Evaluation of the long-term safety of avacopan in ANCA-associated vasculitis: Design of the real-world AvacoStar study

David RW Jayne, Raashid Luqmani, Benjamin Terrier, Achim Obergfell, Charlotte Pollet, Marie Boff, Monica Balcells-Oliver, Bernhard Hellmich

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Abstract

Background: Established treatments for granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA), include use of immunosuppressive agents for remission induction, followed by maintenance therapy. However, patients continue to experience disease progression, organ damage, and adverse events related to current therapies. Avacopan, an oral, selective C5a receptor antagonist, was approved by the European Commission in January 2022 for the treatment of adult patients with severe, active GPA or MPA in combination with rituximab (RTX) or cyclophosphamide (CYC). In the pivotal Phase 3 ADVOCATE study, avacopan was non-inferior to prednisone taper in achieving remission at Week 26 and superior in sustaining remission at Week 52; furthermore, a greater improvement in estimated glomerular filtration rate with avacopan was also observed at Week 52. The AvacoStar study will generate data on the benefit/risk and safety profile of avacopan in patients in a real-world context, including in those where treatment may potentially continue beyond 1 year.

Objective: The primary objective of AvacoStar is to evaluate the incidence of defined medical events of special interest (MESIs) in patients with AAV commencing avacopan. These include liver injury, cardiac safety, serious infections, and malignancy.

Methods: AvacoStar is a non-interventional, multinational, prospective, post-authorization safety study. It will enroll up to 500 patients in Germany and the UK, in 2 groups of approximately 250 participants each: Those treated with avacopan (plus a standard of care at local investigators discretion; usually a RTX or CYC-based regimen), and a second cohort treated with a CYC- or RTX-based induction regimen without avacopan. Avacopan and standard of care will be prescribed in the usual manner in accordance with the corresponding Summary of Product Characteristics under the sole decision of the investigator. The treatment decision will fall within current established practice. Eligible participants will be ?18 years with severe, active GPA or MPA as determined by the investigator, at the time of commencing avacopan or non-avacopan standard of care induction therapy. Patients will be followed for up to 7 years.

Results: This study has been enrolling patients since 11 September 2023. The final report is expected in the second half of 2031; interim reports are planned every 24 months after first patient first visit.

Conclusions: The AvacoStar study will be the largest European prospective real-world evidence comparative study conducted to date which evaluates the long-term safety of avacopan in severe, active GPA or MPA. This study is expected to yield important insights on the use of avacopan in severe, active GPA or MPA in a real-world setting. Clinical Trial: ClinicalTrials.gov NCT05897684; https://clinicaltrials.gov/study/NCT05897684?cond=NCT05897684.

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Trial Registration: ClinicalTrials.gov NCT05897684; https://clinicaltrials.gov/study/NCT05897684?cond=NCT05897684.

Keywords: ANCA-associated vasculitis; AAV; avacopan; C5a receptor; ADVOCATE, GPA, MPA; real-world evidence.

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises a group of rare small- and medium-sized vasculitides [1]. Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are 2 clinicopathological forms of AAV, characterized by inappropriate activation of neutrophils [2]. A third form of AAV, eosinophilic GPA, has a distinct clinical presentation and management pathway outside the scope of

this study [3]. GPA and MPA are associated with the circulating ANCA against the neutrophil-expressed antigens proteinase 3 and myeloperoxidase [2].

AAV can affect several organs, but the kidneys, respiratory tract, eyes, skin, and nervous system are most commonly affected [2, 3]. Despite improvements in the treatment strategies for AAV, it has been shown that long-term mortality and morbidity remain high [4]. Patients with GPA or MPA have a 1-year mortality probability of 11.1% [5]. The main causes of first year mortality in patients with GPA or MPA are infection [5, 6] and active vasculitis [5], whereas after the first year, the major causes of death are cardiovascular disease, malignancy, and infection [7, 8].

