STUDY PROTOCOL AVACOSTAR
A POST-AUTHORISATION SAFETY STUDY (PASS) TO EVALUATE THE INCIDENCE OF SAFETY EVENTS OF INTEREST IN PATIENTS TREATED WITH AVACOPAN FOR ANCA-ASSOCIATED VASCULITIS (AAV)

Study Number:	CS-AVA-2022-0016
Date:	13 January 2023
Version/Amendment Number:	Version 3.0
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SIGNATURE PAGE

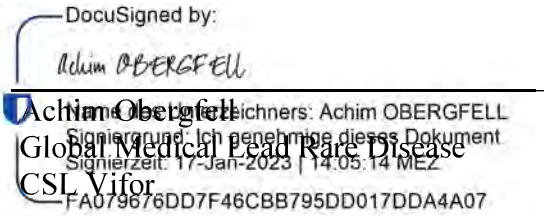
Declaration of Sponsor

Title: AvacoStar: A Post-Authorisation Safety Study (PASS) to Evaluate the Incidence of Safety Events of Interest in Patients Treated with Avacopan for ANCA-associated Vasculitis (AAV)

Clinical Protocol Number: CS-AVA-2022-0016

Version/Amendment Number/Date: Version 3.0, 13 January 2023

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice as amended. List of Study team members, including Medical Monitor, is kept under separate cover.



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INVESTIGATOR AGREEMENT AND SIGNATURE PAGE

Study: AvacoStar

Protocol Number: CS-AVA-2022-0016

Version/Amendment Number/Date: Version 3.0, 13 January 2023

I have read and understand the protocol and agree that it contains the ethical, legal and scientific information necessary to participate in this study. My signature confirms my agreement that the study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to Good Pharmacoepidemiology Practices (GPP), and the ethical principles that have their origins in the Declaration of Helsinki and applicable data privacy laws.

I will provide copies of this protocol as needed to all physicians, nurses, and other professional personnel who will participate in the study under my responsibility. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the conduct of the study. I am aware that this protocol will need to be approved by an appropriate Institutional Review Board or Independent Ethics Committee (IEC) prior to any patients being enrolled and that I am responsible for verifying whether that requirement is met. I agree to adhere to the attached protocol and if requested to provide copies of medical information for the purpose of verification of submitted information, I will comply.

Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

Signature by the Investigator on this Protocol Signature Page documents review, agreement and approval of the requirements contained in this protocol.

Signature of Principal Investigator Name, Title, Address and Telephone Number of Principal Investigator	Date (day month year)

PASS INFORMATION

CS-AVA-2022-0016

Title:	AvacoStar
Sub-title:	A Post-Authorisation Safety Study (PASS) to Evaluate the Incidence of Safety Events of Interest in Patients Treated with Avacopan for ANCA-associated Vasculitis (AAV)
Protocol Version Identifier:	Version 3.0
Date of Last Protocol Version:	Version 2.0, 2 September 2022
Study No.:	CS-AVA-2022-0016
EU PAS Register Number:	Study not yet registered
Active Substance:	Avacopan (Anatomical Therapeutic Chemical code: L04)
Medicinal Product:	Tavneos®
Product Reference:	EU/1/21/1605
Procedure Number:	Not applicable
MAH(s):	Vifor Fresenius Medical Care Renal Pharma France
Joint PASS:	No
Research Question and Objectives:	Research Question: • What are the incidence rates of defined medical events of special interest (MESIs) in a real-world cohort of patients commencing avacopan for AAV? Primary Objective: • To evaluate the incidence of defined MESIs in patients with AAV commencing avacopan. Secondary Objectives: • To evaluate the incidence of adverse events (AEs), AEs leading to discontinuation of therapy, serious adverse events (SAEs), adverse drug reactions (ADRs), serious adverse drug reactions (SADRs), laboratory abnormalities, disease flares as measured by the Birmingham Vasculitis Activity Score (BVAS), and organ damage as measured by the Vasculitis Damage Index (VDI) in patients with AAV commencing avacopan. • To evaluate the background incidence of AEs, MESIs, SAEs, laboratory abnormalities, disease flares as measured by the BVAS, and organ damage as measured by the VDI in a similar population of patients with severe, active AAV but not receiving avacopan. • To compare SAEs and MESIs in patients with AAV between patients with and without avacopan. • To describe patterns of immunosuppression/glucocorticoids (GC) use in a real-world cohort.

	• To describe avacopan use in a real-world cohort.
Country(-ies) of Study:	Germany and the UK. Additional countries may be considered according to availability of avacopan and suitability for the study.
Author:	Achim Obergfell

MARKETING AUTHORISATION HOLDER(S) (MAH)

MAH(s):	Vifor Fresenius Medical Care Renal Pharma France
MAH Contact Person:	Sabine Ellenberger

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2. LIST OF ABBREVIATIONS

AAV	ANCA-associated vasculitis
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
ANCA	anti-neutrophil cytoplasmic antibody
AST	aspartate aminotransferase
BVAS	Birmingham Vasculitis Activity Score
CPK	creatine phosphokinase
CRO	Contract Research Organisation
eCRF	electronic Case Report Form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EULAR	European Alliance of Associations for Rheumatology
GC	glucocorticoids
GPA	granulomatosis with polyangiitis
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practice
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IgG	immunoglobulin G
ISPE	International Society for Pharmacoepidemiology
LFT	liver function test
LPLV	last patient last visit
MAH	Marketing Authorisation Holder
MESI	medical event of special interest
MPA	microscopic polyangiitis
MPO	myeloperoxidase

PASS	Post-authorisation Safety Study
PR3	proteinase 3
PSUR	Periodic Safety Update Report
PT	preferred term
PV	pharmacovigilance
RMP	Risk Management Plan
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SMP	Safety Management Plan
SmPC	Summary of Product Characteristics
SoC	standard of care
SOP	Standard Operating Procedure
UK	United Kingdom
UKIVAS	United Kingdom and Ireland Vasculitis
US	United States
VDI	Vasculitis Damage Index
WBC	white blood cell

3. RESPONSIBLE PARTIES

A list of Scientific Committee members, the Scientific Committee Charter and the list of participating centres are stand-alone documents, listed in Appendix 1. These documents are available upon request.

Changes of responsible persons and/or Scientific Committee members will be documented by updating the relevant documents, but do not require formal protocol amendments.

4. ABSTRACT

Title:	AvacoStar
Sub-title:	A Post-Authorisation Safety Study (PASS) to evaluate the Incidence of Safety Events of Interest in Patients treated with avacopan for ANCA-associated Vasculitis (AAV)
Version:	3.0
Date:	13 January 2023
Author:	Achim Obergfell (Vifor Fresenius Medical Care Renal Pharma)
Rationale and Background:	Avacopan, a novel, first-in-class C5aR antagonist, has been developed for the treatment of patients diagnosed with anti-neutrophil cytoplasmic antibody (ANCA)-AAV; the 2 main forms being granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). Despite treatment advances, AAV remains a serious disease. Patients continue to experience disease progression and cumulative organ damage, as well as AEs related to current therapies. The pivotal Phase 3 study ADVOCATE evaluated whether avacopan could provide an effective treatment for patients with AAV, while simultaneously allowing for the reduction in GC use. Results from this study showed that avacopan was non-inferior to a prednisone comparator for remission at Week 26 and superior to the prednisone comparator for sustained remission at Week 52. Furthermore, a greater improvement in estimated glomerular filtration rate (eGFR) with avacopan was observed at Week 52. The rationale for the present study is to supplement the clinical trial experience of avacopan with information on the safety profile of avacopan as used by physicians in a real-world setting. This will be achieved by an observational study design that follows patients receiving avacopan as part of routine clinical practice for GPA and MPA along with a separate cohort of patients not receiving avacopan but with similar disease severity and receiving a cyclophosphamide or rituximab-based induction regimen.
Research Question and Objectives:	Research Question: • What are the incidence rates of defined MESIs in a real-world cohort of patients commencing avacopan for AAV? Primary Objective: • To evaluate the incidence of defined MESIs in patients with AAV commencing avacopan. Secondary Objectives: • To evaluate the incidence of AEs, AEs leading to discontinuation of therapy, SAEs, ADRs, SADRs, laboratory abnormalities, disease flares as measured by the BVAS, and organ damage as measured by the VDI in patients with AAV commencing avacopan. • To evaluate the background incidence of AEs, MESIs, SAEs, laboratory abnormalities, disease flares as measured by the BVAS, and organ damage as measured by the VDI in a similar population of patients with severe, active AAV but not receiving avacopan.

