Summary Table of Study Protocol

Title	*Effectiveness and Safety of Avacopan as add-on to Standard of Care (SOC) Versus SOC Alone in ANCA-associated Vasculitis (LIBRA)*
Protocol version identifier	20240051 Amendment 1, Version 2.0
Date of last version of the protocol	March 9, 2026
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Medicinal Product	NA
Device	NA
Product Reference	NA
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Marketing authorization holder(s)	Amgen Inc.
Joint PASS	NA

Research Question and Objectives	To estimate the real-world effectiveness of avacopan + SOC versus SOC among adults with ANCA-associated vasculitis (AAV), and to describe the real-world safety outcomes among adults with AAV treated with avacopan + SOC and among adults with AAV treated with SOC alone.
	
	Primary endpoints:
	• Time to first relapse
	• Incidence of Major Adverse Kidney Events (MAKE) within 12 months (composite endpoint of mortality, dialysis, kidney transplant, end-stage kidney disease)
	• 30-day average prednisone-equivalent daily dose (PEDD) ≤ 7.5mg at 90, 120, 180, 270, and 365 days post-index
	
	Secondary endpoints:
	• Incidence of glucocorticoid-related events within 12 months (composite endpoint of serious infection requiring hospitalization, initiation of new class of anti-hyperglycemic medication, major osteoporotic fractures [vertebra, pelvis, humerus, radius/ulna, hip, other femur])
	• Relapse within 12 months
	• Incidence of MAKE components within 12 months
	  ○ Mortality
	  ○ Dialysis
	  ○ Kidney transplant
	  ○ End-stage kidney disease
	• Incidence within 12 months of hepatotoxicity and drug-induced liver injury, and serious hypersensitivity reactions, including angioedema and anaphylaxis (safety endpoints)

Country(ies) of Study	United States
Author	PPD , Target RWE PPD , Center for Observational Research, Amgen Inc. PPD Center for Observational Research, Amgen Inc. PPD Center for Observational Research, Amgen Inc. PPD Medical Affairs, Amgen Inc.

Marketing Authorization Holder (MAH)

MAH(s)	Amgen Inc.
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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, Version 1.0	March 9, 2026	March 9, 2026
Protocol Amendment 1, Version 2.0	April 7, 2026	April 7, 2026

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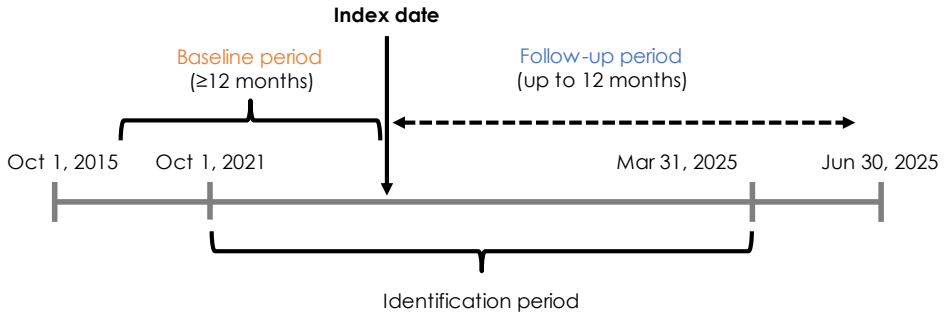
Study Design Schema



Study Design
- Retrospective cohort study with sequential nested trials

Study Period
- 01Oct2015 – 30Jun2025

Disease Date Alignment
- Patients are aligned on the date of their first AAV diagnosis or relapse during the identification period

Index Date
- Sequential trials will be run in 14 -day intervals from the disease date to 125 days after the disease date. For each trial, index dates are defined as:

1. Date of first avacopan claim (avacopan + SOC arm)
2. Two approaches considered for SOC arm (final choice based on propensity scores/NCOs*):
   - Date of first (1) claim for RTX or CYC or (2) encounter with a Nephrologist or Rheumatologist in the interval
   - Date of first (1) claim for RTX or CYC in interval

Inclusion Criteria
- Patients with new or relapsing AAV within 125 days before index date
- 1 year of continuous medical and pharmacy enrollment prior to index date with ≤ 30-day gap
- At least one day of follow-up time
- ≥ 18 years old on index date
- ≥ 1 claim for RTX within 90 days and/or CYC within 45 days before or on index date

Exclusion Criteria
- Pre-index avacopan use
- Pre-index diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA)
- Pre-index use of mepolizumab or benralizumab

Medication Arms
- Avacopan + SOC
- SOC

Primary Outcomes †**Prioritized readout**
- Time to first relapse †
- Incidence of Major Adverse Kidney Events (MAKE) within 12 months (composite endpoint of mortality, dialysis, kidney transplant, end-stage kidney disease [ESKD]) †
- 30-day average prednisone-equivalent daily dose (PEDD) ≤ 7.5mg at 90, 120, 180, 270, and 365 days post-index †

Secondary Outcomes
- Incidence of glucocorticoid-related events within 12 months (composite endpoint of serious infection requiring hospitalization; initiation of new class of anti-hyperglycemic medication; major osteoporotic fractures [pelvis, humerus, radius/ulna, hip, other femur])
- Relapse within 12 months
- Incidence of MAKE components within 12 months (mortality, dialysis, kidney transplant, ESKD)
- Incidence within 12 months of hepatotoxicity and drug-induced liver injury, and serious hypersensitivity reactions, including angioedema and anaphylaxis

Covariate Domains
- Patient demographics and access to care
- Newly diagnosed vs relapsing status and prior disease course
- Disease severity and organ involvement (to address lack of BVAS)
- Induction regimen and concomitant medications
- GC exposure and history of related complications
- Comorbidities
- Liver disease
- Healthcare resource utilization

End of Follow-up
- Earliest of disenrollment, end of administrative follow-up, or outcome under study

*The approach to determining index dates in the SOC arm will be finalized before conducting any analyses of primary, secondary, or safety endpoints.

1. Table of Contents

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2. List of Abbreviations

Abbreviations or Term	Definition/Explanation
AAV	Antineutrophil cytoplasmic antibody-associated vasculitis
AKI	Acute kidney injury
ANCA	Antineutrophil cytoplasmic antibody
AZA	Azathioprine
BVAS	Birmingham Vasculitis Activity Score
CI	Confidence interval
CKD	Chronic kidney disease
CPT	Current Procedural Terminology
CYC	Cyclophosphamide
DAC	Data and Analytic Center
DILI	Drug-induced liver injury
EGPA	Eosinophilic granulomatosis with polyangiitis
EHR	Electronic health record
ENT	Ear, nose, throat
ER	Emergency room
ESKD	End-stage kidney disease
FDA	Food and Drug Administration
GC	Glucocorticoid
GPA	Granulomatosis with polyangiitis
HCPCS	Healthcare Common Procedure Coding System
HR	Hazard ratio
ICMJE	International Committee of Medical Journal Editors
IP	Inpatient
IPCW	Inverse probability of censoring weights
IPTW	Inverse probability of treatment weights
IQR	Interquartile range
ITT	Intention-to-treat
MAKE	Major adverse kidney event

Abbreviations or Term	Definition/Explanation
MMF	mycophenolate mofetil
MPA	Microscopic polyangiitis
MPO	Myeloperoxidase
MTX	methotrexate
NCO	Negative control outcome
NDC	National Drug Code
NPV	Negative predictive value
OP	Outpatient
PEDD	Prednisone-equivalent daily dose
PPV	Positive predictive value
PR3	Proteinase 3
QC	Quality control
RD	Risk difference
RIT	Remission induction therapy
RR	Risk ratio
RTX	rituximab
RWE	Real-world evidence
SALI	Severe acute liver injury
SAP	Statistical analysis plan
SD	Standard deviation
SMD	Standardized mean difference
SMR	Standardized mortality ratio
SOC	Standard of care
TTD	Time to discontinuation
TTNT	Time to next treatment

3. Responsible Parties

- PPD Target RWE
- PPD CfOR, Amgen Inc.
- PPD CfOR, Amgen Inc.
- PPD CfOR, Amgen Inc.
- PPD Medical Affairs, Amgen Inc.

4. Abstract

- Study Title

  Effectiveness and Safety of Avacopan as add-on to Standard of Care (SOC) Versus SOC Alone in ANCA-associated Vasculitis (LIBRA)

- Study Background and Rationale

  Avacopan (brand, TAVNEOS®) is a complement 5a receptor (C5aR1) antagonist available as 10 mg oral capsules, with a recommended adult 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 versus a prednisone taper to induce and sustain remission in patients with newly diagnosed or relapsing granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA). The two primary endpoints were disease remission at Month 6, defined as achieving a Birmingham Vasculitis Activity Score (BVAS) 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 of 0 and not taking glucocorticoids to treat GPA or MPA within 1 month before Month 12), without relapse between Months 6 and 12. Relapse is 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 items for at least two consecutive clinical visits (ADVOCATE definition).

  Based on evidence from this study that a significantly higher percentage of patients receiving avacopan (66%) achieved sustained remission when compared to the 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 adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (GPA and MPA) in combination with standard therapy including glucocorticoids (GC). Since its approval, avacopan was adopted by several international guidelines for the treatment of GPA or MPA as a part of strategies to reduce exposure to GC (KDIGO 2024, Turgeon 2022, Hellmich 2023).

  Avacopan was developed by ChemoCentryx, Inc. and acquired by Amgen in October 2022. On January 16, 2026, the FDA requested that ChemoCentryx voluntarily withdraw TAVNEOS from the U.S. market. The FDA raised concerns about the process followed by ChemoCentryx to re-adjudicate primary endpoint results for 9 of the 331 patients in the ADVOCATE trial. Hepatotoxicity, which is a known infrequent

risk of avacopan treatment for AAV, was also raised in the context of the benefit-risk profile of the medicine. Amgen is not aware of any issues with the underlying patient data and after review of the relevant clinical data and years of real-world evidence, Amgen is confident that avacopan demonstrates effectiveness and a favorable benefit-risk profile.

To further add to the avacopan real-world evidence package being developed, this study will estimate the real-world comparative effectiveness of avacopan + SOC versus SOC alone among adults with newly diagnosed or relapsing AAV. LIBRA is a retrospective cohort study using a prevalent new user design with sequential nested trial emulations, implemented separately in Optum Market Clarity and Komodo Healthcare Map using a common protocol, with database-specific results combined through meta-analysis.

Given the number of endpoints to evaluate under an accelerated timeline, the following will be prioritized for an earlier readout: primary endpoints and safety events of special interest (hepatotoxicity and drug-induced liver injury, and serious hypersensitivity reactions, including angioedema and anaphylaxis).