Established treatments for GPA and MPA are based on the European Alliance of Associations for Rheumatology (EULAR) 2022, American College of Rheumatology (ACR 2021) and Kidney Disease: Improving Global Outcomes (KDIGO) 2024 recommendations and involve the use of biologic and non-biologic immunosuppressive agents for remission induction and maintenance therapy [9-11]. This consists of rituximab (RTX) and/or cyclophosphamide (CYC) with long-term use of glucocorticoids (GCs) [10, 12]. Despite refinements in the dosing regimens of GCs and CYC, and the introduction of RTX, patients with AAV can struggle to control their disease, with relapses occurring in 30–50% of patients over 5 years [13, 14]. The pathology of AAV itself can lead to organ damage and chronic morbidity and mortality [15], while medication toxicity can also result in serious adverse effects, including increased risk of infection, malignancy, and GC-induced diabetes [13, 16]. Furthermore, GCs are major contributors to impaired quality of life [17, 18]. However, despite the adverse events associated with GC therapy, GCs remain central to current induction of remission and maintenance treatment strategies [10, 12].

Growing evidence has identified the role of the alternative complement cascade in the pathogenesis of AAV through activation of the C5a receptor (C5aR) [2]. Avacopan is an orally administered, small-molecule, C5a receptor antagonist that selectively blocks the effects of C5a through the C5aR, including blocking neutrophil chemoattraction and activation [17]. Avacopan does not interfere with the production of C5b or the membrane attack complex and does not block C5a binding to a second receptor, C5L2, which is thought to have anti-inflammatory properties [19].

Avacopan was approved for the treatment of adult patients with severe, active GPA or MPA in combination with RTX or CYC by the European Commission in January 2022 [20]. The assessment of the European Union Marketing Authorisation Application for avacopan was based on data available from the clinical development program. In the Phase 2 CLEAR study, patients treated with avacopan, both with and without a reduced-dose prednisone taper, achieved higher clinical response rates at 12 weeks compared with the control group. Both avacopan regimens demonstrated noninferiority, with adverse event (AE) rates remaining similar across all groups [21]. In the pivotal Phase 3 ADVOCATE study, the avacopan-based regimen was non-inferior to prednisone taper with the achievement of remission at Week 26, was superior in sustaining remission at Week 52, and was associated with improved glomerular filtration rate from baseline in patients with GPA or MPA [17]. In the ADVOCATE study, the incidences of serious AEs (SAEs), life-threatening AEs, and death were recorded. The number of SAEs (excluding events of worsening vasculitis) was 33% higher in the prednisone taper group than in the avacopan group after 52 weeks of treatment, consistent with the higher exposure to GCs in that group. In a safety analysis of combined data from the CLEAR, CLASSIC, and ADVOCATE clinical trials of GPA or MPA, use of avacopan was associated with fewer AEs, SAEs, and white blood cell count reductions and fewer infections compared with the non-avacopan treatment [22].

There are currently some real-world-evidence studies of avacopan use that confirm ADVOCATE data in terms of remission and safety; however, cohorts are small [23, 24]. In addition, the EULAR 2022 recommendations mention that long-term use of avacopan cannot be recommended at this time because there are no data on use beyond 1 year [10]. Limited data from patients treated with an avacopan based regimen as part of an Early Access Program (EAP) confirm the manageable safety profile of avacopan, and suggest it has the potential to be effective beyond 52 weeks in sustaining disease control [25]. Therefore, it is of interest to observe the drug in real-life use and to follow-up on safety in the long-term, including beyond the 12-month period of the Phase 3 ADVOCATE study.

AvacoStar (NCT05897684) is a post-authorization safety study (PASS) designed to evaluate the incidence of defined medical events of special interest (MESIs) during long-term follow-up in a real-world cohort of participants commencing avacopan for severe, active GPA or MPA.

Methods

Study Participants and Sites

AvacoStar is a non-interventional, multinational, prospective cohort study enrolling approximately 500 patients with severe, active GPA or MPA from Germany and the United Kingdom who are receiving treatment as part of routine clinical practice. Inclusion and exclusion criteria are outlined in **Table 1.**