	• To compare SAEs and MESIs in patients with AAV between patients with and without avacopan. • To describe patterns of immunosuppression/GC use in a real-world cohort. • To describe avacopan use in a real-world cohort.
Study Design:	The PASS is a non-interventional, multi-national, prospective cohort study that will collect data from 2 cohorts of patients: those treated with avacopan for active AAV, and a second cohort treated with a cyclophosphamide or rituximab-based induction regimen without avacopan for active AAV. The overall study duration is anticipated to be up to 7 years, including a recruitment period of approximately 3 years. Enrolled patients will be followed until the last patient last visit (LPLV) milestone, which will be 4 years after the last participant is enrolled. Germany and the UK have been selected for the study. Additional countries may be considered according to availability of avacopan and suitability for the study. In the UK, some of the centres expected to be selected are contributing to the United Kingdom and Ireland Vasculitis (UKIVAS) registry, while some others are not. Centres are selected according to a defined list of selection criteria. Patients will be enrolled prospectively, but up to 6 months of data may be collected retrospectively if necessary. Baseline visit is defined as the day that induction treatment (avacopan or non-avacopan standard of care (SoC) cyclophosphamide or rituximab) is started for active AAV. Patients who started avacopan/SoC induction therapy for AAV within 6 months of the enrolment visit and fulfil eligibility criteria may be enrolled in the PASS. Individual participant follow-up data will be collected periodically at routine clinic visits until the LPLV, which will be 4 years after the last participant is enrolled. All decisions on therapeutic or diagnostic procedures, treatments, management of the disease, timing of visits, or resource utilisation will be at the full discretion of the Investigator and are expected to follow the Investigator's usual clinical practice.
Population:	Inclusion Criteria: • Diagnosis of AAV (MPA or GPA), as determined by the Investigator according to their usual practice. • Active, severe AAV at the time of commencing avacopan or non-avacopan SoC induction therapy, in the opinion of the Investigator. • Age ≥18 years of either sex. • Has provided written informed consent. • Has commenced within the previous 6 months, or is planned to commence avacopan, cyclophosphamide or rituximab for the treatment of severe, active AAV outside of an interventional clinical study. Exclusion Criteria: • Concurrent participation in an interventional study, unless prospectively discussed and agreed with the Medical Monitor.

<table>
<tr><td>Variables:</td><td>Variables including patient demographics, smoking status, certain prior and concomitant medications, AAV disease history and vasculitis treatment history, disease activity and major medical comorbidities will be collected at baseline.

Variables including AEs, ADRs, MESIs, SAEs, SADRs, safety laboratory investigations, disease-related damage, flares and use of concomitant immunosuppression and GC use will be collected during follow-up.</td></tr>
<tr><td>Data Sources:</td><td>Data collected after signing the informed consent will be considered primary data collection (primary use of data). It is anticipated that a limited amount of secondary data collection will be undertaken for participants that started avacopan or non-avacopan SoC induction therapy up to 6 months prior to enrolment in the study.

Data sources will include the medical records, routine measurements (e.g., laboratory parameters) and patient reports. The data collected will be indirectly identifiable and reported in the study-specific electronic Case Report Form (eCRF) by the participating centres.

The Sponsor will follow established processes for AE collection and reporting.</td></tr>
<tr><td>Study Size:</td><td>The study sample size will comprise approximately 500 patients. Recruitment will be monitored to ensure approximately 250 of these are in the avacopan group and approximately 250 in the non-avacopan group.</td></tr>
<tr><td>Data Analysis:</td><td>Statistical analyses will be exploratory in nature.</td></tr>
<tr><td>Milestones:</td><td><table>
<tr><td>First patient first visit:</td><td>2H (second half) 2023</td></tr>
<tr><td>Last patient first visit:</td><td>2H 2026</td></tr>
<tr><td>Last patient last visit:</td><td>2H 2030</td></tr>
<tr><td>Progress reports:</td><td>Incorporated in the avacopan Periodic Safety Update Report (PSUR)</td></tr>
<tr><td>Interim reports:</td><td>Every 24 months (after first patient first visit)</td></tr>
<tr><td>Registration in the EU-PAS register:</td><td>After confirmation by EMA</td></tr>
<tr><td>Final report:</td><td>2H 2031</td></tr>
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5. AMENDMENTS AND UPDATES

Version	Date	Section of the Study Protocol	Amendment or Update	Reason
3.0	25-Jan-2023	All sections were updated	• Update of milestones per the actual study timelines • Revision of the primary and secondary objectives and endpoints • Removal of exploratory objectives and endpoints • Revision of safety data review process • Revision of the eligibility criteria for both treatment groups • Follow-up of patients up to the end of the study, i.e., enrolled patients will be followed for at least 4 years up to LPLV • New section added for the data collection of patients enrolled up to 6 months after starting treatment • New section added for the data collection for patients switching therapy during the follow-up period • New section added for patients lost to follow-up • Update of protocol section on Bias, Confounding and Effect-Modifying Factors to include prior treatment exposure as a potential confounding factor to be controlled	Update of the protocol following the Final Assessment Report on the proposed protocol (Version 2.0) from the PRAC received on 15-Dec-2022.
2.0	02-Sep-2022	All sections were updated	• Extension of follow-up period to 4 years • Revision of the primary and secondary objectives and endpoints • Development of rationale for the study and rationale for study design • Revision of the eligibility criteria with different eligibility criteria per treatment group • Update of the list of variables and of the visit schedule (Table 1)	Update of the protocol following the Final Assessment Report on the proposed protocol (Version 1.0) and feasibility assessment from the PRAC received on 21-Jul-2022.

Version	Date	Section of the Study Protocol	Amendment or Update	Reason
			• Description on management of patients switching treatment group • Clarification of use of primary data and update of the data management section accordingly • Development of Bias, Confounding and Effect-Modifying Factors • Development of limitations • Revision of management and reporting of safety events • Provision of list of MESIs in Appendix 3	
1.0	31-Mar-2022		First version	

Notes: LPLV=Last patient last visit; MESI=Medical event of special interest; PRAC=Pharmacovigilance Risk Assessment Committee.

6. MILESTONES

Milestones	Planned Date
First patient first visit	2H 2023
Last patient first visit	2H 2026
Last patient last visit	2H 2030
Study progress report	Incorporated in the PSUR
Interim reports	Every 24 months (after first patient first visit)
Registration in the EU-PAS register	After confirmation by EMA
Final report of study results	2H 2031

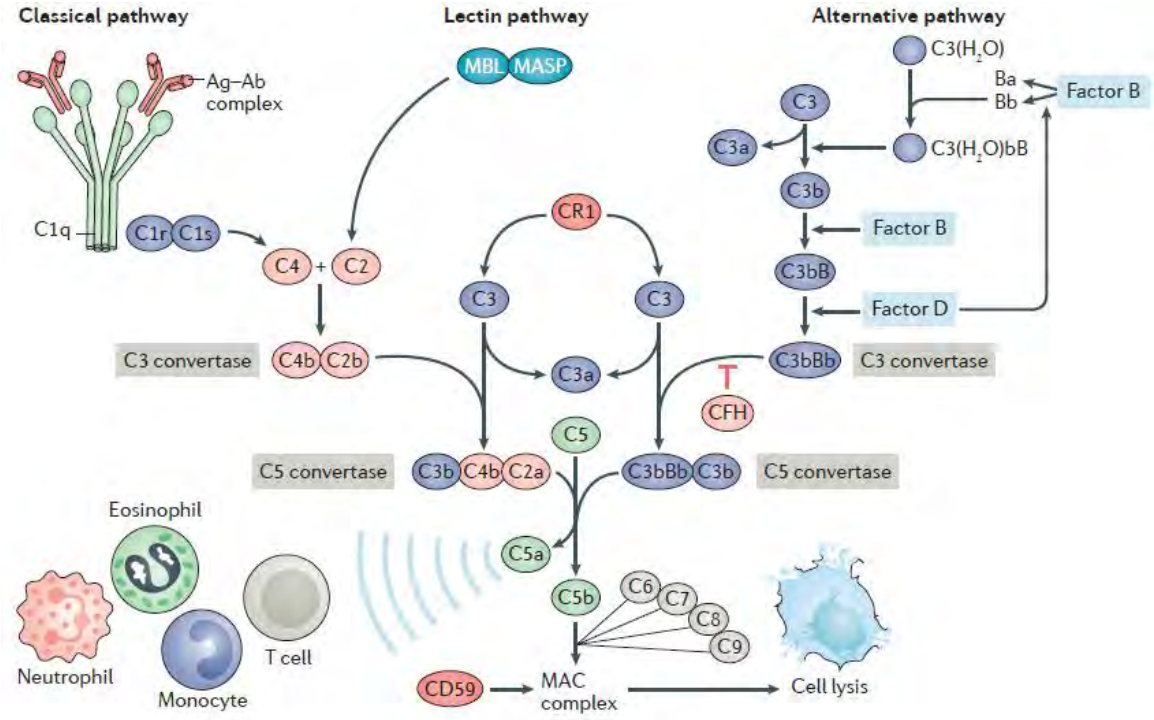
Notes: 2H=Second half; EU-PAS=European Post-authorisation Study; PSUR=Periodic Safety Update Report.

