, organ involvement, new or relapsing disease) • Comorbidities at index date (e.g., hypertension, hyperlipidemia, Charlson Comorbidity Index) • Healthcare resource utilization up to 12 months prior to index date
To evaluate the association of glucocorticoid 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. 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)
To evaluate healthcare resource utilization during follow-up in patients who initiate avacopan	Per patient per month estimates of all-cause and GPA/MPA-related healthcare resource utilization (HCRU) including outpatient visits, hospitalization rates and length of stay, Emergency Room visits
Exploratory	
To evaluate baseline healthcare costs in patients who are and are not prescribed avacopan for GPA/MPA (analysis from MGH only)	Per patient per month costs of all-cause and GPA/MPA-related resource use associated with outpatient visits, hospitalizations, Emergency Room visits
To evaluate baseline healthcare costs in patients who do and those who do not initiate avacopan (analysis from MGH only)	
To evaluate healthcare costs during follow-up in patients who initiate avacopan (analysis from MGH only)	All-cause and GPA/MPA-related costs associated with outpatient visits, hospitalizations, Emergency Room visits
To explore the outcomes, including disease- and treatment-specific outcomes, of patients who use avacopan for greater than 12 months	Descriptive analysis of demographic and clinical characteristics and outcomes • Demographic features (e.g., age, sex, race/ethnicity) • GPA/MPA features (e.g., BVAS v3, organ involvement, new or relapsing disease) • Comorbidities at index date (e.g., hypertension, hyperlipidemia, Charlson Comorbidity Index) • Healthcare resource utilization

	• Glucocorticoid exposure, glucocorticoid toxicity • Disease activity, renal outcomes, ANCA titer changes • Change in comorbidities/biomarkers (e.g., BMI, lipids, A1c) • Healthcare resource utilization (analysis from MGH only) • Patient reported outcome measures • Adverse events attributed to avacopan, infection, relapse, mortality

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 April 2024 (12 months of follow-up for patients identified up to 6 months after study launch). 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 may also be expanded to include the Cleveland Clinic Foundation's Center for Vasculitis Care and Research.

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).

<u>Analysis 1</u>

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

<u>Analysis 2</u>

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. Prescribed avacopan

Analysis 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

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)

Analysis 3: Month 1, 3, 6, and 12 outcomes among patients who initiate avacopan

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

Clinical Outcomes

- Date of relapse (any and stratified by major or minor), (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.

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 Month 6 (BVAS v3 = 0); 3) Sustained remission at Month 12; 4) Glucocorticoid toxicity; 5) Disease activity; 6) Renal outcomes; 7) ANCA titer changes; 8) Healthcare resource utilization; 9) Healthcare costs (analysis from MGH only); 10) Adverse events attributed to avacopan; 11) Infection; 12) 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); 13) Mortality; 14) Patient reported outcome measures (RAPID-3, mHAQ, PHQ-8, GAD-7, and PROMIS)

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, 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. Glucocorticoid exposure has varied but the majority of patients have discontinued glucocorticoids 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 glucocorticoid toxicities, infections, and relapse. Given the variable follow-up time, healthcare resource utilization (HCRU) and costs will be presented as per patient per month (PPPM) metrics. Time to event outcomes (e.g., time to discontinuation of glucocorticoids) 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 glucocorticoid exposure with the risk of relapse will be assessed using an emulated target trial framework with a clone, censor, weighting approach. 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.

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