Study Design and Treatment

Patients are enrolled into 1 of the 2 groups: those treated with avacopan plus a standard of care, at local investigators' discretion; usually a RTX or CYC-based regimen ('the avacopan group'), and a second cohort treated with a CYC- or RTX-based induction regimen without avacopan ('the non avacopan group'). Avacopan and standard of care are prescribed in the usual manner in accordance with the corresponding Summary of Product Characteristics (SmPC), under the sole decision of the investigator. As per the SmPC, avacopan in combination with a RTX or CYC regimen is indicated for the treatment of adult patients with severe, active GPA or MPA [26]. Participants may start or stop avacopan during the study, in line with usual practice. The baseline visit is defined as the day that induction treatment (avacopan or non-avacopan standard of care CYC or RTX) is started for active AAV. Patients are being enrolled prospectively, but up to 6 months of data may be collected retrospectively, if necessary. The overall study duration is anticipated to be up to 7 years, including a recruitment period of approximately 3 years. Follow-up of enrolled patients will continue until the last patient last visit (LPLV) milestone, 4 years after the last participant is enrolled (**Figure 1**). Participants in the non-avacopan group who initiate avacopan during follow-up due to disease flare will be withdrawn from the study at that time but may crossover and re-enroll in the avacopan group if eligibility criteria are met and recruitment is still ongoing. Re-enrollment will require a new informed consent and assignment of a new patient identification number. Participants in the avacopan group who discontinue avacopan treatment during follow-up will remain in the study and data will be collected as part of the avacopan group. All decisions on therapeutic or diagnostic procedures, treatments, disease management, timing of visits and resource utilization are made following the investigator's usual clinical practice. Individual participant follow-up data will be collected periodically at routine clinic visits from enrollment until the last patient last visit.

Study Objectives

The primary objective of this study is to evaluate the incidence of defined MESIs in patients with

AAV commencing avacopan (**Figure 2**). In this study, secondary objectives include: to evaluate incidence of AEs, AEs leading to discontinuation of therapy, SAEs, adverse drug reactions (ADRs), serious adverse drug reactions (SADRs), laboratory abnormalities, disease flares as measured by the Birmingham Vasculitis Activity Score version 3.0 (BVAS), and organ damage as measured by the Vasculitis Damage Index (VDI) in patients with GPA or MPA commencing avacopan; to evaluate the background incidence of AEs, MESIs, SAEs, laboratory abnormalities, disease flares as measured by BVAS, and organ damage as measured by the VDI, in a similar population of patients with severe, active GPA or MPA but not receiving avacopan; to compare SAEs and MESIs in patients with GPA or MPA between patients who received avacopan and those who did not; to describe patterns of immunosuppression and GC use in a real-world cohort; and to describe avacopan use in a real-world cohort. Identified MESIs include liver injury, cardiac safety, serious infections, and malignancy. This protocol fulfils the requirements of the European Medicinal Agency (EMA) to conduct a PASS as a post-marketing commitment.

Statistical Analysis

Statistical analyses will be exploratory in nature, performed using SAS statistical software Version 9.4 or later. All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by descriptive statistics (ie, number of patients, mean, standard deviation, minimum, median, quartiles, and maximum). Continuous variables will be summarized by absolute value and changes from baseline per analysis time point, if applicable. Where appropriate, 95% confidence intervals will be provided. Comparisons between treatment groups will be performed using appropriate methods to adjust for potential bias. A propensity score will be constructed by estimating the probability of exposure by regressing the treatment assignment on baseline characteristics using logistic regression. Treatment group comparisons will be done using two methods: adjustment (the propensity score is included in the regression model) and inverse probability weighting. Outcomes of statistical comparisons will be interpreted with caution.

Sample Size and Power Calculations

The sample size of 250 participants in the avacopan group was considered reasonable; given an expected attrition rate of 15% or 10% per year, the power of the study to detect a single event will be 77% or 81%, respectively for an AE with an incidence rate per year of 0.2%, for a follow-up duration of 4 years. The most infrequent form of the expected AEs, malignancy related to immunosuppression is the most uncommon with literature reporting an incidence of 1.4% per year. A sample size sufficient to detect an AE with an incidence rate of 0.2% per year is well placed to detect a malignancy event related to immunosuppression. Skin cancer is the most common malignancy related to immunosuppression after organ transplantation, with a US study reporting a 1.4% annual incidence, well within the detection limit of this study [27].

Analysis of Primary Endpoint

For MESIs, the incidence (number and percentage of patients with events and total number of events) as well as the incidence per patient-year will be provided for the avacopan group. For each MESI, both incidence rate and exposure-adjusted incidence rate will be calculated with confidence intervals. The incidence of MESIs will be presented by year as well as cumulatively over the full period of observation.

Analysis of Secondary Endpoints

Incidence rates of AEs leading to discontinuation of therapy, SADRs, and ADRs for the avacopan group will be presented. For AEs, SAEs, and MESIs, the incidence as well as the incidence per patient-year will be provided by treatment group, overall and by Medical Dictionary of Regulatory Activities system organ classes and preferred term. All AEs and treatment-emergent AEs will be reported separately. For SAEs and MESIs, treatment groups will be compared for the proportion of patients with at least 1 event and the number of events per year. Descriptive statistics will also be provided by treatment group for change in VDI, change in laboratory assessments over time, proportion of GC-free patients over time, concomitant immunosuppression over time and cumulative, incidence of disease flares, and time to first flare as assessed with the BVAS for patients achieving remission. The duration of treatment with avacopan by reason for treatment discontinuation will be summarized descriptively.