7. RATIONALE AND BACKGROUND

7.1 The Role of the Complement System in Innate Immunity

As illustrated in Figure 1, the activation of the complement pathway generates biologically active fragments of complement proteins, e.g., anaphylatoxins complement 3a (C3a), complement 4a (C4a), and complement 5a (C5a), and the C5b-9 membrane attack complex or terminal complement complex, all of which mediate inflammatory responses by inducing leukocyte chemotaxis, activating macrophages, neutrophils, platelets, mast cells and endothelial cells, and by increasing vascular permeability, cytolysis, and tissue injury [1]. C5a is one of the most potent proinflammatory mediators of the complement system, being at least 100 times more potent than C3a. This 8.3 kD polypeptide, along with a C5b fragment, is produced by enzymatic cleavage of a C5 precursor protein during activation of any of the 3 complement pathways. C5a induces expression of adhesion molecules and chemotactic migration of neutrophils, eosinophils, basophils, and monocytes. It also mediates inflammatory reactions by causing smooth muscle contraction, increasing vascular permeability, inducing basophil and mast cell degranulation, and inducing release of lysosomal proteases and oxidative free radicals. The anaphylactoid and chemotactic effects of C5a are mediated through its interaction with the C5a receptor (C5aR), which is expressed on human neutrophils, monocytes, basophils, eosinophils, renal glomerular tissues, and lung smooth muscle and endothelial cells [2].

Figure 1 Complement Cascade Showing the Classical, Lectin, and Alternative Pathways



Notes: Ab=Antibody; Ag=Antigen; CFH=Complement factor H; MAC=Membrane attack complex; MASP=Mannan-binding lectin serine protease; MBL=Mannan-binding lectin.
Source: Chen et al, 2017 [3].

7.2 ANCA-Associated Vasculitis

AAV is a small vessel vasculitis and includes the diseases GPA (formerly called Wegener's granulomatosis) and MPA. These diseases have been associated with the production of circulating autoantibodies against the neutrophil-expressed antigens myeloperoxidase and proteinase 3 (PR3). A third form of AAV, eosinophilic GPA, has a quite distinct clinical presentation and management pathway and is not in the scope of this PASS. MPA or GPA are classified per the American College of Rheumatology/European League Against Rheumatism (EULAR) classification criteria 2022 [4].

Based on EULAR/European Renal Association-European Dialysis and Transplant Association recommendations, current treatment of AAV relies primarily on potent immunosuppression regimens using either the alkylating agent cyclophosphamide plus GC or the B-cell depleting biologic treatment rituximab plus GC to induce remission in patients with organ-threatening or life-threatening AAV. Methotrexate or mycophenolate mofetil plus GC are also recommended to induce remission in non-organ-threatening AAV. For remission maintenance, a combination of low-dose GC and either azathioprine, rituximab, methotrexate or mycophenolate mofetil is recommended for at least 2 years [5].

GC are still an essential component of the treatment of AAV but are associated with important morbidity, particularly in the context of long-term use. This includes weight gain, increased blood glucose, peripheral oedema, hypertension, psychiatric side effects, metabolic bone demineralisation and osteoporosis, cataracts, and long-term cardiac risks.

Despite treatment advances, AAV remains a serious disease. Patients continue to suffer from both organ-threatening active inflammation and cumulative organ damage as well as clinically important side effects from currently used pharmacological treatment options.

7.3 Complement and the Pathophysiology of AAV

Although the aetiology of ANCA-associated disease is not fully understood, its pathogenesis is strongly linked to activation of the alternative complement pathway and the ensuing generation of C5a in an inflammatory environment, where neutrophils are primed to express ANCA antigens [6,7].

7.4 Avacopan

Avacopan (previously known as CCX168) is an orally administered, first-in-class, selective inhibitor of the binding of C5a to the C5a receptor (C5aR, also called CD88). As of January 2022, avacopan has been approved in Japan, Europe (via Centralised Procedure), Canada, the UK, Switzerland ,the US, and United Arab Emirates for the treatment of AAV (GPA and MPA).

Approval was primarily based on data from the pivotal Phase 3 ADVOCATE study (CL010_168), which evaluated the efficacy and safety of avacopan in patients with AAV over a 52-week treatment period and an 8-week follow-up period using a randomised, double-blind, double-dummy, active-controlled design. This study enrolled 331 patients in

18 countries in North America, Europe, Australia, New Zealand and Japan. Enrolled patients were randomised 1:1 to 2 groups: avacopan 30 mg oral twice daily or tapering prednisone, both with SoC background immunosuppression of cyclophosphamide followed by azathioprine or rituximab.

This study met both primary endpoints, showing that avacopan was non-inferior to a tapering prednisone regimen in achieving remission at Week 26 and superior in achieving sustained remission at Week 52. In addition, mean cumulative steroid use was substantially less in the avacopan-treated patients. Furthermore, a greater improvement in eGFR with avacopan was observed at Week 52.

Across the clinical development programme, avacopan was generally well tolerated. In Phase 3 Study CL010_168, the number of treatment-emergent AEs and SAEs observed in the avacopan group was lower compared to the prednisone group. The number of SAEs (excluding events of worsening vasculitis) was 33% higher in the prednisone group than in the avacopan group, a finding consistent with a higher exposure to GC in that group, and there were more deaths, life-threatening SAEs, and infections in the prednisone group than in the avacopan group. The longest treatment duration studied during clinical development of avacopan has been 52 weeks.

The avacopan EU Risk Management Plan (RMP) has identified liver injury as an important identified risk. In the Phase 3 study, study treatment was paused or discontinued in 5.4% patients in the avacopan group and 3.0% of patients in the prednisone group because of liver function tests (LFTs) increased. The RMP also describes important potential risks, based on an integrated analysis of the avacopan mechanism of action and safety data obtained during the clinical development programme. These are the potential risks of serious infection, cardiac safety and malignancy.

7.5 Rationale for This Study

Avacopan was approved for the treatment of GPA and MPA in the EU by the European Commission on 11 January 2022. The assessment of the EU Marketing Authorisation Application of avacopan was based on available data from the clinical development programme. It is therefore of interest to observe the drug in daily use and generate long-term safety data under real-world settings. Such information will be gathered in the context of this PASS. 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 in additional patients in a real-world context, where treatment may potentially continue beyond 1 year. This study will generate important information on avacopan's benefit/risk and safety profile in those patients where avacopan is continued beyond 1 year. This protocol fulfils the requirements of the EMA to conduct a PASS as a post-marketing commitment.

8. RESEARCH QUESTION AND OBJECTIVES

Research Question:

- What are the incidence rates of defined MESIs in a real-world cohort of patients commencing avacopan for AAV?

Primary Objective:

- To evaluate the incidence of defined MESIs in patients with AAV commencing avacopan.

Secondary Objectives:

- To evaluate the incidence of AEs, AEs leading to discontinuation of therapy, SAEs, ADRs, SADRs, laboratory abnormalities, disease flares as measured by the BVAS, and organ damage as measured by the VDI in patients with AAV commencing avacopan.