- Study Feasibility and Futility Considerations

  Claims-based algorithms to identify (1) patients with newly diagnosed AAV and (2) relapse among patients diagnosed with AAV have been developed in collaboration with subject matter experts in the diagnosis and treatment of patients with AAV. These algorithms will be used to identify patients potentially eligible for study entry.

  The study team evaluated the use of avacopan, RTX, and CYC among patients with AAV in two large real-world data sets to assess sample size. Examination of the MarketScan Commercial and Medicare database identified 95 patients with AAV who were prescribed avacopan and had ≥ 12 months of baseline enrolment, regardless of incident or relapsing AAV status. An additional 2,792 patients prescribed SOC since 2015 were identified. In contrast, an analysis of the Optum Market Clarity database identified over 16,000 patients with newly diagnosed or relapsing AAV. Among these patients, approximately 430 were prescribed avacopan within 120 days of their new or relapsing disease, of whom roughly 200 met inclusion criteria for the current study. We expect approximately 2,500 patients on SOC to meet study inclusion criteria. The sample size may likely change after additionally requiring recency of RTX/CYC exposure prior to indexing. A similar estimate of the Komodo Healthcare Map provided by Komodo yielded approximately 260 patients with newly diagnosed AAV who were prescribed avacopan and met study inclusion criteria. Assuming a similar distribution of newly diagnosed (69.4%) and relapsing patients (31.6%) as observed in the Optum analysis (which are broadly consistent with findings from an EHR-based study [Patel et al, 2025] reporting 66.4% newly diagnosed and 33.6% relapsing disease), this corresponds to an estimated total of approximately 375–390 eligible patients prescribed avacopan in the Komodo dataset. Given the expected sample size available from each database, the comparative analysis may yield imprecise effect estimates and should therefore be interpreted primarily as directional. However, the probability of reporting a qualitatively incorrect effect direction (eg, estimating a hazard ratio greater than 1 when the true hazard ratio is

less than 1) was calculated to be low, supporting the use of the analysis for directional interpretation.

- Research Question and Objective(s)

Objectives	Endpoints
Primary*	
• Estimate the real-world effectiveness of avacopan + standard of care (SOC) versus SOC among adults with ANCA-associated vasculitis (AAV)	• Time to first relapse • Incidence of Major Adverse Kidney Events (MAKE) within 12 months (composite endpoint of mortality, dialysis, kidney transplant, end-stage kidney disease) • 30-day average prednisone-equivalent daily dose (PEDD) ≤ 7.5mg at 90, 120, 180, 270, and 365 days post-index
Secondary	
• Estimate the real-world effectiveness of avacopan + SOC versus SOC among adults with AAV	• Incidence of GC-related events within 12 months (composite of serious infection requiring hospitalization, initiation of new class of anti-hyperglycemic medication, major osteoporotic fractures [vertebra, pelvis, humerus, radius/ulna, hip, other femur]) • Incidence of relapse within 12 months • Incidence of MAKE components within 12 months o Mortality o Dialysis o Kidney transplant o End-stage kidney disease
• Describe the real-world safety outcomes among adults with AAV treated with avacopan + SOC and among adults with AAV treated with SOC alone	• Incidence within 12 months of hepatotoxicity and drug-induced liver injury, and serious hypersensitivity reactions, including angioedema and anaphylaxis (safety endpoints)*
*These endpoints will be prioritized to read out first.	

- Hypothesis(es)/Estimation

This study is designed to estimate the hazard ratio (HR) for first relapse and the risk ratio (RR) for major adverse kidney events (MAKE) with 95% confidence intervals (CI) comparing treatment with avacopan + SOC to SOC only. The study is also designed to quantify the incidence of major adverse safety outcomes across treatment groups,

including hepatotoxicity and drug-induced liver injury, and serious hypersensitivity reactions, including angioedema and anaphylaxis.

Generalized null hypothesis: There is no difference in the hazard (or risk) of Outcome Y between patients initiating avacopan + SOC vs patients initiating SOC alone.

Primary endpoints:

- **Endpoint**: Time to first relapse. **Effect Measure**: Hazard ratio
- **Endpoint**: Incidence of MAKE within 12 months. **Effect Measure**: Risk ratio (ratio of cumulative risks) and risk difference
- **Endpoint**: 30-day average PEDD ≤ 7.5mg by 90, 120, 180, 270, 365 days. **Effect Measure**: Risk ratio (ratio of proportions) and risk difference

Secondary endpoints:

- **Endpoint**: Incidence of GC-related events (composite endpoint) within 12 months. **Effect Measure**: Risk ratio (ratio of cumulative risks) and risk difference
- **Endpoint**: Relapse within 12 months. **Effect Measure**: Risk ratio (ratio of cumulative risks) and risk difference
- **Endpoints**: Incidence of MAKE components within 12 months (separate analyses for mortality, dialysis, kidney transplant, and ESKD). **Effect Measure**: Risk ratio (ratio of cumulative risks) and risk difference
- **Endpoint**: Incidence of hepatotoxicity and drug-induced liver injury within 12 months. **Effect Measure**: Cumulative incidence
- **Endpoint**: Incidence of serious hypersensitivity reactions within 12 months, including angioedema and anaphylaxis. **Effect Measure**: Cumulative incidence
- Study Design/Type

Retrospective cohort study using a prevalent new user design with sequential nested trial emulations, implemented separately in two databases using a harmonized protocol, with database-specific results combined through meta-analysis.

- Study Population or Data Resource

This study will be conducted in multiple real-world data sources, including the Optum Market Clarity database and the Komodo Healthcare Map. Only closed claims will be used for this study; the one potential use of open claims would be to define a broader population of avacopan users for assessment of safety events. The study period (including all time used to assess pre-index variables and follow-up for all members of the cohort) will be from October 1, 2015, to the latest available date. The indexing period (used to define potential index dates) will be October 1, 2021, to 3 months prior to the latest available date.

The study will be implemented using a common protocol and harmonized analytic approach across databases. Database-specific estimates of effectiveness and safety outcomes will be generated independently and subsequently combined using meta-analytic methods to obtain overall effect estimates.

- Index date

Patients with AAV will be aligned on their disease date, defined as the date during the identification period (October 1, 2021, to 3 months before end of data) when they meet criteria for a new AAV diagnosis or relapse. Sequential nested trials will be emulated every 14 days starting from the disease date for new or relapsing GPA/MPA. Within each trial, index dates will be defined as:

1. Date of first avacopan claim (avacopan + SOC arm)
2. Two methods of defining the index date in the SOC arm will be considered:
    a. Earliest date of a claim for CYC or RTX during the trial window
    b. Earliest date of (1) claim for CYC or RTX, or (2) an encounter (inpatient or outpatient) with a provider whose specialty is nephrology or rheumatology during the trial window

Standard of care medications are often used to define the index date in the comparator arm in prevalent new user designs (see e.g., Simms-Williams et al., 2024). However, because rituximab is expected to be administered more frequently early in the disease course and less frequently later on, it is possible that only allowing SOC arm individuals to index on RTX or CYC claims would lead to SOC index dates that are earlier in the disease course compared to avacopan arm index dates. For this reason, we also consider allowing SOC arm individuals to have an index date based on an encounter with a Nephrologist or Rheumatologist. Indexing on healthcare visits is also a common approach in sequential trial emulations because these visits represent a decision point at which a provider could decide to add on a medication (see e.g., Brookhart et al., 2024). We will choose between the two SOC arm indexing approaches based on unweighted and weighted baseline characteristics, propensity score distributions and weights, and potentially negative control outcome analyses prior to running any analyses of the primary or secondary endpoints. The final SOC indexing approach will be specified in the SAP.

Because patients in both arms are required to have initiated RTX and/or CYC prior to or on the index date, this preserves the label indication of avacopan as add-on therapy to SOC

- Summary of Patient Eligibility Criteria

Inclusion Criteria

- New or relapsing GPA/MPA within 125 days prior to index date
- Age ≥ 18 years on index date

- ≥ 1 claim for RTX within 90 days and/or 1 claim for CYC within 45 days prior to or on the index date
- At least 12 months of continuous pre-index enrollment, with no more than a 30-day gap
- At least one day of follow-up time

Exclusion Criteria:

Patients are excluded if they have evidence of

- Pre-index avacopan use
- Pre-index diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA)
- Pre-index use of mepolizumab or benralizumab

For the endpoints of hepatotoxicity/DILI and serious hypersensitivity reactions, we will also provide a clinical narrative review for any patient age ≥18 years who has the safety event within 1 year of their first recorded claim for avacopan among all patients with avacopan claims in the closed claims datasets, without applying other study eligibility criteria. Clinical narratives will also be created for patients with either acute/subacute hepatic necrosis or at least one additional SALI diagnosis code from the prespecified code list. The purpose of this expanded population is to better characterize the real-world safety of avacopan across a broader patient population.

- Follow-up

Patients will be followed from the day after the index date to disenrollment, end of administrative follow-up, the outcome (including death), or 12 months. Patients in the SOC arm will be censored at the time of first avacopan claim if they initiate avacopan within 30 days after their index date, consistent with the modified intention-to-treat estimand described in Table 1.

- Variables

Appendix C of the SAP lists the concept set IDs associated with the diagnosis, procedure, and pharmacy codes for the variables below.

  - *Outcome Variables*

    Primary outcomes

    - Time to first relapse
    - Incidence of Major Adverse Kidney Events (MAKE) within 12 months (composite endpoint of mortality, dialysis, kidney transplant, end-stage kidney disease [ESKD])
    - 30-day average prednisone-equivalent daily dose (PEDD) ≤ 7.5mg at 90, 120, 180, 270, and 365 days post-index

    Secondary outcomes

  - Incidence of glucocorticoid-related events within 12 months (composite of serious infection requiring hospitalization; initiation of a new class of anti-hyperglycemic medication; major osteoporotic fractures [vertebra, pelvis, humerus, radius/ulna, hip, other femur])
  - Relapse within 12 months
  - Incidence of MAKE components within 12 months (mortality, dialysis, kidney transplant, ESKD)
  - Incidence within 12 months of hepatotoxicity and drug-induced liver injury, and serious hypersensitivity reactions, including angioedema and anaphylaxis
- Negative control outcomes
  - Incidence of influenza vaccination within 12 months
  - Incidence of preventive screening (mammography or prostate cancer) within 12 months
  - Incidence of wellness visit within 12 months
- *Exposure Variable(s)*
  - Avacopan: identified through claims for pharmacy codes
  - Rituximab: identified through claims for pharmacy and procedure codes
  - Cyclophosphamide: identified through claims for pharmacy and procedure codes
- *Other Covariate(s)*
  - We will assess the following domains during the baseline period: patient demographics and access to care; newly diagnosed vs relapsing status and prior disease course; disease severity and organ involvement (lack of BVAS); induction regimen and concomitant medications; GC exposure and history of related complications; comorbidities; liver disease; healthcare resource utilization.
  - Table 2 in Covariate Assessment lists the specific covariates. We will apply a 1 IP / 2 OP algorithm to diagnosis codes and a 1 IP / 1 OP algorithm to procedure codes within a concept set. The 2 OP codes must be within 30-365 days apart. Any deviations from these rules for specific variables are specified in the SAP.