Assessments

Baseline data being collected include demographics; smoking history; MPA or GPA diagnosis; medical history and comorbidities; prior treatment with immunosuppressive drugs; treatment group and exposure; investigator's reason for choosing the treatment group; ANCA titers; laboratory values, BVAS, and VDI. Variables for each of the treatment groups being collected during the follow-up period include information on the use of immunosuppressives alongside avacopan and non-avacopan based regimens, ANCA titers, laboratory values, BVAS, VDI, AEs, MESIs, SAEs, selected safety laboratory investigations, disease-related damage, flares, and use of concomitant immunosuppression and GCs. Data on AEs observed from baseline, including the seriousness, timing of onset, duration, causal relationship to avacopan, action taken with regards to avacopan administration/dosing in response to the event, and outcome of the event will also be collected. The expected timings for the collection of each variable are presented in **Table 2.**

Ethics and Dissemination of Results

This study is being conducted within an approved indication in accordance with the Declaration of Helsinki, the International Society for Pharmacoepidemiology (ISPE) Guidelines for good publication practice (GPP), the EMA Guideline on good pharmacovigilance practices Module VI and VIII for PASS, and local laws and regulations as applicable in each participating country. The PASS will comply with Revision 6 of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) methodological standards for study protocols, the ENCePP Checklist for Study Protocols, and the GPP of the ISPE, as well as the data vendor's quality management system, IQVIA. Additionally, guidelines of the International Council on Harmonisation concerning Good Clinical Practice are being followed whenever possible.

Patient data collected in the study are collected in a pseudonymized/de-identified form. Any new information that might influence the evaluation of the benefit/risk balance of the product shall be immediately communicated to Competent Authorities of Member States. The analysis will be performed on the pseudonymized/de-identified patient-level dataset. The data system will be maintained and secured as required by applicable laws and regulations. Processes assuring data security will be employed during data extraction, storage, and back-up. The progress reports and final analysis will be reviewed and evaluated by a Medical Monitor and/or pharmacovigilance delegate.

Results (Enrollment Status)

This study has been enrolling patients since the study start on 11 September 2023, with 35 sites actively participating in enrolling patients. The final report is expected in the second half of 2031. Interim reports are planned every 2 years from the start of enrollment and will provide information about the progress of the study.

Discussion

Overview

Despite current treatments for AAV, disease burden still has a high impact on quality of life of individuals with GPA or MPA [17, 18, 28] and many do not achieve or sustain remission [29, 30]. Existing treatments cannot induce sustained disease control in all patients and immunosuppressive agents including GCs are associated with frequent clinically relevant AEs and comorbidities, both resulting in impaired quality of life [13, 15]. There is an unmet need for alternative, more targeted, and less toxic therapeutic options [31].

The avacopan-based regimen in combination with RTX or CYC may be considered for induction of remission in AAV, as part of a strategy to substantially reduce exposure to a tapering prednisone regimen [10, 11, 17, 32]. However, the safety of avacopan beyond 52 weeks has not been assessed. It is, therefore, of interest to monitor the drug in daily use as per clinical practice and generate long-term safety data under real-world settings. This information will be gathered in the context of this study. The main rationale for this PASS is to further understand the identified and potential risks of avacopan described above by studying the use of avacopan among patients in a real-world context, where treatment may extend beyond 1 year. The AvacoStar study is designed to assess long-term safety and observe avacopan in daily use in a real-world context.

Study Design Features

Given the heterogeneous clinical presentation of patients with AAV, the planned multicenter, multinational large sample size will provide an adequate representative number of patients. The data collected in this study will be frequently monitored during the study lifetime. Data collection will ensure that applicable variables of interest, and critical data elements are routinely collected as part of real-world clinical care and are available via medical charts and physician reporting.

Strengths of the Study Design

To our knowledge, this is the largest European prospective real-world evidence study of an avacopan in patients with GPA or MPA. This study evaluates long-term safety data on the use of avacopan and is the longest study to date. This study will also generate data that reflect real-world management of AAV. Although recruiting from a European population, the multicenter, multi-national study design will facilitate the generalizability of the study results.