- To evaluate the background incidence of AEs, MESIs, SAEs, laboratory abnormalities, disease flares as measured by the BVAS, and organ damage as measured by the VDI in a similar population of patients with severe, active AAV but not receiving avacopan.

- To compare SAEs and MESIs in patients with AAV between patients with and without avacopan.

- To describe patterns of immunosuppression/GC use in a real-world cohort.

- To describe avacopan use in a real-world cohort.

9. RESEARCH METHODS

9.1 Study Design

This study is a non-interventional, multi-national, prospective cohort study. The overall study duration is anticipated to be up to 7 years, including a recruitment period of approximately 3 years. Enrolled patients will be followed until the LPLV milestone, which will be 4 years after the last participant is enrolled.

The study will enrol approximately 500 adult patients diagnosed with AAV (MPA or GPA) into 2 cohorts: those treated with avacopan for active AAV (target number 250 patients), and a second cohort treated with a cyclophosphamide or rituximab-based induction regimen without avacopan for active AAV (target number 250 patients).

Recruitment will be tracked and if necessary, certain measures may be implemented to ensure balanced recruitment to each group, and to ensure an appropriate mix of treatment regimens (cyclophosphamide-based versus rituximab-based) in the non-avacopan group. Potential measures could include opening additional study centres or temporarily pausing recruitment to one or other treatment group.

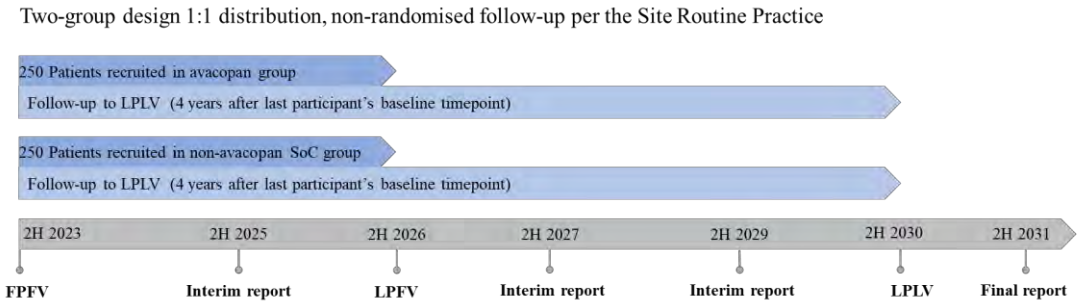
Germany and the UK have been selected for the study. Additional countries may be considered according to availability of avacopan and suitability for the study. In the UK, some of the centres expected to be selected are contributing to the UKIVAS registry, while some others are not. Centres will be selected according to a defined list of selection criteria, as described in Section 9.5.1.

Patients will be enrolled prospectively, but up to 6 months of data may be collected retrospectively if necessary, as described in Section 9.2.3. Baseline visit is defined as the day that induction treatment (avacopan or non-avacopan SoC cyclophosphamide or rituximab) is started for active AAV. The list of variables collected at each time point is described in Table 1. Variables including patient demographics, smoking status, certain prior and concomitant medications, AAV disease history and vasculitis treatment history, baseline disease activity and major medical comorbidities will be collected at baseline.

Individual participant follow-up data will be collected periodically at routine clinic visits from enrolment until the LPLV (e.g., for at least 4 years up to LPLV). Variables collected during follow-up include AEs, MESIs, SAEs, selected safety laboratory investigations, disease-related damage, flares and use of concomitant immunosuppression and GC. The data will be collected from the medical records, routine measurements (e.g., laboratory parameters) and patient reports, and will only include data from visits or investigations conducted as part of a patient's usual vasculitis management. All decisions on therapeutic or diagnostic procedures, treatments, management of the disease, timing of visits, or resource utilisation will be at the full discretion of the Investigator and are expected to follow the Investigator's usual clinical practice.

The study begins on the date when the first patient is enrolled and ends at the LPLV (Figure 2). Expected study visits are illustrated in Table 1, reflecting anticipated SoC clinic visits.

Figure 2 Study Flow Chart



Notes: 2H=Second half; FPFV=First patient first visit; LPFV=Last patient first visit; LPLV=Last patient last visit; SoC=Standard of care.

9.1.1 Rationale for Study Design

Study Design

The non-interventional design of this PASS was chosen in order to study avacopan use in patients during routine clinical practice and collect real-world data.

Study Duration and Sample Size

Five hundred patients, including 250 patients in the avacopan group and 250 patients in the non-avacopan group will be enrolled in this study. This sample size provides sufficient power to detect a single event where the underlying event incidence is at least 0.2% per year. Individual participant follow-up data will be collected for at least 4 years. The approach to follow-up was chosen to provide an opportunity to better characterise the MESIs and permit the detection of any other rare potential safety concerns that might not have been identified during the clinical development programme, where the maximum treatment duration was 1 year.

Inclusion of a Non-avacopan Group and Eligibility Criteria

The inclusion of a non-avacopan group has the potential to provide information on the background incidence rate of safety events of interest. The value of the comparator cohort will be defined by how well it: (i) represents a cohort of patients who would otherwise be eligible to receive avacopan and (ii) is sufficiently homogenous (e.g., patients receiving a limited number of regimens) to permit comparisons to be made where appropriate. There is however a substantial risk that any between-group comparisons will be confounded by baseline differences between these groups. Therefore, the non-avacopan comparator group will be limited to participants receiving cyclophosphamide- or rituximab-based induction regimens only. This will serve the dual function of reinforcing the requirement for active, severe disease in participants recruited to the non-avacopan group and improving the properties of the non-avacopan group for making comparisons.

Retrospective Data Collection

Allowing up to 6 months retrospective data collection is important for the feasibility of the study and will not compromise study or data integrity. It will substantially improve the ability of centres to recruit participants, because it means centres will not necessarily need to recruit and consent patients during the short window period between diagnosis and commencing induction therapy, time during which patients are often confronted by an overwhelming amount of new information and when instituting appropriate treatment is the priority. In addition, allowing retrospective data collection will support early recruitment in countries where avacopan is already marketed, with the benefit of increasing the number of patients available for early interim analyses. A period of 6 months for retrospective data collection was selected because this is a reasonable window in which to expect that retrospective data collection can be conducted without significant loss of quality.

Risk Windows for MESIs

In determining whether MESIs occurring after avacopan has been discontinued should be assigned to the avacopan group, the following risk window will be used:

- Malignancy events will be analysed using an indefinite risk window.

  This risk window is selected because of the long lead time of malignancies and importance for patients.

- Other events will be analysed using a risk window of 9 weeks.

  This risk window is selected because of the concentration-time profiles of avacopan and metabolite M1. As described in the Summary of Product Characteristics (SmPC) [8], the concentration-time profiles were simulated assuming a dosing regimen of 30 mg twice daily for 3 months (reaching steady state) followed by a washout period of 4 months. In the washout period, the residual plasma concentrations of avacopan decreased to <10% of the maximum concentration under steady state approximately 50 days after the last dose. With regard to the main metabolite M1, in the washout period, the residual plasma concentrations of M1 decreased to <10% of the maximum concentration under steady state approximately 63 days (9 weeks) after the last dose. Based on the aforementioned data showing reasonable washout (~10% or lower) after 3 months of treatment, a 9-week risk window for all events, excluding malignancies will be applied.

9.1.2 Reasons for Choice of Treatment

This is a non-interventional study. All decisions on therapeutic or diagnostic procedures, treatments, management of the disease or resource utilisation will be at the full discretion of the Investigator without interference by the Sponsor or the study protocol. It is expected that in making treatment decisions Investigators will be mindful of product SmPCs. All treatment decisions will therefore reflect real-life use in clinical practice.

9.1.3 Endpoints

Primary Endpoint:

- Incidence rates of defined MESIs (liver injury, cardiac safety, serious infection, and malignancy) for the avacopan group.

Secondary Endpoints:

- Incidence rates of AEs, AEs leading to discontinuation of therapy, SAEs, ADRs SADRs, change in recorded laboratory assessments over time, time to first flare, and change in VDI score over time for the avacopan group.

  A flare is defined in the BVAS as a score of more than 0. No flare is defined as a BVAS score equal to 0.