- Data sources

This analysis will use two administrative claims-based real-world data sources: the Optum Market Clarity database and the Komodo Healthcare Map. Only closed claims will be used for this study; the one potential use of open claims would be to define a broader population of avacopan users for assessment of safety events. The study will be implemented separately in each database using harmonized definitions of eligibility, exposure, outcomes, covariates, and analytic methods. Database-specific estimates will be generated independently and subsequently synthesized using meta-analytic methods.

The study period (including all time used to assess pre-index variables and follow-up for all members of the cohort) will be from October 1, 2015, to the latest available date. The indexing period (used to define potential index dates) will be October 1, 2021, to 3 months prior to the latest available date.

- Study Sample Size

A recent internal Amgen analysis of the Optum Market Clarity database identified over 16,000 patients with newly diagnosed or relapsing AAV. Among these patients, approximately 430 were prescribed avacopan within 120 days of their new or relapsing disease, of whom roughly 200 met inclusion criteria for the current study. We expect approximately 2,500 patients on SOC to meet study inclusion criteria. The sample size may likely change after additionally requiring recency of RTX/CYC exposure prior to indexing. A similar estimate of the Komodo Healthcare Map provided by Komodo yielded approximately 260 patients with newly diagnosed AAV who were prescribed avacopan and met study inclusion criteria. Assuming a similar distribution of newly diagnosed (69.4%) and relapsing patients (31.6%) as observed in the Optum analysis (which are broadly consistent with findings from an EHR-based study [Patel et al, 2025] reporting 66.4% newly diagnosed and 33.6% relapsing disease), this corresponds to an estimated total of approximately 375–390 eligible patients prescribed avacopan in the Komodo dataset. Given the expected sample size available from each database, the comparative analysis may yield imprecise effect estimates and should therefore be interpreted primarily as directional. However, the probability of reporting a qualitatively incorrect effect direction (eg, estimating a hazard ratio greater than 1 when the true hazard ratio is less than 1) was calculated to be low, supporting the use of the analysis for directional interpretation.

- Data Analysis

Demographic and baseline characteristics will be summarized by exposure cohort within each database. If, after applying standardized mortality ratio weights, the two groups are deemed comparable, formal comparative analyses will be undertaken separately within each database to estimate the risk difference, risk ratio, or hazard ratio and corresponding 95% confidence intervals. Standardized mortality ratio weights will be used to account for baseline confounding. Inverse probability of censoring weights will be used to account for informative censoring. Database-specific estimates will then be combined using meta-analytic methods to obtain pooled estimates.

Note that for all analyses, 95% confidence intervals will be estimated based on the 2.5th and 97.5th percentiles of an individual-level Bayesian bootstrap distribution of the target parameter with Dirichlet weights (α=1).

Characteristics of patients between exposure groups will be compared individually via standardized mean differences, both before and after propensity score weighting. Histograms showing overlap of the propensity scores will also be examined. In the presence of extreme weights and/or poor overlap, the following strategies may be taken. First, the characteristics of patients with extreme weights may be examined to determine the reasons for the near-violation of the positivity assumption. The target population may need to be modified to only include patients who may realistically receive either intervention in the real world. Additional terms, such as non-linear terms or interaction terms, may be added to the propensity score models to improve balance of baseline characteristics in the weighted populations. Any trimming of weights, other modifications to the target population, or modifications to the propensity score models will be done prior to any treatment arm-specific evaluation of outcomes. If treatment cohorts are deemed comparable and residual bias is likely small enough to proceed, modified intention-to-treat estimands comparing the avacopan + SOC and SOC-only arms will be estimated as risk ratios or hazard ratios, depending on the outcome. Standardized mortality ratio weights will be used to account for confounding.

5. Amendments and Updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	07Apr2026	Summary Table of Study Protocol; Sections 4, 6.4, 7.1, 8.1, 8.3.2, 8.7.2; Table 1	Promoted PEDD ≤ 7.5 mg from secondary to primary endpoint/objective	Elevate glucocorticoid-sparing effectiveness as a primary study objective
		Summary Table of Study Protocol; Sections 4, 6.4, 7.2, 8.3.2, 8.7.2	Reclassified hepatotoxicity/DILI and serious hypersensitivity reactions as secondary endpoints and described broader cohort of avacopan patients for clinical narrative review of these endpoints	Align safety endpoint classification with the amended analysis framework and better characterize real-world safety of avacopan across broader patient population

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
		Summary Table of Study Protocol, Sections 4, 6.3, 8.1, 8.4, 8.5, 8.7, 8.9.2	Updated study design to specify implementation in Optum Market Clarity and Komodo Healthcare Map, with database-specific analyses and meta-analysis of results	Enhance robustness and generalizability of study findings
		Sections 4, 8.2, 8.2.6, 8.3.1, 8.3.3, 8.7.2; Table 1	Updated index date, follow-up, and estimand language, including comparator indexing options, ≥1 day follow-up, 30-day censoring for SOC patients initiating avacopan, and modified ITT framing	Improve time alignment and better reflect real-world treatment initiation patterns
		Sections 4, 6.3, 8.5, 8.7, 8.9, 10.1	Updated feasibility, analysis, limitations, and safety reporting language for the amended multi-database design	Align interpretation, reporting, and study operations with revised methodology
		Sections 4, 8.7.2, 8.7.2.5.3	Updated NCOs by adding influenza vaccination and wellness visits, plus removing acute appendicitis and unintentional injuries	Informed by event rates from feasibility analyses in the SOC cohort
		Sections 8.4, 8.7.2, 8.9, 9.1	Added language on potential patient overlap across databases and evaluation of de-duplication methods	Address potential duplicate patients across databases and impact on pooled analyses
		Throughout	Administrative changes	Corrected typographical errors, punctuation, grammar, and abbreviations.

6. Rationale and Background

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a heterogeneous group of rare systemic autoimmune conditions characterized by necrotizing inflammation of small- 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 glucocorticoids (GC) and other immunosuppressive medications as part of a strategy to induce remission (Chung et al. 2021, KDIGO 2024, Turgeon 2022). 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 (eg neuropathy), and neurologic deficits (eg 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 (eg COVID-19), and atypical chronic lung infections.

Avacopan (brand, TAVNEOS®) is a complement 5a receptor (C5aR1) 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 (n=166) had a significantly higher percentage (66%) of sustained remission of symptoms at week 52 when compared to an active control group (55%) with a prednisone taper, 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 adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (GPA and MPA) in combination with standard therapy including glucocorticoids (GC). Over 80% of patients enrolled in ADVOCATE had renal involvement whereas manifestations in the ear, nose, and throat, chest, and other sites were less common (~43% each).

Avacopan was developed by ChemoCentryx, Inc. and acquired by Amgen in October 2022. On January 16, 2026, the FDA requested that ChemoCentryx voluntarily withdraw TAVNEOS from the U.S. market. The FDA raised concerns about the process followed by ChemoCentryx to re-adjudicate primary endpoint results for 9 of the 331 patients in the ADVOCATE trial. Hepatotoxicity, which is a known infrequent risk of avacopan treatment for AAV, was also raised in the context of the benefit-risk profile of the medicine. Amgen is not aware of any issues with the underlying patient data and after

review of the relevant clinical data and years of real-world evidence, Amgen is confident that avacopan demonstrates effectiveness and a favorable benefit-risk profile.

To further add to the avacopan real-world evidence package being developed, this study will estimate the real-world comparative effectiveness of avacopan + SOC versus SOC alone among adults with new or relapsing AAV. The incidence of safety events of special interest will also be assessed (hepatotoxicity and drug-induced liver injury, and serious hypersensitivity reactions, including angioedema and anaphylaxis).

6.1 Diseases and Therapeutic Area

ANCA-associated vasculitis (AAV) is a rare, systemic small- to medium-vessel vasculitis most commonly presenting as granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA). Despite modern immunosuppressive induction and maintenance strategies, relapse remains common, and AAV is associated with substantial morbidity including progression to end-stage kidney disease (ESKD) and an increased risk of death compared with the general population.

Standard of care (SOC) for severe, active GPA/MPA typically includes induction therapy with rituximab (RTX) or cyclophosphamide (CYC) in combination with glucocorticoids (GCs), followed by maintenance therapy. Glucocorticoid exposure contributes to short- and long-term toxicity (eg infections, metabolic effects, fracture risk).

TAVNEOS (avacopan) is approved as an add-on therapy used in combination with standard therapy including glucocorticoids; it is not intended to fully eliminate glucocorticoid use.

6.2 Rationale

Randomized clinical trial evidence (eg, ADVOCATE) demonstrated that avacopan-based regimens, administered with RTX or CYC and a reduced prednisone taper, achieved clinically meaningful outcomes including sustained remission and reduced glucocorticoid exposure.

However, questions remain regarding real-world effectiveness and safety when avacopan is used in routine clinical practice, where patient characteristics (eg, baseline renal function, comorbidity burden, prior disease course) and treatment pathways (eg, timing of avacopan initiation as add-on therapy) may differ from clinical trials. Because avacopan may be initiated after or during SOC induction, valid real-world comparisons must address confounding by indication/disease severity and must align “time zero” to avoid immortal time bias.

This comparative effectiveness and descriptive safety study ("LIBRA") is intended to estimate the real-world effectiveness and safety of avacopan + SOC vs SOC among adults with newly diagnosed or relapsing GPA/MPA using a principled, staged observational approach with prespecified checkpoints ("gates").

6.3 Feasibility and Futility Considerations

The study team evaluated the use of avacopan, RTX, and CYC among patients with AAV in two large real-world data sets to assess sample size. Examination of the MarketScan Commercial and Medicare database identified 95 patients with AAV who were prescribed avacopan and had ≥ 12 months of baseline enrolment, regardless of incident or relapsing AAV status. An additional 2,792 patients prescribed SOC since 2015 were identified. In contrast, an analysis of the Optum Market Clarity database identified over 16,000 patients with newly diagnosed or relapsing AAV. Among these patients, approximately 430 were prescribed avacopan within 120 days of their new or relapsing disease, of whom roughly 200 met inclusion criteria for the current study. We expect approximately 2,500 patients on SOC to meet study inclusion criteria. The sample size may likely change after additionally requiring recency of RTX/CYC exposure prior to indexing. A similar estimate of the Komodo Healthcare Map provided by Komodo yielded approximately 260 patients with newly diagnosed AAV who were prescribed avacopan and met study inclusion criteria. Assuming a similar distribution of newly diagnosed (69.4%) and relapsing patients (31.6%) as observed in the Optum analysis (which are broadly consistent with findings from an EHR-based study [Patel et al, 2025] reporting 66.4% newly diagnosed and 33.6% relapsing disease), this corresponds to an estimated total of approximately 375–390 eligible patients prescribed avacopan in the Komodo dataset.