Limitations of the Research Methods

As this is a non-interventional study, there are several potential confounding factors to be considered. Although several steps were taken to minimize bias, it is likely that some residual bias remains and therefore the results of any direct comparisons between the avacopan and non-avacopan groups will need to be interpreted with this in mind. For example, avacopan may be used by clinicians preferentially in patient subgroups where randomized controlled trial (RCT) data have shown the greatest benefit (eg, severe, active renal disease, or presence of GC-related

comorbidities). Eligibility criteria have been selected to ensure that baseline characteristics for the non-avacopan group is similar to the avacopan group. Additionally, detailed information will be collected at baseline on potential confounding factors, including those relating to disease severity, diagnosis, prior immunosuppression exposure, and MESI-related risk factors. To account for the risk of bias resulting from confounding factors, treatment groups will be compared using propensity scoring methodology.

Conclusions

The AvacoStar study will be a large prospective real-world-evidence study that evaluates the long-term safety of avacopan in GPA or MPA. The study is expected to yield important insights on the use of avacopan in GPA or MPA in a real-world setting, including treatment beyond 12 months.

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Conflicts of Interest

- DRWJ received consulting fees from: Alentis, Amgen, AstraZeneca, Aurinia, BMS, Boehringer, Chinook, GSK, Novartis, Otsuka, Roche/Genentech, Takeda, CSL Vifor; lecture fees from: Amgen, CSL Vifor, Otsuka; and holds stocks with: Alentis, Aurinia.
- RL received grants from: BMS, Celgene, CSL Vifor; consulting fees from: GSK, Roche, CSL Vifor; lecture fees from: GSK, CSL Vifor; and advisory board fees from: GSK.
- BT received advisory board fees from: AstraZeneca, GSK, Boehringer Ingelheim, CSL Vifor, Novartis; lecture fees from: AstraZeneca, GSK, Boehringer Ingelheim, CSL Vifor, Novartis.
- AO, CP, MBo are employees of CSL Vifor.
- MBa is an employee of CSL Vifor and owns stocks in Amgen and CSL Vifor.
- BH received fees for consulting and/or lectures from AbbVie, AstraZeneca, BMS, GSK, Janssen, InflaRx, Novartis, Pfizer, Novartis, Pfizer, Recordati, Roche, CSL Vifor.

Abbreviations

ADR: adverse drug reactions
AE: adverse event
ANCA: antineutrophil cytoplasmic antibody
BVAS: Birmingham Vasculitis Activity Score
C5aR: C5a receptor
CYC: cyclophosphamide
ENCePP: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EULAR: European Alliance of Associations for Rheumatology
GC: glucocorticoid
GPA: granulomatosis with polyangiitis

GPP: good publication practice
ISPE: International Society for Pharmacoepidemiology
KDIGO: Kidney Disease: Improving Global Outcomes
LPLV: last patient last visit
MESI: medical event of special interest
MPA: microscopic polyangiitis
PASS: post-authorization safety study
RTX: rituximab
SADR: serious adverse drug reaction
SAE: serious adverse event
SmPC: Summary of Product Characteristics
VDI: Vasculitis Damage Index

Figures and Tables

Figure 1. AvacoStar study design. The schematic outlines participant enrollment, treatment decision, follow-up visits, and assessment timepoints, including the measurement of medical events of special interest (MESIs) from first patient first visit (FPFV) to last patient last visit (LPLV)