- Incidence rates of AEs, MESIs, SAEs, change in recorded laboratory assessments over time, time to first flare, and change in VDI score over time for the non-avacopan group.

- Incidence rates of SAEs and MESIs in the avacopan group compared to the non-avacopan group, using an exploratory propensity score approach.

- Use of concomitant immunosuppression over time and cumulative by treatment group, duration of GC-free periods and proportion of GC-free patients over time by treatment group.

- Duration of treatment with avacopan by reason for treatment discontinuation.

9.2 Setting

9.2.1 Eligibility

Patients fulfilling all the following inclusion criteria and none of the exclusion criteria may be enrolled in the study. Investigators should not be influenced by the eligibility criteria when making patient management decisions: they should follow their usual clinical practice irrespective of the opportunity to participate in this study.

9.2.1.1 Inclusion Criteria

- Diagnosis of AAV (MPA or GPA), as determined by the Investigator according to their usual practice.

- Active, severe AAV at the time of commencing avacopan or non-avacopan SoC induction therapy, in the opinion of the Investigator.

- Age ≥18 years of either sex.

- Has provided written informed consent.

- Has commenced within the previous 6 months, or is planned to commence avacopan, cyclophosphamide or rituximab for the treatment of severe, active AAV outside of an interventional clinical study.

9.2.1.2 Exclusion Criteria

- Concurrent participation in an interventional study, unless prospectively discussed and agreed with the Medical Monitor.

9.2.2 Schedule

Data will be collected at the visit undertaken for routine clinical care that aligns most closely with the approximate visit schedule outlined in Table 1.

Visits will not be scheduled for the purpose of this study. Therefore:

- If no visit was undertaken per the site's practice, time points outlined in Table 1 may be missed.

- In case frequency of visits in routine clinical care is higher than scheduled in Table 1, the additional time points will not be collected for the study. Instead the visit occurring closest to the target date of follow-up visits outlined in Table 1 will be used.

Assuming that routine clinical care permits, the data will be collected at the enrolment visit, baseline visit (which may be the same as the enrolment visit), then every 3 months during the first year and every 6 months thereafter until the end of the study. For patients who started avacopan/SoC induction therapy before enrolment, baseline data and first 3-month follow-up visit may be collected retrospectively. Data to be recorded for this study at each time point (if available) are outlined in the schedule presented in Table 1. Safety events will be collected on a continuous basis during the patient's follow-up period.

An individual participant completes their participation in the study after completing an end of follow-up visit. The end of study visit will replace the 6-monthly follow-up visit that would otherwise be scheduled during the window 6 months prior to the planned LPLV milestone.

Table 1 Planned Schedule for the PASS

	Enrolment Visit	Baseline (Treatment Start)[1,2]	Approximate Visit Schedule per the Site Routine Practice (Relative to Treatment Start)		
			1 Visit Every 3 Months in the 1st Year	1 Visit Every 6 Months After the 1st Year	End of Follow-up
			3[2], 6, 9, 12 Months	18, 24, 30, 36 Months	Study Exit/ End of Study
Signed informed consent[3]	X	–	–	–	–
Inclusion/exclusion criteria	X	–	–	–	–
Year of birth, gender, ethnicity, race	X	–	–	–	–
Height and body weight	–	X	–	–	–
Smoking history and current status	–	X	–	–	–
MPA or GPA diagnosis[4]	–	X	–	–	–
Medical history/comorbidities[5]	–	X	–	–	–
Prior treatment with immunosuppressive drugs[6]	–	X	–	–	–
Treatment group and exposure[7]	–	X	X	X	–
Reason for choosing the treatment group	–	X	–	–	–
ANCA titres[8]	–	X	–	–	–
ANCA positivity[9]	–	–	X	X	X
Laboratory values[10]	–	X	X	X	X
BVAS[11]	–	X	X	X	X
VDI[12]	–	X	X	X	X
Concomitant medication[13]	–	X	X	X	X
Treatment discontinuation and reasons	–	–	X	X	X

	Enrolment Visit	Baseline (Treatment Start)[1,2]	Approximate Visit Schedule per the Site Routine Practice (Relative to Treatment Start)		
			1 Visit Every 3 Months in the 1st Year	1 Visit Every 6 Months After the 1st Year	End of Follow-up
			3[2], 6, 9, 12 Months	18, 24, 30, 36 Months	Study Exit/ End of Study
Study discontinuation and reasons	–	–	–	–	X
Recording of AEs, SAEs, ADRs, SADRs, MESIs (liver injury, serious infections, malignancy, and serious cardiac events)[14]	–	X	X	X	X

1 Baseline visit corresponds to date of start of avacopan or non-avacopan induction therapy (cyclophosphamide or rituximab).
2 Patients who started avacopan/SoC within 6 months of study start may have these data documented retrospectively.
3 The informed consent includes the approval to collect retrospective data.
4 It includes 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 titre and specificity.
5 Medical history includes aetiology of underlying disease, history of major related health issues and procedures, e.g., surgery due to underlying disease.
6 Including dose, duration before start of treatment, reason for change in dose/medication.
7 Including start date, stop date (if applicable), daily dose/frequency, route of administration (intravenous or oral), and reason for treatment initiation/switch, rationale for starting, stopping or changing the dose (completion of planned course, AE, Investigator/patient's decision, withdrawal of consent, administrative problems, death, other).
8 At baseline: if the patient is ANCA positive, PR3 and/or MPO titres will be collected (if available). Highest PR3 and MPO titres in patient medical history will be collected (if available).
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/frequency, route of administration (intravenous or oral), and reason for treatment initiation/switch, rationale for starting, stopping or changing the dose (completion of planned course, AE, Investigator/patient's decision, withdrawal of consent, administrative problems, other). Limited to GC and immunosuppressants.
14 AEs/SAEs/ADRs/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.

Notes: AAV=ANCA-associated vasculitis; ADR=Adverse drug reaction; AE=Adverse event; ALT=Alanine transaminase; ANCA=Anti-neutrophil cytoplasmic antibody; AST=Aspartate aminotransferase; BVAS=Birmingham Vasculitis Activity Score; CPK=Creatine phosphokinase; eGFR=Estimated glomerular filtration rate; IgG=Immunoglobulin G; GC=Glucocorticoids; GPA=Granulomatosis with polyangiitis; MESI=Medical event of special interest; MPA=Microscopic polyangiitis; MPO=Myeloperoxidase; PASS=Post-authorisation Safety Study; PR3=Proteinase 3; SADR=Serious adverse drug reaction; SAE=Serious adverse event; SoC=Standard of care; VDI=Vasculitis Damage Index; WBC=White blood cell.

9.2.3 Retrospective Data Collection for Baseline and 3-Month Time Points

Patients will be enrolled prospectively, but up to 6 months of data may be collected retrospectively if necessary for a minority of patients.

With 6 months retrospective data collection, there would be a need to collect retrospective data for at most 2 time points (e.g., baseline and the visit occurring at approximately 3 months post-baseline):

- Data required for the baseline time point include historical information on disease history, comorbidities and prior treatment. This will be extracted from the medical records (including patient notes, pharmacy records, laboratory results and other site-specific sources) in the same way as for patient enrolled at the point of commencing induction therapy.

- The baseline time point also requires the collection of contemporaneous information (e.g., height, weight, smoking status, concomitant medications and laboratory results). Investigators are instructed to collect this from the most recent relevant medical records entry prior to or on the date of initiation of induction therapy. It is anticipated that all necessary information will be recorded in the medical records as part of routine medical care. For example, height and weight will be documented as it is necessary to calculate the cyclophosphamide or rituximab dose. The required laboratory values including eGFR, IgG, LFTs and ANCA levels will be available on or near baseline because they are important for the diagnosis and safe treatment of patients with active, severe AAV. Concomitant medications will also be documented in the medical records for similar reasons.

- Additional data collection at the 3-month time point will include AEs occurring during the previous 3 months, new laboratory values and relevant clinical and concomitant medication changes. These will be extracted from the medical records entry corresponding to the 3-month time point, together with a review of the medical records for the intervening period to ensure that data ascertainment has been completed (as would also occur at a standard prospective visit). Patient recall of AEs, medication changes and clinical events will provide an additional check on the completeness of the medical records.