Given the expected sample size available from each database, comparative analyses may yield imprecise effect estimates and will therefore be interpreted primarily with respect to the direction of effect. To assess whether the analysis provides a meaningful directional signal, the probability of a directionally discordant (flipped) estimate (eg, estimating a hazard ratio greater than 1 when the true hazard ratio is less than 1) was evaluated. This probability was estimated to be low, supporting the use of the analysis for directional interpretation.

The LIBRA study will use a structured and staged approach to cohort comparability assessment (Muntner et al. 2024). This will include evaluation of sample size, follow-up time, and anticipated statistical precision. Given that AAV is a rare disease and event

counts may be limited, statistical precision will be carefully considered in interpretation. After cohort construction, treatment group comparability will be assessed using propensity score–based methods to balance measured baseline characteristics between avacopan + SOC and SOC-only cohorts. Diagnostics will evaluate covariate balance, overlap between treatment groups, and stability of weighting procedures. If adequate balance cannot be achieved, refinement of eligibility criteria or analytic specifications may be undertaken. If meaningful comparability remains unattainable despite reasonable modifications, limitations will be transparently reported and considered in interpretation.

To further evaluate the potential for residual confounding, negative control outcome (NCO) analyses will be conducted. Findings from these analyses will be used to inform interpretation of the primary comparative effectiveness results. The study will proceed with the comparative analyses regardless of the negative control findings. However, if negative controls suggest systematic deviation from the null that is unlikely to be explained by random variation alone and that could meaningfully influence interpretation of the primary treatment effect estimates, additional model refinement, alternative confounding adjustment approaches, or quantitative bias summaries (eg E-values for key associations) may be considered. The magnitude and direction of negative control associations will be incorporated into the interpretation of treatment effect estimates.

6.4 Statistical Inference (Estimation or Hypothesis[es])

This study is designed to estimate the comparative effectiveness of avacopan + SOC vs SOC on relapse and clinically meaningful hard outcomes (eg, death, dialysis, ESKD), and to characterize safety outcomes of interest. Effect measures are reported as risk ratios (RRs) for endpoints assessed as cumulative incidence over the prespecified assessment window. Time to first relapse is a time-to-event endpoint subject to censoring; therefore, the treatment effect is summarized using a hazard ratio (HR) from a Cox proportional hazards model (with corresponding confidence interval and p-value), consistent with standard survival analysis practice.

Primary endpoints:

- **Endpoint**: Time to first relapse. **Effect Measure**: Hazard ratio
- **Endpoint**: Incidence of MAKE within 12 months. **Effect Measure**: Risk ratio (ratio of cumulative risks) and risk difference
- **Endpoint**: 30-day average PEDD $\leq$ 7.5mg by 90, 120, 180, 270, 365 days. **Effect Measure**: Risk ratio (ratio of proportions) and risk difference

Secondary endpoints:

- **Endpoint:** Incidence of GC-related events (composite endpoint) within 12 months. **Effect Measure:** Risk ratio (ratio of cumulative risks) and risk difference
- **Endpoint**: Incidence of relapse within 12 months. **Effect Measure**: Risk ratio (ratio of cumulative risks) and risk difference
- **Endpoints**: Incidence of MAKE components within 12 months (separate analyses for mortality, dialysis, kidney transplant, and ESKD). **Effect Measure**: Risk ratio (ratio of cumulative risks) and risk difference
- **Endpoint**: Incidence of hepatotoxicity and drug-induced liver injury within 12 months. **Effect Measure**: Cumulative incidence
- **Endpoint**: Incidence of serious hypersensitivity reactions within 12 months, including angioedema and anaphylaxis. **Effect Measure**: Cumulative incidence

All estimates will be accompanied by 95% confidence intervals. Statistical testing (eg, p-values) will not be emphasized; interpretation will focus on effect size, precision, and robustness across sensitivity analyses.

7. Research Question and Objectives

7.1 Primary Objectives

1. To estimate the real-world comparative effectiveness of avacopan + SOC vs SOC in adults with newly diagnosed or relapsing GPA/MPA on the hazard for first relapse.
2. To estimate the real-world comparative effectiveness of avacopan + SOC vs SOC on the cumulative risk of a composite outcome of death, dialysis, kidney transplant, or ESKD through 12 months of follow-up.
3. To estimate the real-world comparative effectiveness of avacopan + SOC vs SOC on the proportion of patients reaching a 30-day average PEDD ≤ 7.5mg by 90, 120, 180, 270, 365 days.

7.2 Secondary Objective

To estimate comparative effectiveness of avacopan + SOC vs SOC on the following secondary outcomes through 12 months:

- Mortality within 12 months
- ESKD incidence within 12 months
- Dialysis incidence within 12 months
- Relapse within 12 months
- Incidence of GC-related events within 12 months (composite outcome composed of serious infection requiring hospitalization, major osteoporotic fractures [vertebra, pelvis, humerus, radius/ulna, hip, other femur], and initiation of a new class of anti-hyperglycemic medication)

To estimate the incidence of real-world safety outcomes among adults with AAV treated with avacopan + SOC and among adults with AAV treated with SOC alone.

- Incidence of hepatotoxicity and drug-induced liver injury within 12 months
- Incidence of serious hypersensitivity reactions, including angioedema and anaphylaxis within 12 months

8. Research Methods

8.1 Study Design

This is a retrospective observational comparative effectiveness study of avacopan + SOC vs SOC among adults with newly diagnosed or relapsing GPA/MPA. The study will be conducted across multiple real-world data sources using a common protocol, harmonized operational definitions, and the same analytic framework. In each database, a prevalent new user design with sequential nested trials will be used to emulate a "target trial" framework and to mitigate confounding and time-alignment biases. Database-specific analyses will be performed independently, and the resulting effect estimates will subsequently be combined using meta-analytic techniques to generate pooled overall estimates. Details of the target trial emulation are provided in Table 1.

Sequential nested trials will be emulated every 14 days starting from each patient's disease date (new or relapsing GPA/MPA). Within each trial, eligible patients will contribute an index date if they meet eligibility criteria. Database-specific analyses will be conducted independently, and results will be combined using meta-analytic techniques to generate pooled estimates of treatment effects.

Table 1. Modified ITT Estimands for Comparative Effectiveness and Safety

Target Trial Protocol Component (Hernán and Robins, 2016)	**Target Trial Specification**	**Target Trial Emulation**
Eligibility Criteria	• New or relapsing GPA/MPA within the past 125 days • Age ≥ 18 years • Recent RTX (within 90 days) and/or CYC (within 45 days) • No prior avacopan use	• Patients meeting the criteria for new or relapsing GPA/MPA within 125 days prior to the index date using the specified claims-based algorithms • Age ≥ 18 years at index • ≥ 1 claim for RTX within 90 days and/or CYC within 45 days prior to or on the index date

	• No prior diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) • No prior use of mepolizumab or benralizumab The target population is the population represented by the avacopan-treated (treatment effect in the treated).	• No filled prescriptions for avacopan prior to the index date, using all lookback • No diagnosis of EGPA, in the lookback period • No filled prescriptions for mepolizumab or benralizumab, in the lookback period • 1 year of continuous medical and pharmacy enrollment prior to the index date with ≤30-day gap • At least 1 day of follow-up time The target population is the population represented by the avacopan-treated (treatment effect in the treated).
Treatment Strategies	Among the eligible patients who are receiving standard of care: 1. Initiate avacopan at time zero. 2. Do not initiate avacopan at time zero or for 30 days after time zero.	Among the eligible patients who meet the claims-based criteria for receiving standard of care: 1. Fill one prescription for avacopan on the index date. 2. Do not fill a prescription for avacopan on the index date or for 30 days after the index date.
Assignment Procedures	Randomization	Pseudo-randomization mimicked using standardized mortality ratio (SMR) weights to balance measured confounders at baseline.
Follow-up Period	Randomization to loss to follow-up, the outcome (including death), 12 months.	The day after the index date to disenrollment, end of administrative follow-up, the outcome (including death), or 12 months. Index date: Sequential nested trials will be emulated every 14 days starting from the disease date for new or relapsing GPA/MPA. Within each trial, index dates will be defined as: • Avacopan arm: Prescription fill date for avacopan • SOC arm: Two methods of defining the SOC index date will be considered. The final method will be chosen based on unweighted and weighted balance of baseline covariates,

		propensity scores, and potentially NCO results prior to running any outcomes analyses and will be noted in a future version of the SAP. o Method 1: The first date of either a claim for rituximab, a claim for cyclophosphamide, or an encounter with a Nephrologist or Rheumatologist in the interval o Method 2: The first date of either a claim for rituximab or a claim for cyclophosphamide in the interval

Outcomes	Primary endpoints:
	• Time to first relapse
	• Incidence of Major Adverse Kidney Events (MAKE) within 12 months (composite endpoint of mortality, dialysis, kidney transplant, ESKD)
	• 30-day average PEDD ≤ 7.5mg at 90, 120, 180, 270, and 365 days
	
	Secondary endpoints:
	• Relapse within 12 months
	• Incidence of MAKE components within 12 months
	  • Mortality
	  • Dialysis
	  • Kidney transplant
	  • ESKD
	• Incidence of GC-related events within 12 months (composite of serious infection requiring hospitalization; initiation of a new class of anti-hyperglycemic medication; major osteoporotic fractures [vertebra, pelvis, humerus, radius/ulna, hip, other femur])
	• Hepatotoxicity and drug-induced liver injury
		Same as in target trial, as captured in claims data. See SAP.

	• Serious hypersensitivity reactions, including angioedema and anaphylaxis	
Causal Contrasts	Effects will be summarized as cumulative risk by arm, proportion by arm, risk ratios, risk differences, or hazard ratios, as appropriate for the outcome. We estimate treatment effects in the treated (avacopan initiators).	Effects will be summarized as cumulative risk by arm, proportion by arm, risk ratios, risk differences, or hazard ratios, as appropriate for the outcome. We estimate treatment effects in the treated (avacopan initiators).

8.2 Setting and Study Population

8.2.1 Study Period

The study period (used for any variable assessment) will be from October 1, 2015 to the latest available date in each database. The indexing period will be October 1, 2021 (the start of availability of avacopan), to 3 months prior to the latest available date

8.2.2 Selection and Number of Sites

Not applicable. This is a secondary data study using administrative claims data; no study sites will be recruited.