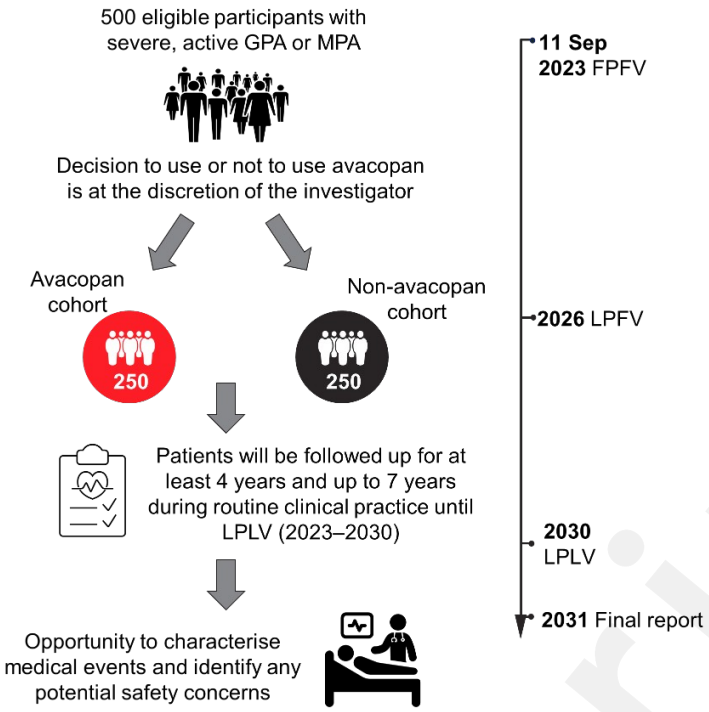

Figure 2. Timing of medical events of special interest (MESIs) incident rates during the AvacoStar study including any data collected at either the end of follow-up or the last avacopan dose

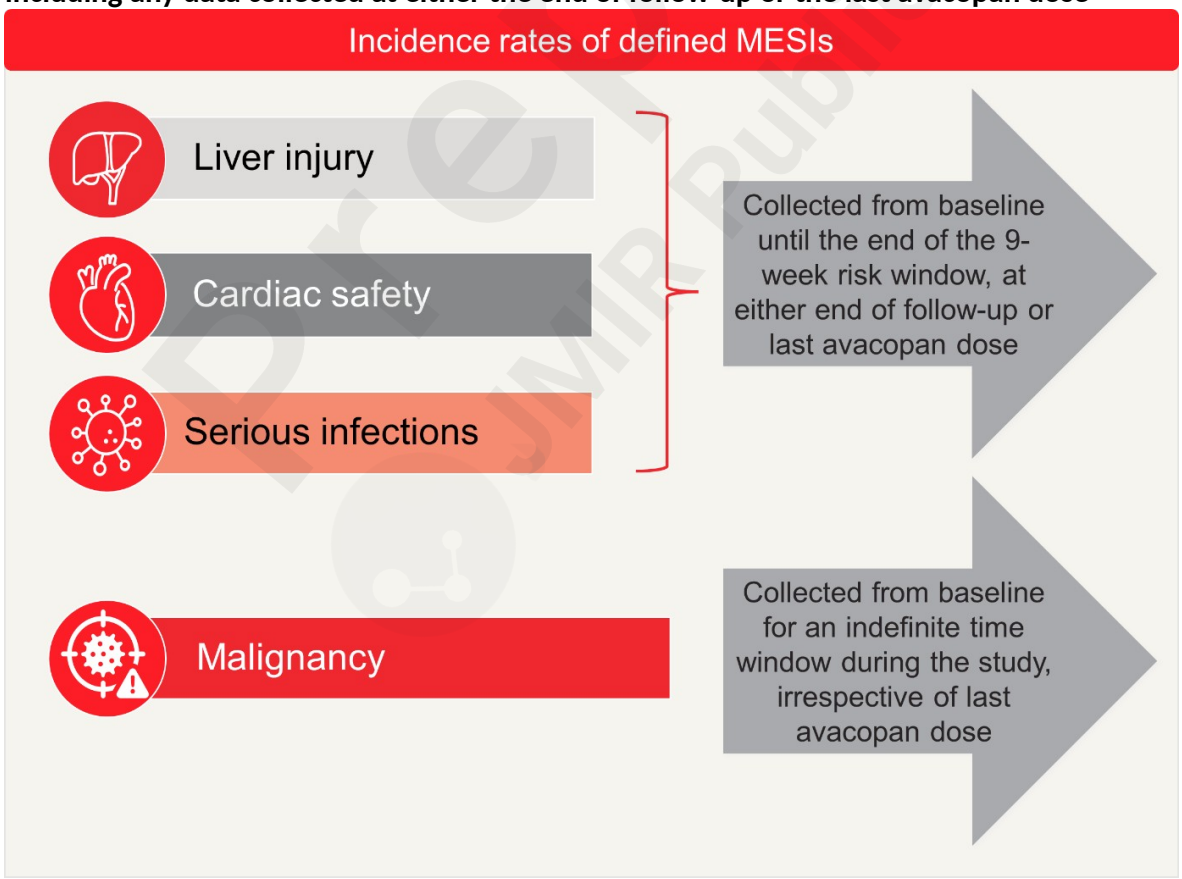

Table 1. Study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Diagnosis of AAV (GPA or MPA), as determined by the investigator according to their usual practice. • Severe, active AAV at the time of commencing avacopan or non-avacopan standard of care induction therapy, in the opinion of the investigator. • Age ≥18 years and of either sex at the time of commencing avacopan or non-avacopan standard of care induction therapy. • Has provided written informed consent. • Has commenced within the previous 6 months, or is planned to commence, avacopan, CYC or RTX for the treatment of severe, active AAV outside of an interventional clinical study.	• Concurrent participation in an interventional study, unless prospectively discussed and agreed with the Medical Monitor.