- AE collection and documentation should be routine and ongoing as part of patient care. Documentation and management of AEs identified through secondary use of data will follow Good Pharmacovigilance Practice (GVP) guidance, as per Section 11.6. Therefore, complete ascertainment of the most important events – SAEs and MESIs – should be straightforward for Investigators within a retrospective window of 6 months for the following reasons: (i) criteria for seriousness should be readily evident from the medical records (e.g., hospital admission); (ii) liver injury can be specifically screened for by reviewing LFTs obtained since starting induction therapy; (iii) infection can be specifically screened for by reviewing investigations and antimicrobial prescriptions;

(iv) malignancy is a significant event that should be well documented in the medical records given its critical relevance to the management of immunosuppression; and (v) significant cardiac events should likewise be well documented and could be sought by screening admissions, troponin and B-type natriuretic peptide measurements. In addition, patient recall of major AEs over a 6-month period is expected to be good.

9.2.4 Patients Stopping or Starting Avacopan During the Study

Participants may stop or start avacopan during their participation in the study (as a non-interventional study, participants must be managed according to usual practice), but this will have the following implications for their participation in the study:

- Participants in the non-avacopan group who start avacopan during the follow-up period due to a flare will be discontinued from the study at that point but may re-enrol in the avacopan group if the study eligibility criteria are fulfilled and the recruitment period is still open. These participants will have to re-sign an informed consent at the time of re-enrolment and will be attributed with a new patient identification number.

- Participants in the avacopan group who cease avacopan during the follow-up period will continue in the study and will continue to be followed up as part of the avacopan group.

This approach is aligned with the objectives of the study (e.g., safety profile of avacopan) and recognises the fact that any events occurring after avacopan is started can no longer be reasonably analysed within the non-avacopan group. Continuing to follow up participants in the avacopan group who cease avacopan during the follow-up period as part of the avacopan group will also allow for specified AEs with a long lead time (e.g., malignancy) to be captured if they occur, as well as allow for information on flare risk and progression of organ damage during the period after discontinuing avacopan to be obtained.

9.2.5 Patients Lost to Follow-up

Patients will be considered as lost to follow-up following 3 phone attempts and 1 written attempt to contact the patient for a follow-up visit, documented in the medical records. At that time, the study discontinuation form will be completed. Lost to follow-up patients will not be replaced in the study. All data already collected until study discontinuation may be used in analysis.

9.2.6 Representativeness

Data from patients enrolled in the study and meeting all eligibility criteria will be used for the study. In addition, geographic spread and site characteristics will be considered in selecting centres for this study (see Section 9.5.1).

Therefore, the avacopan group in this study is expected to be highly representative of the population of patients receiving avacopan outside of clinical studies.

9.3 Variables

The expected data to be collected will be summarised as follows. The expected timing for the collection of each variable is presented in Table 1.

9.3.1 Baseline Data

- Demographics (year of birth, gender, height, body weight, ethnicity, race)
- Smoking history and current status
- MPA or GPA diagnosis and history (AAV phenotype, year of diagnosis, pattern of organ involvement, year of last relapse, number of relapses in the past 5 years prior to baseline, history of positive ANCA, specificity and maximum titre)
- Medical history (aetiology of underlying disease, history of major related health issues and procedures, e.g., surgery due to underlying disease)
- History on ANCA positivity (MPO and/or PR3): highest PR3 and MPO titres in patient medical history will be collected as well if available
- Comorbidities
- Prior treatment with immunosuppressive drugs, including dose, duration before start of treatment, reason for change in dose/medication
- Treatment group and exposure (per Section 9.3.2)
- Reason for choosing the treatment group
- ANCA titres (MPO and/or PR3) if positive at baseline
- Laboratory assessment (if assessed per the site's routine practice). It includes creatinine, eGFR, IgG, CPK, ALT, AST, bilirubin, WBC count and albumin
- BVAS
- VDI (modified at baseline to capture prior (non-vasculitis related) damage, including infections)

9.3.2 Exposure/Treatment

Information on avacopan and the following non-avacopan immunosuppressive medications will be collected: cyclophosphamide, azathioprine, mycophenolate, rituximab and GC. The following variables for each of the medications above will be collected at each visit:

- Start date
- Stop date, if applicable
- Daily dose/frequency
- Route of administration (intravenous or oral)
- Reason of treatment initiation/switch
- Rationale for starting, stopping or changing the dose (e.g., completion of planned course, AE, Investigator/patient's decision, withdrawal of consent, administrative problems, death, other)

9.3.3 AE Data Collection

Collection of AEs from baseline include the seriousness, timing of onset, duration, causal relationship to avacopan, action taken with avacopan in response to the event, and outcome of the event. These variables will be collected for:

- MESIs (definitions provided in Section 11.3). The defined preferred terms (PTs) for MESIs are listed in Appendix 3.
- SAEs
- AEs
- ADRs
- SADRs

9.3.4 Additional Follow-up Data

- ANCA positivity (MPO and/or PR3), if the patient is ANCA positive
- Laboratory assessments (if assessed per the site's routine practice). This includes creatinine, eGFR, IgG, CPK, ALT, AST, bilirubin, WBC count and albumin
- BVAS, collected at each episode of flare
- VDI

9.3.5 Visits

For each visit the date (day, month, year) will be documented. An expected visit schedule is presented in Table 1, but actual visits will be performed per site's routine practice.

9.4 Data Sources

Data collected after signing the informed consent will be considered primary data collection (primary use of data). It is anticipated that a limited amount of secondary data collection will be undertaken for participants that started avacopan or non-avacopan SoC induction regimen up to 6 months prior to enrolment in the study.

Data sources will include the medical records, routine measurements (e.g., laboratory parameters) and patient reports. The data collected will be indirectly identifiable and reported in the study-specific eCRF by the participating centres.

The Sponsor will follow established processes for AE collection and reporting.

9.5 Study Size

The study sample will comprise approximately 500 adult patients diagnosed with severe, active AAV (MPA or GPA). Two separate cohorts will be recruited: patients treated with avacopan (target number of 250 patients) and patients treated with non-avacopan SoC induction regimen (target number of 250 patients).

9.5.1 Participating Centres

The PASS will be conducted in countries where avacopan is commercially available. UK and Germany have been selected as initial countries for this study. In the UK, some of the centres expected to be selected are contributing to the UKIVAS registry, while some others are not. Additional European countries may be considered during the study, selected according to suitability for the study and availability of avacopan.

Patients will be recruited from specialist vasculitis centres with geographic spread, with individual centres selected according to the following principles:

- Have experience in the treatment and management of severe active AAV patients
- Have a high potential to treat AAV patients with avacopan and have a large AAV population
- Are routinely performing patient evaluation and follow-up per the schedule outlined in the study protocol
- May have experience in use of BVAS and VDI
- Have access to avacopan (or will have access to avacopan in the near future)

- Have proven experience in managing non-interventional studies
- Have sufficient time and resources to perform the PASS
- Are willing to comply with local requirements and regulations

9.5.2 Justification for Sample Size

Five hundred patients, including 250 patients in the avacopan group and 250 patients in the non-avacopan group will be enrolled in this study. Based on this number of patients, the properties of the study were determined to ensure that the objectives of the study could be assessed. As per Table 2, considering a reasonable attrition rate of 15% per year, the power of the study to detect a single event will be 77% for an AE with an incidence rate per year of 0.2%, a follow-up duration of 4 years and 250 participants in the avacopan group. With an attrition rate of 10% per year, the power of the study would be 81% with an incidence rate per year of 0.2% and a follow-up duration of 4 years. Considering the yearly event rate over 4 years, the power of the study is close to 80%; the sample size of 250 participants in the avacopan group is reasonable.

Table 2 Probabilities of Observing at Least 1 Event Assuming Yearly Rate of Event is 0.2%

Year on Study	Attrition Rate per Year (%)	Number of Patients			By Year, Probability to Observe		Cumulative Probability to Observe	
		Start	End	Average Patients	0 Events (%)	At Least 1 Event (%)	0 Events (%)	At Least 1 Event (%)
1	10	250	225	238	62	38	62	38
2	10	225	203	214	65	35	41	59
3	10	203	182	192	68	32	28	72
4	10	182	164	173	71	29	19	81
1	15	250	213	231	63	37	63	37
2	15	213	181	197	67	33	42	58
3	15	181	154	167	72	28	30	70
4	15	154	131	142	75	25	23	77

Malignancy is the rarest of the MESIs under investigation in this study. Based on the literature from transplantation, 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 [9]. The experience in transplantation is relevant because similar intensities of immunosuppression are used and because the available data for cancer incidence in AAV are much less robust. Skin cancer is the commonest malignancy related to immunosuppression after organ transplantation, and in a recent US study of 10,649 transplant recipients this was found to have an incidence of 1,437 per 100,000 person-years, or 1.437% per year and well within the detection limit for this study [9].