8.2.3 Participant/Patient/Healthcare Professional Eligibility

8.2.3.1 Inclusion Criteria

- Adults aged ≥ 18 years with evidence of a new or relapsing granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) episode within 125 days prior to index.
- Recent use of RTX and/or CYC (RTX claim within 90 days and/or CYC claim within 45 days) prior to or on the index date.
- Continuous medical and pharmacy enrollment for ≥12 months prior to index (allowing ≤ 30-day enrollment gap) and at least one day of follow-up.

8.2.3.2 Exclusion Criteria

- Prior avacopan use before the index date; prior diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA); or prior use of mepolizumab or benralizumab.

8.2.4 Matching

Matching is not planned as the primary approach. The primary adjustment strategy will be propensity score-based weighting.

8.2.5 Baseline Period

Baseline covariates will be measured during the 12-month period prior to the index date/time zero and on the index date, unless otherwise specified (eg, disease-severity proxies measured in proximity to the anchoring event).

8.2.6 Study Follow-up

Follow-up will extend through 12 months after time zero. A 12-month follow-up period was selected in part because major AAV induction trials have assessed remission durability within the first year, and available trial data show that loss of remission occurs during this interval. In the RAVE follow-up, remission rates declined between 6 and 12 months in both treatment groups (rituximab or cyclophosphamide), supporting the use of 12 months as a clinically relevant timeframe to evaluate early relapse-related outcomes (Specks et al. 2013).

Censoring will occur at the time of disenrollment, end of administrative follow-up, or 12 months. Because the treatment strategies of the target trial require that patients in the SOC arm do not initiate avacopan for 30 days after index, patients in the SOC arm will be censored if they fill a claim for avacopan within 30 days after index. For many of these patients whose first claim for avacopan is shortly after index, the intention may have been to treat with avacopan at the time of index. The modified ITT estimand described in Table 1 aims to account for this delay between the timing of the intention to treat and the treatment claim, itself.

8.3 Variables

8.3.1 Exposure Assessment

Treatment strategies:

- **Avacopan** + **SOC**: initiation of avacopan in combination with SOC induction regimen (RTX or CYC).
- **SOC**: SOC induction regimen (RTX or CYC) without avacopan for at least 30 days.

Exposure will be identified using pharmacy and medical claims (NDC for avacopan; HCPCS/CPT/procedure claims for rituximab and cyclophosphamide). For avacopan, pharmacy days' supply will be used to construct continuous exposure allowing stockpiling (overlapping fills extend coverage). Avacopan discontinuation will be defined as the end of the first observed 90-day gap after the end of days' supply (stockpiling allowed). For rituximab/cyclophosphamide, exposure will be assessed using

infusion/procedure claims and pharmacy codes (NDC) and will be used to define SOC induction at/around the index date.

8.3.2 Outcome Assessment

Primary endpoint #1: Time to first relapse

Relapse will be defined using a prespecified claims algorithm intended to capture clinically meaningful relapse events among patients diagnosed with AAV while minimizing misclassification. To reduce false positives from new-onset disease, the first possible relapse must occur at least 45 days after the medication associated with new AAV diagnosis and at least 90 days after a GPA/MPA/AAV code. The relapse algorithm includes:

- A prednisone claim corresponding to ≥20 mg/day for >14 days, met by a single claim (not multiple fills combined).
- Prednisone claim start date within ±30 days of a qualifying ICD-10 code for GPA (M31.30, M31.31), MPA (M31.7), AAV (I77.82), or a major AAV relapse-associated manifestation in inpatient or outpatient settings.
- Manifestation codes to include: alveolar hemorrhage, respiratory failure, renal failure, scleritis, retinal exudates/hemorrhage, gangrene, sensorineural deafness, mesenteric ischemia, meningitis, cord lesion, stroke, cranial nerve palsy, sensory neuropathy, mononeuritis multiplex.
- Relapse event date = the qualified AAV diagnosis or relapse-related manifestation claim date.
- To define distinct relapse events, the next eligible relapse must occur at least 45 days after the most recent qualifying relapse-related claim date.

Primary endpoint #2: Major Adverse Kidney Events (MAKE) within 12 months

MAKE will be defined as a composite of all-cause mortality, dialysis, kidney transplant, or end-stage kidney disease (ESKD) through 12 months after index.

- MAKE component definitions will be prespecified and implemented using claims-based algorithms (see SAP for full code lists and operational rules). Briefly: (1) Death will be identified using the database death flag; because Market Clarity provides month and year (not day) of death, the death date will be assigned as the last day of the month. (2) ESKD will be defined by an ESKD diagnosis code together with a dialysis code within 7 days (event date = later of the two codes) or by evidence of kidney transplant. (3) Dialysis initiation will be defined by the presence of chronic dialysis, operationalized as at least 2 dialysis procedure codes at least 30 days apart (event date = the later of the two codes). (4) Kidney transplant will be defined by a kidney transplant procedure code indicating transplant.

Primary endpoint #3: Proportion reaching 30-day average PEDD ≤ 7.5 at prespecified landmark times.

Glucocorticoids will be converted to prednisone dose equivalents, accounting for the different available strengths of products as specified in the SAP.

Secondary endpoints (summarized; operational detail in SAP):

- Incidence of relapse within 12 months.
- Incidence of MAKE components within 12 months: mortality, dialysis, kidney transplant, and ESKD.
- Incidence of glucocorticoid-related events within 12 months: composite of serious infection requiring hospitalization, initiation of a new class of anti-hyperglycemic medication, and major osteoporotic fractures (vertebra, pelvis, humerus, radius/ulna, hip, other femur).
- Incidence of hepatotoxicity and drug-induced liver injury within 12 months (safety endpoint).
    - Hepatotoxicity/DILI will be defined as an inpatient severe acute liver injury (SALI) event identified using a high-specificity claims algorithm (inpatient encounter with diagnosis codes for acute and subacute hepatic necrosis and at least one additional SALI diagnosis code from the prespecified code list). The event date will be the admission/claim date of the qualifying inpatient encounter (see SAP for full operational details).
- Incidence of serious hypersensitivity reactions, including angioedema and anaphylaxis within 12 months (safety endpoint).

For each safety endpoint, we will estimate the cumulative incidence within 12 months after the index date using baseline propensity score SMR weights (no IPC weights), separately for each arm. IPC weights will not be used in the estimation of the safety endpoints based on the safety profile of avacopan from ADVOCATE and a growing body of real-world studies, which indicate that the number of incident safety events to be observed in this study is expected to be low.

A detailed claims-based profile review will also be provided summarizing relevant characteristics (eg age, sex, disease characteristics, concomitant medications, comorbidities, and other relevant risk factors) for each patient with a hepatotoxicity/drug induced liver injury and/or serious hypersensitivity reaction event. The review will also describe specific event details, including:

- The timing of the event
- The exact codes associated with the event
- And if the patient was in the avacopan arm:
    - Duration of avacopan use at time of event
    - Whether event occurred while patient was on avacopan or time since stopping avacopan

Outcome code lists, diagnosis-position requirements, washout rules, and (where available) validated claims algorithms will be prespecified in the SAP. Emphasis will be placed on definitions with demonstrated or face-valid high PPV (eg, inpatient primary-position algorithms) to minimize misclassification.

8.3.3 Covariate Assessment

Measured confounders will be derived primarily from the 12-month baseline period and, where applicable, from defined time windows around the disease date and prior to or including the index date to better capture episode severity and treatment trajectory. The following domains will be captured, and their inclusion as baseline covariates is summarized in Table 2 below.

- Patient demographics and access to care
- Newly diagnosed vs relapsing disease status and prior disease course
- Organ involvement (noting lack of BVAS in claims)
- Induction regimen and concomitant medications
- Glucocorticoid exposure and history of related complications
- Comorbidities
- Healthcare resource utilization

Table 2. Baseline Covariates

Variable
Patient demographic
Age, Age group (18-34, 35-44, 45-54, 55-64, 65-74,>=75)
Sex (male, female)
Race
Insurance type
Comorbidities burden
Charlson comorbidity index
Metabolic disease
Type 2 diabetes mellitus
Hyperlipidemia/Dyslipidemia
Obesity
Hypertension
Cardiovascular disease
Peripheral vascular disease
Acute myocardial infarction
Congestive heart failure

Venous thromboembolism
Ischemic stroke
Hemorrhagic stroke
Transient ischemic attack
Pulmonary involvement
Diffuse alveolar hemorrhage
Interstitial lung fibrosis
Bronchiectasis
Chronic sinusitis
Other chest condition (BVAS component)
Renal involvement (BVAS component)
Glomerulonephritis
Proteinuria
Hematuria
CKD
AKI (acute kidney injury)
Dialysis, categorized as: • Never: no procedure codes in baseline period, • Chronic: ≥ 1 procedure code from 365 to 61 days prior to index and ≥ 1 procedure code from 60 days prior to or including the index, • Remote: ≥ 1 procedure code from 365 to 61 days prior to index but no procedure codes from 60 days prior to or including the index, • New: No procedure codes from 365 to 61 days prior to index and ≥1 procedure code from 60 days prior to or including the index
Kidney transplant
Other autoimmune disease
Rheumatoid arthritis
Inflammatory bowel disease
Sjögren's syndrome
Systemic lupus erythematosus
Other
Malignancy
Liver disease
ENT (BVAS component)
Arthralgia (BVAS component)
Serious infection
Osteoporosis
Plasma exchange
Diffuse alveolar hemorrhage
Medication use / Other Treatment
Average PEDD in 60 days prior to index and the index date

Pulse dose steroids (>125 mg IV methylprednisolone in 1 day) in 60 days prior to index or on index
Pulse dose steroids (>125 mg IV methylprednisolone in 1 day) in 365 to 61 days prior to index
High dose oral steroids (prednisone equivalent > 20mg daily) in 60 days prior to index or on index
High dose oral steroids (prednisone equivalent > 20mg daily) in 365 to 61 days prior to index
Rituximab in 90 days prior to index or on index
Rituximab in 365 to 91 days prior to index
Cyclophosphamide in 45 days prior to index or on index
Cyclophosphamide in 365 to 46 days prior to index
RTX plus CYC (first claim for RTX on or after disease date within 30 days of CYC claim)
Methotrexate within 60 days prior to or on index
Methotrexate within 365 to 61 days prior to index
Azathioprine within 60 days prior to or on index
Azathioprine within 365 to 61 days prior to index
Mycophenolic acid within 60 days prior to or on index
Mycophenolic acid within 365 to 61 days prior to index
Mycophenolate mofetil within 60 days prior to or on index
Mycophenolate mofetil within 365 to 61 days prior to index
Plasma exchange
Health care resource utilization
IP admission for AAV
Number of OP visits
Number of IP visits
Number of ER visits
Disease status
New or relapsing AAV
Days from the disease date
Index year (2021, 2022, 2023, 2024, 2025)

We will specify in the SAP the final set of covariates to be included in the propensity score models once the final sample size is determined.