Abbreviations: AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; CYC, cyclophosphamide; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; RTX, rituximab.

Table 2. Planned study schedule

Specific measurement variable	Frequency of measurements
Signed informed consent (1)	At enrollment
Inclusion and exclusion criteria	
Year of birth, sex, ethnicity, race	
Height and body weight	At baseline (6,7)
Smoking history and current status	
MPA or GPA diagnosis (2)	
Medical history and comorbidities (3)	
Prior treatment with immunosuppressive drugs (4)	
Reason for choosing the treatment group	
ANCA binding levels (5)	
Treatment group and exposure (8)	At baseline Every 3 months for the first year (7) Every 6 months after the first year
ANCA positivity (9)	Every 3 months for the first year Every 6 months after the first year Study exit or end of study
Treatment discontinuation and reasons	
Laboratory values (10)	At baseline Every 3 months for the first year Every 6 months after the first year Study exit or end of study
BVAS (version 3.0) (11)	
VDI (12)	
Concomitant medication (13)	
Recording of AEs, SAEs, ADRs, SADRs, MESIs (liver injury, serious infections, malignancy, and serious cardiac events) (14)	
Study discontinuation and reasons	Study exit or end of study

1. The informed consent includes the approval to collect retrospective data; 2. Including AAV phenotype, year of diagnosis, pattern of organ involvement, year of last relapse, number of relapses in the past 5 years, history of positive ANCA titer, and specificity; 3. Medical history includes etiology of underlying disease, history of major related health issues and procedures, e.g. surgery due to underlying disease; 4. Including dose, duration before start of treatment, reason for change in dose or medication; 5. At baseline: if the patient is ANCA positive, PR3 and/or MPO binding levels will be collected (if available). Highest PR3 and MPO titers in patient medical history will be collected (if available); 6. Baseline visit corresponds to date of start of avacopan or non-avacopan induction therapy (CYC or RTX); 7. Patients who started avacopan or standard of care within 6 months of study start may have these data documented retrospectively; 8. Including start date, stop date (if applicable), daily dose or frequency, route of administration (intravenous or oral), and reason for treatment initiation or switch, rationale for starting, stopping or changing the dose (completion of planned course, AE, investigator or patient's decision, withdrawal of consent, administrative problems, death, other); 9. During follow-up: PR3 or MPO positivity will be collected; 10. Includes creatinine, eGFR, IgG, CPK, ALT, AST, bilirubin, WBC, and albumin, if collected per the site routine practice; 11. During the follow-up, the BVAS will be collected at each episode of flare; 12. At baseline, the VDI is modified to permit a baseline assessment that captures prior (non-vasculitis related) damage, including infections; 13. Including start date, stop date (if applicable), daily dose or frequency, route of administration (intravenous or oral), and reason for treatment initiation or switch, rationale for starting, stopping or changing the dose (completion of planned course, AE, investigator or patient's decision, withdrawal of consent, administrative problems, other). Limited to GC and immunosuppressants; 14. AEs, SAEs, ADRs or MESIs will be collected from baseline up to 9 weeks after end of follow-up. Collection of safety events include the seriousness, duration, causal relationship to avacopan, action taken with avacopan in response to the event, and outcome of the event.

Abbreviations : AAV, ANCA-associated vasculitis; ADR, adverse drug reaction; AE, adverse event; ALT, alanine transaminase; ANCA, antineutrophil cytoplasmic antibody; AST, aspartate transaminase; BVAS, Birmingham Vasculitis Activity Score; CPK, creatine phosphokinase; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; eGFR, estimated

glomerular filtration rate; IgG, immunoglobulin G; MESI, medical event of special interest; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; SADR, serious adverse drug reaction; SAE, serious adverse event; VDI, Vasculitis Damage Index; WBC, white blood cell.

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