9.6 Data Management

The PASS will be a primary data collection programme (primary use of data) for most of the enrolled patients. Data collected after signing the informed consent will be considered primary data collection (primary use of data). It is anticipated that a limited amount of secondary data collection will be undertaken for participants that started avacopan or non-avacopan SoC induction treatment up to 6 months prior to enrolment in the study. Collection of data for these patients is described in Section 9.2.3.

In all cases, data will be collected primarily from the hospital charts (source data) at the participating centres and reported in the study-specific eCRF. The study-specific eCRF will be hosted on a fully validated electronic data capture (EDC) system named MERATIVE Clinical Development (formerly IBM-Clinical Development), supplied by the Contract Research Organisation (CRO) named IQVIA. This EDC is compliant with the applicable computer system validation requirements including quality management system, system development lifecycle process, validation, change control, 21 CFR Part 11 compliance, audit trail, qualification and management of IT infrastructure, archiving and back-up.

Access to the eCRF and study dataset will be restricted, with access granted to delegated team members of the CRO and the Sponsor only where necessary to fulfil their roles. Data will be recorded by the centres in the eCRF. The Sponsor, supported by the CRO IQVIA, will monitor timeliness and completeness of data entry during the study. Automated computer checks and manual checks will be performed on the data to ensure data quality. All changes to the data will be authorised by the Investigator.

Details of continuous and end-of-study checks for missing and inconsistent data are described in a separate Data Management Plan.

Data extraction and analysis will be performed according to established protocols of the data controller(s). Data extraction and analysis will be performed by designated personnel who will be trained and authorised to work with the database. The data controller(s) will ensure data integrity, security, and anonymity by providing appropriate methods of data storage and back-up, including encryption of any confidential data elements, and ensuring that access is strictly limited to relevant user profiles. These methods will comply with the local regulatory guidelines.

Collection of data for AvacoStar will run separately from data collection in the UKIVAS registry. No data in the UKIVAS registry will be imported in the AvacoStar eCRF, i.e., no UKIVAS secondary data will be used in AvacoStar analyses.

9.7 Data Analysis

9.7.1 Statistical Considerations

Statistical analyses will be performed using SAS statistical software Version 9.4 or later version, unless otherwise noted.

Statistical analyses will be exploratory in nature. All variables will be analysed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by descriptive statistics (i.e., number of patients, mean, standard deviation, minimum, median, quartiles, and maximum). Continuous variables will be summarised by absolute value and changes from baseline per analysis time point, if applicable. 95% confidence intervals will be provided where appropriate. Comparisons between treatment groups will be performed using appropriate methods to adjust for potential bias. Outcomes of statistical comparisons will be interpreted with caution.

All statistical issues including calculated variables, handling of missing data, and the format and content of tables will be detailed in the Statistical Analysis Plan (SAP). The SAP will be finalised before study database lock.

In general, baseline for each endpoint will be defined as the data most recently collected prior to first dose of avacopan for patients in avacopan group, or first dose of either rituximab or cyclophosphamide for the current disease episode for the non-avacopan group. For patients who started avacopan before enrolment, baseline data will be collected retrospectively.

Interim analyses are described in Section 9.7.5. The final data analysis will be performed after database lock.

9.7.2 Study Population

The primary analysis and the secondary analysis of treatment duration with avacopan by reason for treatment discontinuation will be performed on the avacopan group only. All other secondary endpoints analyses will be performed for each treatment group (avacopan and non-avacopan) except where specified in the endpoint.

Whenever reasonable and dependent on the number of patients in each specific subgroup, data may be stratified by further parameters (e.g., country, age, gender, previous treatments, time since diagnosis, other relevant clinical characteristics, etc.). Further information will be specified in the SAP.

9.7.3 Analysis of Variables

9.7.3.1 Analysis of Demography, Disease History, Comorbidities, Prior and Concomitant Medication and Other Baseline Data

Baseline data will be described by presenting frequency distributions and/or summary statistics along with 95% confidence intervals by treatment group.

Concomitant medication at baseline will be described by presenting frequency distributions and/or basic summary statistics.

9.7.3.2 Analysis of Exposure/Treatment Data

For avacopan, statistical summaries will be provided for dosing, duration of treatment, reasons for treatment initiation/switch, dose change, treatment interruption, or premature discontinuation.

For SoC treatment, treatment regimens will be described.

9.7.3.3 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. MESIs will be identified as described in Appendix 3. 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.

In determining whether MESIs occurring after avacopan has been discontinued should be reported in the avacopan group, the following risk window will be used:

- Malignancy events will be analysed using an indefinite risk window.
- Other events will be analysed using a risk window of 9 weeks.

MESIs occurring outside the defined risk window will still also be reported by original treatment group but separately to those occurring within the risk window.

Rationale is provided in Section 9.1.1 and further details will be specified in the SAP.

9.7.3.4 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, MESIs, the incidence (number and percentage of patients with these events and total number of events) 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 PT. 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. Respectively, binomial regression model and negative binomial model (with the log of observation duration as offset) will be used for the 2 summary statistics. 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 2 methods: adjustment (the propensity score is included in the regression model) and inverse probability weighting. Full details will be provided in the SAP.

If there are a substantial number of patients moving from the non-avacopan group to the avacopan group, sensitivity analyses will be performed to confirm that no bias has been introduced by this approach. Comparisons of MESI rates between avacopan and the 2 types of SoC treatment (cyclophosphamide or rituximab) may also be performed for exploratory purposes.

For each MESI, similar summary statistics will be provided over time by treatment group.

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 summarised descriptively.

9.7.4 Bias, Confounding and Effect-modifying Factors

The results of observational studies could be affected by potential bias and confounding.

Bias and Confounding Affecting Between-Group Comparisons

For this study, bias and confounding are most likely to impact comparisons made between the treatment groups, related to systematic differences in the type of patients who started on avacopan versus non-avacopan SoC induction regimens. For this reason, and given the difficulty in controlling for this even by implementing all the measures described below the planned comparisons between groups are considered secondary.

The following steps have been taken to minimise this to the extent possible:

- Detailed information will be collected at baseline on potential confounding factors, including relating to disease severity (e.g., BVAS, VDI), diagnosis (e.g., 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 titre), prior immunosuppression exposure, and MESI-related risk factors (e.g., infection – prior lung disease, prior immunosuppression burden; cardiac – traditional cardiac risk factors; malignancy – prior history of cancer, prior immunosuppression burden, diabetes, obesity/body mass index, hypercholesterolaemia, history of psychiatric disease, metabolic bone disease, smoking). These will be used to describe the extent of potential confounding and may form the basis of measures taken to control for this at the analysis stage.

- An important driver of the baseline differences may be the types of patients in whom clinicians may choose to use avacopan, for example with a view to minimising GC exposure in patients with one or more of obesity, diabetes, psychiatric disease, bone disease, refractory disease and substantial previous treatment exposure. These patients may have a higher risk of experiencing a MESI.

- Eligibility criteria have been selected to ensure that the non-avacopan group is similar to the avacopan group (all participants would be potentially eligible to receive avacopan according to the European SmPCs, even if being enrolled into the non-avacopan group).

- To account for the risk of bias resulting from confounding, treatment groups will be compared using propensity scoring methodology. Though efforts will be made to collect information on all known confounders to include in multivariable analyses and to allow for adjustment methodologies, it is possible that unknown confounding factors will remain.

- The duration of treatment by reason for discontinuation will be monitored and reported. Differences in exposure duration of avacopan versus SoC will be accounted for when treatment groups are compared through methods including binomial regression model and negative binomial model with the log of observation duration as offset.

- Patients who switch treatment will be handled as described in Section 9.2.4.