8.3.4 Validity and Reliability

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. While the BVAS is routinely collected in clinical trials to assess important endpoints, such as remission and relapse of disease, it is not available in claims data and rarely collected routinely in electronic health records.

A claims-based approach to identifying relapse was recently developed among patients diagnosed with AAV in the retrospective Mass General Brigham AAV registry who were linked to the Medicare fee for service claims database (submitted to EULAR 2026). This algorithm will be used to identify relapse events in the current study. The algorithm defines claims-based relapse as the occurrence of a prednisone claim ≥20 mg/day for >14 days within 30 days before or after of a qualifying (recorded ≥90 days prior to the claims-identified relapse) ICD-10 code, defined as a code for GPA (M31.30, M31.31), MPA (M31.7), AAV (I77.82) or a major AAV relapse-associated manifestation (SAP Appendix C). The algorithm's performance was assessed by using EHR-reviewed data from all identified claims-based relapses and a stratified random sample of claims-based non-relapse events (the observed set). Inverse probability weighting was applied to project Algorithm 2 performance metrics to the full population of claims-identified relapse and non-relapse events (observed and unobserved). This approach accounted for the true event distribution in the source population and for the oversampling of claims-based relapses in the observed set. In the observed set, the performance of Algorithm 2 demonstrated: sensitivity 91.9%, specificity 86.2%, PPV 69.4%, NPV 96.9%, and Cohen's kappa (κ) 0.7. Projected Algorithm 2 performance after applying inverse probability weighting demonstrated: sensitivity 44.3%, specificity 99.2%, NPV 97.7%, prevalence ratio 28.7 and κ=0.5.

8.4 Data Sources

This study will use multiple real-world data sources:

- Optum Market Clarity database: a linked dataset of electronic health records and administrative claims.
- Komodo Healthcare Map: a large-scale, longitudinal claims database capturing medical and pharmacy encounters across the United States.

Each database will be analyzed separately using a harmonized protocol with consistent definitions of exposures, outcomes, covariates, and analytic methods. Differences in data structure and coding systems across databases will be addressed through standardized variable definitions and database-specific implementation. Study periods and indexing periods will be aligned as closely as possible across databases based on data availability.

The Optum Market Clarity database (n ~197 million patients) links Optum EHR data with Optum and third-party medical and pharmacy claims data. Approximately 45% of Market Clarity patients have Commercial insurance coverage, 13% have Medicaid coverage, 12% have Medicare coverage, 15% have an unknown or other payor type, and 15% are uninsured. Compared to the US Census, Market Clarity patients are slightly older (patients 65+ years: 28% in Market Clarity vs 17% in the US Census).

The Komodo Healthcare Map database (n ~330+ million patients) links medical and pharmacy claims with select electronic health record and laboratory data. The database includes patients with Commercial, Medicare, and Medicaid coverage and integrates both open and closed claims, with broad representation of the U.S. insured population. Compared to traditional claims databases, the Healthcare Map provides more comprehensive population coverage and more frequent data refresh.

The LIBRA study will use the administrative claims component from the Optum and Komodo databases. The study objectives focus on healthcare utilization, treatment patterns, medication exposure, and coded clinical events, all of which are reliably captured using standardized diagnosis (ICD), procedure (CPT/HCPCS), and pharmacy (NDC) codes available in claims data. Pharmacy claims reflect medications dispensed and reimbursed, providing a more accurate measure of real-world treatment exposure than prescriptions ordered in electronic health records (EHR), which may not be filled. Additionally, claims enrollment files allow precise definition of continuous coverage and observable person-time, enabling clear specification of baseline and follow-up periods.

Because these are large US claims-based data assets, some patients may be represented in more than one source. As a result, overlap of the same underlying patients across databases could violate the assumption that database-specific estimates arise from fully distinct populations and could lead to overrepresentation of some individuals in pooled results. To address this, the study team will evaluate feasible approaches to identifying and reducing cross-database duplication. These approaches

may include privacy-preserving record linkage and de-duplication methods implemented directly by the data partners and/or through a qualified third-party linkage vendor (for example, Datavant or a similar vendor), subject to data availability, technical feasibility, contractual approvals, and privacy requirements. If de-duplication is not feasible or is only partially feasible, this limitation will be documented, and pooled estimates will be interpreted with appropriate caution.

8.5 Study Size

The study team evaluated the use of avacopan, RTX, and CYC among patients with AAV in two large real-world data sets to assess sample size. Examination of the MarketScan Commercial and Medicare database identified 95 patients with AAV who were prescribed avacopan and had ≥ 12 months of baseline enrolment, regardless of incident or relapsing AAV status. An additional 2,792 patients prescribed SOC since 2015 were identified. In contrast, an analysis of the Optum Market Clarity database identified over 16,000 patients with newly diagnosed or relapsing AAV. Among these patients, approximately 430 were prescribed avacopan within 120 days of their new or relapsing disease, of whom roughly 200 met inclusion criteria for the current study. We expect approximately 2,500 patients on SOC to meet study inclusion criteria. A similar estimate of the Komodo Healthcare Map provided by Komodo yielded approximately 260 patients with newly diagnosed AAV who were prescribed avacopan and met study inclusion criteria. Assuming a similar distribution of newly diagnosed (69.4%) and relapsing patients (31.6%) as observed in the Optum analysis (which are broadly consistent with findings from an EHR-based study [Patel et al, 2025] reporting 66.4% newly diagnosed and 33.6% relapsing disease), this corresponds to an estimated total of approximately 375–390 eligible patients prescribed avacopan in the Komodo dataset. The sample size may likely change after additionally requiring recency of RTX/CYC exposure prior to indexing. Given the expected sample size from each database, the comparative analysis may yield imprecise effect estimates and should therefore be interpreted primarily as directional. However, the probability of reporting a qualitatively incorrect effect direction (eg, estimating a hazard ratio greater than 1 when the true hazard ratio is less than 1) was calculated to be low, supporting the use of the analysis for directional interpretation.

Where sample size and event counts for some outcomes may lack sufficient precision, results may be presented as SMR-weighted cumulative risk with CIs. The number of incident safety events, for example, is expected to be low based on the safety profile of

avacopan from ADVOCATE and a growing body of real-world studies. Each safety endpoint will therefore be estimated by the cumulative risk within 12 months after the index date using baseline propensity score SMR weights (no IPC weights), separately for each arm.

8.6 Data Management

Not applicable

8.6.1 Obtaining Data Files

Not applicable

8.6.2 Linking Data Files

Not applicable

8.6.3 Review and Verification of Data Quality

The Market Clarity database is constructed through collection and standardization of raw data from the appropriate payers, and linking files across time and data type to create a comprehensive and efficient set of database tables. Variables specific to particular employers are added, as are details on clinical information such as therapeutic class, generic product identifier, therapeutic group, etc. Other enhancements are made to improve the data quality and efficiency; for example, updating diagnosis and procedure codes to reflect changes in codes over time if necessary; creating a common synthetic patient identifier that enables patients to be tracked over time and across data types; integrating benefit plan characteristics, enrollment, outpatient pharmaceutical claims, and medical/surgical data. A comprehensive series of edits on the reasonableness and validity of the data are conducted. For example, checking diagnosis against age and gender, charge against payment, and diagnosis and procedure codes against lists of valid values, etc. No data editing, beyond what is applied in the database production process, will be conducted for this study.

8.7 Data Analysis

8.7.1 Planned Analyses

Analyses will be conducted separately within Optum Market Clarity and Komodo Healthcare Map using the same prespecified analytic framework. Within each database, analyses will proceed in stages with prespecified checkpoints to (a) confirm comparability of treatment groups after weighting, and (b) review of results from negative control outcome analyses. Descriptive analyses will summarize baseline characteristics overall and by treatment group, including disease severity proxies and treatment

patterns. After completion of database-specific analyses, estimates from the two databases will be combined using meta-analytic methods.

8.7.1.1 Primary Analysis

The primary analysis, to be performed separately in each database, will describe baseline patient characteristics and estimate the risk of (1) relapse, (2) major adverse kidney events, (3) GC-related events, and (4) hepatotoxicity and drug-induced liver injury, and serious hypersensitivity reactions, including angioedema and anaphylaxis, among patients with AAV being treated with avacopan + SOC and among patients treated with SOC alone. If appropriate based on comparability analyses, additional comparative effectiveness analyses will separately compare the hazard or risk of relapse, major adverse kidney events, and GC-related events among patients with AAV being treated with avacopan + SOC and among patients treated with SOC alone. Database-specific comparative estimates will then be synthesized using meta-analytic methods to obtain pooled estimates for each endpoint.

8.7.2 Planned Method of Analysis

Primary analytical approach (effectiveness): sequential trial pooling with propensity score SMR weighting

- Pooled across all 14-day trials, a propensity score model will estimate the probability of initiating avacopan on the index date (avacopan + SOC) versus not initiating (SOC). Standardized mortality ratio (SMR) weights will be applied to reweight the SOC arm to the covariate distribution of avacopan initiators (treated population). Trials will be pooled to estimate overall effects.
- The primary estimand is a modified ITT estimand (see Table 1) with follow-up through 12 months (or administrative censoring).
- Covariate balance and positivity will be assessed using standardized mean differences (SMDs) and propensity score overlap diagnostics. Gatekeepers will make decisions about changes to the target population and/or propensity score models to improve balance based on these diagnostics and prior to running analyses of the outcomes. Detailed model specifications are provided in the SAP.

Primary endpoints

1. Time to first relapse: analyzed as time-to-event from index to first relapse through 12 months using weighted survival methods (weighted hazard ratio from a Cox model and weighted risk ratio accounting for right-censoring).
2. Incidence of MAKE within 12 months: analyzed as 12-month risk (risk ratio and risk difference).
3. PEDD outcomes: glucocorticoid exposure will be derived from pharmacy claims for oral glucocorticoids by converting doses to prednisone-equivalent daily dose (PEDD)

using prespecified conversion factors and day-level exposure construction rules (Appendix D; SAP). The primary PEDD summary is the 30-day average PEDD ≤ 7.5 mg at 90, 120, 180, 270, and 365 days after index.

Secondary endpoints

- Incidence of glucocorticoid-related events within 12 months (composite of serious infection requiring hospitalization; initiation of a new class of anti-hyperglycemic medication; major osteoporotic fractures [vertebra, pelvis, humerus, radius/ulna, hip, other femur])
- Relapse within 12 months: weighted cumulative risk and RR/RD at 12 months.
- Incidence of MAKE components within 12 months (separately: mortality, kidney transplant, dialysis, ESKD): weighted cumulative risk and RR/RD at 12 months.
- Incidence of hepatotoxicity and drug-induced liver injury within 12 months (safety endpoint)
- Incidence of serious hypersensitivity reactions, including angioedema and anaphylaxis within 12 months (safety endpoint)

For each safety endpoint, we will estimate the cumulative risk within 12 months after the index date using baseline propensity score SMR weights (no IPC weights), separately for each arm. IPC weights will not be used in the estimation of the safety endpoints based on the safety profile of avacopan from ADVOCATE and a growing body of real-world studies that the number of incident safety events is expected to be low.

Residual confounding diagnostics (planned):

Key threats include confounding by indication, imperfect measurement of disease activity, and time-alignment challenges due to avacopan add-on use. The study will mitigate these through (1) design choices that align time zero based on sequential nested target trial emulations, (2) inverse probability of treatment and censoring weighting to balance measured confounders and causes of informative censoring, and (3) residual bias diagnostics using negative control outcomes and quantitative bias analysis with E-values.

Negative control outcomes will be evaluated after PS model finalization to assess residual bias. The NCOs will consist of (1) preventive cancer screening mammography (women) or prostate cancer screening (men) (2) influenza vaccination, and (3) wellness visits.

All primary and secondary analyses will first be implemented independently within each database. Before generation of pooled estimates, the study team will assess the potential for cross-database patient overlap and determine whether de-duplication is feasible. If a feasible and acceptable de-duplication approach is available, pooled

analyses will use database-specific results derived from populations that have been made as mutually exclusive as possible across databases. If such an approach is unavailable, database-specific estimates will still be generated, but pooled meta-analytic estimates will be interpreted in light of potential cross-database duplication.

8.7.2.1 General Considerations

Effect estimates will be reported with 95% confidence intervals and interpreted based on magnitude, precision, and consistency across sensitivity analyses rather than statistical significance testing. Individual-level bootstrap confidence intervals will account for multiple index dates per patient. Results will be presented both by database and as pooled meta-analyzed estimates, where applicable. Interpretation will consider consistency of direction, magnitude, and precision across databases as well as the pooled estimate. Pooled estimates will be considered in the context of known or suspected patient overlap between databases and the degree to which overlap could affect precision or representativeness.

A major challenge in observational comparative analyses is the lack of exchangeability, with baseline characteristics that may be unbalanced between study groups and potential differential drop-out across the two arms of the study. Causal Studio is a tool designed to address exchangeability in observational studies. More specifically, the application allows for the estimation of the cumulative risk of a right-censored counterfactual outcome that may be subject to dependent censoring and confounding. Causal Studio is structured as follows: (1) based on user-specified propensity score models and/or censoring models, generate inverse probability of treatment weights (IPTWs) (in this case SMR weights) and inverse probability of censoring weights (IPCWs); (2) provide diagnostics (eg, distribution of the propensity score, by treatment groups; and, standardized mean differences between treatment groups for categorical and continuous variables) that enable the user to assess whether the analyses should proceed to the comparative stage, and, if appropriate, (3) execute the structural (ie, weighted) model to estimate the effect of treatment on the outcome. Causal Studio will be used to compare the real-world effectiveness of avacopan + SOC versus SOC among adults with AAV.

A staged analysis workflow with prespecified checkpoints will be implemented, including review of comparability/bias diagnostics (Checkpoint 1) and negative control outcomes analysis (Checkpoint 2) before proceeding to primary endpoint estimation.

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Claims-based variables will generally be treated as “absence of evidence” rather than missing (eg, no claim recorded). For variables with true missingness (eg gender, race, insurance type), missingness patterns will be summarized; analyses will use missing-indicator or categorized “unknown” approaches when feasible.

Loss to follow-up: follow-up will be censored at disenrollment or end of data availability.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

Study enrollment (cohort construction) will be summarized using a stepwise attrition table and, where applicable, for outcome-specific analysis sets (eg exclusions for baseline ESKD for MAKE analyses). The attrition table will report counts of unique patients, qualifying disease episodes, and trial-eligible index rows at each step, including: identification of potentially eligible new/relapsing GPA/MPA episodes; application of inclusion/exclusion criteria (eg age, EGPA, prior avacopan, mepolizumab/benralizumab); index assignment within sequential 14-day trials; and outcome-specific exclusions. Final counts will be populated after cohort extraction and will be reported overall and by treatment group.

8.7.2.3.2 Description of Participant/Patient Characteristics

Baseline participant/patient characteristics will be summarized overall and by treatment group at the index date/time zero. Characteristics will include demographics (age, sex, race/ethnicity where available), insurance type, calendar time, episode type (new vs relapsing), comorbidity burden (eg Charlson Comorbidity Index and key conditions such as CKD and liver disease), prior and concomitant medications (including glucocorticoids, RTX/CYC, and other immunosuppressives), proxies of disease severity/organ involvement, and healthcare utilization. Continuous variables will be summarized using mean (SD) or median (IQR) and categorical variables using counts and percentages. Covariate balance will be assessed before and after SMR weighting using standardized mean differences (SMDs) and graphical PS overlap diagnostics.

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

Primary and secondary endpoints will be evaluated using prespecified weighted estimators consistent with the target trial emulation framework. Time-to-event endpoints (eg time to first relapse) will be analyzed from index to first event using weighted survival methods, including weighted cumulative risk curves and weighted Cox proportional hazards models with bootstrap confidence interval estimation. Right-censored binary

endpoints over 12 months (eg MAKE and its components, GC-related events, and safety endpoints when feasible) will be analyzed as 12-month cumulative risks with weighted risk ratios (RR) and risk differences (RD), with supportive time-to-event analyses for composite outcomes as appropriate. PEDD endpoints will be analyzed using the day-level PEDD construction described in the SAP, including the proportion with a 30-day average PEDD ≤ 7.5 mg at prespecified landmark times (90/120/180/270/365 days). All confidence intervals will be two-sided 95% intervals.

8.7.2.5 Sensitivity Analysis

8.7.2.5.1 Subgroup Analysis

Key subgroup analyses to evaluate the consistency of treatment effects across clinically relevant baseline characteristics (as sample size permits) may include: (1) new vs relapsing GPA/MPA episodes at index; (2) SOC induction regimen (rituximab vs cyclophosphamide vs both); (3) proxies of baseline renal involvement/severity (eg, CKD stage or recent AKI/dialysis history); (4) baseline glucocorticoid intensity (eg, recent high-dose/pulse steroid use); and (5) repeating the primary analyses after excluding patients indexed during the first 2 years of the identification period, as sicker patients may be channeled to avacopan.

8.7.2.5.2 Stratified Analysis

Not planned.

8.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

Residual confounding and bias will be assessed using a combination of design diagnostics and empirical checks. Negative control outcomes (influenza vaccination, wellness visits, and preventive cancer screening) will be evaluated after weighting to probe for residual bias. However, if negative controls suggest systematic deviation from the null that is unlikely to be explained by random variation alone and that could meaningfully influence interpretation of the primary treatment effect estimates, additional model refinement, alternative confounding adjustment approaches, or quantitative bias summaries (eg E-values for key associations) may be considered. The magnitude and direction of negative control associations will be incorporated into the interpretation of treatment effect estimates.

8.7.2.5.4 Other Sensitivity Analysis

Additional sensitivity analyses may include different weight truncation thresholds and alternative exposure definitions for avacopan initiation in the SOC arm (eg, varying allowable initiation timepoints).

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

Safety endpoints are derived from routinely collected claims data and are not collected as spontaneous adverse event reports; therefore, MedDRA coding is not applicable for this study. Safety analyses will follow the prespecified framework described the SAP. In the primary (expected) approach, we will report crude and baseline SMR-weighted cumulative risk by 12 months after the index date for each safety endpoint, separately by treatment group.

8.8 Quality Control

Data source quality assurance. The administrative claims data used for this study are obtained from established healthcare databases that undergo routine quality assurance processes by the data vendor, including checks for internal consistency, completeness of enrollment information, and validity of coding structures. Only data meeting the vendor's quality standards will be used for study analyses.

Data management and processing. All study datasets will be created using prespecified programming specifications. Data extraction, transformation, and cohort construction steps will follow documented procedures to ensure consistent application of study definitions. Logical checks will be conducted to identify data anomalies (eg implausible dates, duplicate records, inconsistent enrollment periods, or missing key variables).

Analytic quality control. Analyses will be conducted using validated statistical software and reproducible programming workflows. Analyses will be conducted by a primary programmer and independently QC'ed by another programmer. Such QC processes include a review of the methodology, scrutinization of programming codes, as well as review of the final study deliverables and study report. Analytic code, programming specifications, and output will be version-controlled and archived to allow traceability and reproducibility of results.

8.9 Limitations of the Research Methods

Key limitations and practical mitigations include:

- Confounding by indication and disease severity (BVAS not available in claims; episode severity imperfectly captured). Mitigation: target-trial emulation with aligned time zero; rich baseline covariates including treatment history, renal disease proxies, prior relapses, and healthcare utilization; PS SMR weighting; negative control outcome diagnostics; and prespecified sensitivity analyses.
- Time alignment and treatment-pathway complexity (avacopan is commonly added during induction), which can induce immortal time and time-lag biases if not aligned. Mitigation: sequential nested trials anchored on disease date with consistent index rules.
- Outcome misclassification (eg, relapse defined from medication and diagnosis codes; mortality completeness may vary by linkage). Mitigation: use validated/high-specificity claims algorithms where available; require strong signals (eg, high-dose prednisone) for relapse; component analyses for MAKE.
- Limited power for rare safety outcomes and heterogeneity of follow-up. Mitigation: prioritize absolute risk summaries; avoid use of IPC weights based on low number of expected safety events.
- Potential cross-database patient overlap. Mitigation: evaluate privacy-preserving approaches to overlap assessment and de-duplication, including the possible use of a qualified third-party linkage vendor. Database-specific estimates will be presented, and pooled results will be interpreted in the context of the success, completeness, and assumptions of any de-duplication effort.

Given the expected sample size from each database, the comparative analysis may yield imprecise effect estimates and should therefore be interpreted primarily as directional. However, the probability of reporting a qualitatively incorrect effect direction (eg, estimating a hazard ratio greater than 1 when the true hazard ratio is less than 1) was calculated to be low, supporting the use of the analysis for directional interpretation.

Use of multiple databases strengthens the study by allowing replication of the analysis in an independent claims source and by enabling pooled estimation through meta-analysis. However, differences in database composition, coding practices, completeness of captured claims, enrollment structure, and death ascertainment may contribute to heterogeneity in database-specific results. To address this, the study will use harmonized definitions and analytic methods, present database-specific results alongside pooled estimates, and interpret findings in light of consistency across databases.

8.9.1 Internal Validity of Study Design

Internal validity considerations are central given the nonrandomized, claims-based design. The primary threats to internal validity include residual confounding (particularly confounding by indication and episode severity), time-alignment biases because avacopan is commonly added during induction, differential surveillance (more frequent

specialist care and monitoring among avacopan users), and informative censoring driven by disenrollment. This study will use a number of strategies to limit and evaluate bias.

Design-based mitigation: LIBRA emulates a target trial using sequential nested trials. This design aligns time zero across treatment strategies, reduces immortal time and time-lag bias, and compares avacopan initiators to SOC patients who were eligible to initiate avacopan at the same point in the episode.

Confounding control: measured baseline covariates capturing demographics, access to care, prior disease history, renal involvement proxies, baseline glucocorticoid burden (PEDD), comorbidities, concomitant medications, and healthcare utilization will be used in propensity score models. Because treatment initiation decisions are most strongly influenced by patients' current clinical status, key baseline covariates will be operationalized in two temporal windows: the 60 days immediately preceding index (recent baseline period) and the 365 to 61 days prior to index (earlier baseline period). We anticipate that covariate activity in the recent window will be more strongly associated with treatment selection and short-term outcome risk, while the earlier window will capture underlying chronic comorbidity and longitudinal disease history. Modeling these periods separately is intended to enhance confounding control by more precisely representing both proximal and distal determinants of treatment initiation. Standardized mortality ratio (SMR) weights will reweight the SOC arm to the covariate distribution of avacopan initiators, targeting the treatment effect in the treated population. Covariate balance will be assessed using SMDs and PS overlap diagnostics. Gatekeepers will make decisions about modifications to the target population and/or the propensity score models based on these diagnostics to avoid extrapolation beyond regions of common support before any of the safety or comparative effectiveness analyses are run.

Bias diagnostics and uncertainty: negative control outcomes will be used to probe residual bias after adjustment. Uncertainty will be quantified using two-sided 95% confidence intervals with patient-level bootstrap resampling, which also accounts for correlation when individuals contribute multiple sequential trial rows.

8.9.1.1 Measurement Error(s)/Misclassification(s)

Measurement error/misclassification: pharmacy claims reflect dispensing rather than ingestion; lack of visibility into inpatient medication administration may misclassify medication exposure; days' supply may not represent true exposure; relapse algorithms

in claims may have limited sensitivity; and MAKE components require operational assumptions. Mitigations include using high-specificity definitions, ensuring balance on inpatient admissions for AAV in the baseline period, and using component endpoints.

8.9.1.2 Information Bias

Information bias: avacopan users may have more specialist follow-up and laboratory monitoring, increasing detection of outcomes. Mitigation: adjust for baseline utilization; focus on 'hard' outcomes (hospitalizations/procedures) when possible; and assess surveillance-sensitive outcomes separately.

8.9.1.3 Selection Bias

Selection bias: continuous enrollment requirements and database coverage may exclude patients with fragmented care, potentially affecting comparability and generalizability. Mitigation: report attrition and cohort construction transparently; and use weighting diagnostics to avoid extrapolation beyond regions of overlap.

8.9.1.4 Confounding

Confounding: confounding control will rely on prespecified covariate sets capturing disease history, comorbidities, concomitant medications, renal involvement proxies, and healthcare utilization. Robustness will be evaluated using SMDs and PS overlap diagnostics and residual bias diagnostics (eg, negative controls; quantitative bias summaries such as E-values where appropriate). Because this study is based on observational administrative claims data, treatment selection may also be influenced by clinical factors that are incompletely measured or unavailable in claims (eg detailed measures of disease severity, physician treatment preference, or other clinical characteristics). As a result, confounding by indication and other forms of residual confounding may remain despite these adjustment strategies, and this possibility will be considered when interpreting the study findings.

8.9.2 External Validity of Study Design

External validity (generalizability) will depend on how well the combined populations in Optum Market Clarity and Komodo Healthcare Map reflect the broader US population of adults with AAV. Because the two databases differ in source composition and coverage, examining consistency of findings across them may improve the robustness and transportability of the evidence. Comparative estimates will primarily generalize to patients similar to avacopan initiators represented in the contributing databases during the study period.

Population representation: Market Clarity and Healthcare Map include individuals with Commercial, Medicare, Medicaid, and other/unknown payor types, but each database's composition may differ from the overall US AAV population (eg differences in insurance coverage, geography, and healthcare access). Patients with fragmented care, limited insurance continuity, or care delivered outside captured networks may be underrepresented due to the continuous enrollment requirement and reliance on reimbursed claims.

Clinical scope: This study focuses on adults with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) meeting operational criteria for a new or relapsing episode. Results should not be generalized to eosinophilic granulomatosis with polyangiitis (EGPA) or other vasculitides, or to pediatric populations.

Estimand-specific generalizability: Because the primary adjustment strategy targets the effect in avacopan initiators (effect on treated under SMR weighting), comparative estimates primarily generalize to patients similar to those who initiate avacopan in routine practice during the study period. They may not represent effects in all eligible patients who could, in principle, be treated with avacopan.

Temporal and practice-pattern considerations: Real-world treatment patterns (eg timing of avacopan initiation relative to SOC induction, steroid taper practices, and monitoring intensity) may vary across calendar time, health systems, and clinician specialty. We will describe calendar time and treatment patterns to support interpretation of the transportability of findings.

8.9.3 Analysis Limitations

Several analytical limitations are anticipated due to the rarity of AAV, the expected low prevalence of avacopan use in routine practice, and the sparsity of some outcomes (particularly rare safety outcomes).

Precision and sparse data: For outcomes with low event counts, estimates may be imprecise with wide confidence intervals, and some adjusted models may be unstable. In these settings, we will prioritize transparent reporting of absolute risks and event counts, and we will default to estimating the cumulative risk within 12 months after the index date using baseline propensity score SMR weights (no IPC weights), separately for each arm.

Weighting diagnostics and model dependence: Propensity score weighting can yield extreme weights when overlap is limited, leading to unstable estimates and increased

variance. We will evaluate weight distributions and overlap; modifications to the target population and alternative model specifications may be applied to improve stability and balance prior to outcome analysis. Interpretation will be restricted to the target population included in the final analyses.

Time-to-event model assumptions: Using IPTW and IPCW, we fit a weighted Cox model to estimate a population-level hazard ratio; if hazards are non-proportional, this parameter should be viewed as a risk-set–weighted average over time on the log-hazard scale, not as a constant hazard ratio. We also estimate nonparametric weighted cumulative risks and risk ratios.

Estimand limitation: Because the study will use a modified ITT estimand only, the analysis answers a treatment-initiation (treatment policy) question and does not directly estimate an on-treatment effect of sustained avacopan use. This is appropriate for the primary decision context (initiation in routine care) but should be considered when interpreting results, especially if treatment discontinuation or cross-over is common.

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

For variables that are determined based on claims data, the absence of a claim indicating a particular diagnosis or prescription will be taken as an indication that the patient did not have that diagnosis or prescription. Thus, the primary issue of concern for claims-based variables is mismeasurement of recorded exposures, outcomes, and covariates, rather than known missingness of these variables. For example, we will not detect medications given as an inpatient.

For baseline demographic characteristics used as adjustment covariates, after application of the inclusion and exclusion criteria, missingness would only be expected in sex and insurance. Based on prior analyses of new medication users from Optum CDM, missingness in these covariates is expected to be low, and the existing categories of “unknown” or “missing” values will be treated as separate categories or combined with an “other” category, as described in the SAP. Number and percent of missing data for each adjustment covariate will be reported

8.10 Other Aspects

Additional methodological considerations: (1) Reproducibility and transparency—cohort definitions, code lists (concept sets), and analytic code will be version controlled and aligned with the finalized SAP; any deviations will be documented in the final study report. (2) Quality assurance—key derivations (cohort construction, endpoints, and

weights) will undergo independent programming review and reasonableness checks; prespecified checkpoints will review covariate balance and bias diagnostics before primary outcome estimation. (3) Reporting—results will be presented with both unweighted and weighted summaries, including diagnostics to support interpretability (eg overlap and weight distributions) and clear statements of the estimand.

9. Protection of Human Participants

The databases used in this study are fully de-identified, and the data are fully compliant with the HIPAA privacy rule. The tracking of a patient's course of disease and therapy over time is possible whereas patient identification is not possible since patient and practice identifiable information are not available in the database. Confidentiality of all patient data is therefore automatically guaranteed by the anonymization of patient identities by the data providers before the transfer of the data to Amgen. Therefore, informed consent and approval from an institutional review board (IRB) or an ethics committee is not required for the use of this secondary de-identified data.

9.1 Patient Confidentiality

This is a retrospective observational study based on secondary use of existing de-identified HIPAA-compliant data from the Optum Market Clarity and Komodo Healthcare Map databases. The secondary data cannot be linked back to the patients from whom the data were originally collected. The study results will be reported at aggregate levels.

If cross-database de-duplication is pursued, linkage activities will be performed using privacy-preserving methods and in accordance with applicable data-use and contractual requirements. The study team will not receive direct patient identifiers. Any third-party vendor used for privacy-preserving linkage will operate under appropriate contractual and data protection controls.

9.2 Participants Decision to Withdraw

Not applicable. This is a secondary database analysis.

10. Collection, Recording, and Reporting of Safety Information and Product Complaints (PCs)

10.1 Safety Collection, Recording and Submission to Amgen Requirements

This study is analyzing secondary data from the Optum Market Clarity database and the Komodo Healthcare Map. Each safety outcome that is listed in section Outcome Assessment 8.3.2 will be documented and analyzed in this study. These will be reported in aggregate in the final study report and reported as the cumulative incidence within 12

months after the index date using baseline propensity score SMR weights (no IPC weights), separately for each arm. Additionally, a detailed claims-based profile review will also be provided summarizing relevant characteristics (eg, age, sex, disease characteristics, concomitant medications, comorbidities, and other relevant risk factors) for each patient with a hepatotoxicity/drug induced liver injury and/or serious hypersensitivity reaction event. See section Outcome Assessment 8.3.2 for safety outcomes and definitions.

11. Administrative and Legal Obligations

11.1 Protocol Amendments and Study Termination

Amgen may amend or terminate the protocol at any time.

12. Plans for Disseminating and Communicating Study Results

12.1 Publication Policy

The results of the study will be submitted for publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states authors need to fulfil all of the following criteria (defined in SOP-429662):

1. Make substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work.
2. Draft the work or review it critically for important intellectual content.
3. Approve of the version to be submitted for publication.
4. Agree to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All publications (eg, 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