Despite these steps, it is likely that some residual confounding will remain and therefore the results of any direct comparisons between the avacopan and non-avacopan groups will need to be interpreted with this in mind.

Information Bias

Another important source of bias is anticipated to be information bias. For example, in any observational study there may be a risk that AEs are underreported, and that there may be systematic differences in the reporting of AEs related to knowledge of treatment group or concomitant medications. This risk will be mitigated by ensuring Investigators have specific training on the reporting of MESIs and SAEs in this study.

Retrospective data collection for some patients in both groups may happen for the baseline and 3-month time points. This may result in missing data, which itself may introduce bias, but given the nature of the data being collected at baseline and early follow-up and the time window of 6 months, it is believed that this will be minimal. Nonetheless, the completeness of retrospective data collection will be monitored. Subgroup analyses will also be conducted to assess differences for patients with retrospective versus no retrospective data collection to detect any systematic impact on the study analysis.

Missing data will be queried and details of methods for handling missing data will be detailed in the SAP. To minimise missing information overall, data collection will ensure that applicable variables of interest are those that are routinely collected as part of real-world clinical care and are available via medical charts and physician reporting, as appropriate; only critical data elements (i.e., variables aligned with the study objectives) will be collected to minimise site burden; collection of important variables will include the options "not applicable" or "not done" in the eCRFs to differentiate these from values that are truly unknown, where applicable; centres will be trained regarding data collection procedures overall.

Bias Affecting the Generalisability of Study Findings

Selection bias may affect the generalisability of this PASS. In particular there is a risk that centres and patients who agree to participate might differ in important aspects from those who decline participation. The potential impact of this will be mitigated by ensuring a sufficient number of centres with geographic spread participate in the study and by comparing the study population with that of similar observational studies.

There is a risk that the characteristics of patients treated with avacopan may evolve over time as access increases and physicians gain experience in its use. This may also influence the type of patient recruited to the non-avacopan group if avacopan use becomes more routine in this population. Thus patients enrolled earlier in the study may differ in important aspects to those enrolled toward the end of the recruitment period. This will be assessed through subgroup analyses as appropriate, for example analyses of baseline characteristics and AEs for patients recruited earlier versus those recruited later.

It is also anticipated that the avacopan and non-avacopan groups may not be recruited at the same rate, with the risk that any evolution in treatment practices over time may not be reflected evenly between the 2 groups. To mitigate this risk, enrolment will be monitored closely and measures taken to adapt if substantial differences emerge (e.g., capping).

Bias Affecting Reported Event Rates in Either Group

Patients who started avacopan or non-avacopan induction therapy in the 6 months prior to the start of the study but who die or discontinue treatment due to an AE will not be enrolled, potentially resulting in incomplete ascertainment of events during this period.

9.7.5 Interim Analyses

Progress reports (e.g., for recruitment updates) will be incorporated in the PSUR.

Interim reports will be prepared based on data cuts at approximately 24-month intervals from first patient first visit, with further interim reports prepared if needed. Study data may be presented at appropriate congresses.

9.8 Quality Control

An external Scientific Committee has been established to provide expert input into the design, conduct and reporting of the study. It acts in the role of expert advisor to the Sponsor, with the ultimate objective of ensuring that the study is feasible, scientifically rigorous and conducted to a high standard. To achieve this objective, the activities of the Scientific Committee may include:

- Advice on the study protocol including endpoints, data collection and schedule of events
- Advice on site identification

- Review of other AvacoStar-specific data and materials as required
- Advice on the scientific and operational conduct of the study
- Advice on further project development risks and opportunities arising from the AvacoStar dataset
- Review of study data, which will be provided as a regular report including information on enrolment, baseline, and safety. Ad hoc data reviews may also be arranged if necessary
- An opinion may be sought on optimising recruitment, representativeness of the study population and any potential safety issues or bias
- Review and interpretation of interim and final study analyses, and advice on the communication and publication strategy for study findings

In addition to addressing questions raised by the Sponsor and clinical study team, the Scientific Committee may also propose additional topics related to the design and conduct of the study.

The PASS will be conducted according to the Standard Operating Procedures (SOPs) of the Sponsor and the CRO. The SOPs will be used to guide the conduct of Investigators in delivering the study and will include procedures related to internal quality audits of the data, accuracy and consistency of transferred data, validation of coding, creation of a data model, data transformations, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, standards for writing SAPs, and requirements for senior scientific review. Written programming will be reviewed independently. The secure storage of data, log files, output files and back-up will be ensured as required by regulatory guidelines. All key study documents, such as the SAP and study reports, will undergo quality control, regular review, as well as version control. Custom reports will be available live within the database to guide ongoing quality control efforts by the CRO.

9.9 Limitations of the Research Methods

This is a non-interventional study. This study design has important advantages, not least that it generates data that reflects real-world use of the treatments under study. However, this study design also has a number of well-recognised limitations:

- Data collection will reflect routine clinical practice as it occurs. This may impact the amount of data available and its interpretation. This is mitigated through the design of a realistic expected schedule of visits that is anticipated to closely match routine clinical practice.

- Potential biases related to the non-interventional design and their mitigation are described in detail in Section 9.7.4.

- The sample size is based on assumptions around avacopan exposure. It is possible that patients discontinue avacopan or the study early, leading to a lower duration of exposure and shorter AE observation period than anticipated.

- The inherently unblinded nature of the study design may influence the reporting patterns of both patients and Investigators.

- Finally, this is a multicentre, multi-national study to allow for the recruitment of enough patients with AAV. While this has advantages for the generalisability of the study results, heterogeneity between centres and countries may also reduce the ability to draw conclusions from the study dataset, for example by reducing the precision of estimates of MESI incidence rates.

10. PROTECTION OF HUMAN SUBJECTS

10.1 Ethical Conduct of the Study

This PASS is non-interventional. Avacopan and SoC are prescribed in the usual manner in accordance with the corresponding SmPC under the sole decision of the Investigator. The treatment decision falls within current established practice. No additional diagnostic, therapeutic or monitoring processes are required for participation in the PASS and the prescription of the medicine is clearly separated from the decision to enrol the patient in the study. Epidemiological methods will be used for the analysis of the collected data.

This PASS will be conducted within an approved indication in accordance with the Declaration of Helsinki [10], the International Society for Pharmacoepidemiology (ISPE) Guidelines for GPP [11], the EMA Guideline on GVP Module VI and VIII for PASS [12,13], and local laws and regulations as applicable in each country. Additionally, guidelines of the International Council on Harmonisation concerning Good Clinical Practice will be followed whenever possible in the context of a non-interventional study.

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 [13,14,15]. The study will be registered in the ENCePP electronic register of studies.

All study information will be handled and stored in a manner that allows for accurate reporting, interpretation, and verification of that information. Patient data collected in the study will be collected in a pseudonymised/de-identified form. The analysis will be performed on the pseudonymised/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 data and all study documents will be kept until written notification by the Sponsor that records may be destroyed.

The progress reports and final analysis will be reviewed and evaluated by a Medical Monitor and/or pharmacovigilance (PV) delegate. 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. If such a change occurs, it may be necessary to alter the core safety information and SmPC. The results of the study with any updates to the AEs of special interest or safety concerns shall be documented in the respective sections of the PSUR and RMP as per the GVP Module VI and VIII [3,13].

10.2 Regulatory Authorities Approvals/Authorisations

The PASS will be carried out within an approved indication in accordance with guidelines and regulations of EMA and applicable local law(s) and regulation(s) [16].

10.3 Independent Ethics Committee

Consistent with local regulations and prior to enrolment of patients at a given centre, the study protocol will be submitted together with its associated documents (e.g., Informed Consent Form (ICF)) to the responsible IECs for its review. Documented approval from adequate IECs will be obtained in all centres where required. The IEC will be asked to provide documentation of the date of the meeting at which the favourable opinion/approval was given that clearly identifies the study, the protocol version, and the ICF version reviewed. The IEC must supply to the Sponsor upon request a list of the IEC members involved in the vote and a statement to confirm that the IEC is organised and operates according to applicable laws and regulations. Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IEC in a manner consistent with local regulations. Pertinent safety information will be submitted to the relevant IECs during the course of the study in accordance with local regulations and requirements. It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, and ICF, and other relevant documents, if applicable, from their local IEC and provide documentation of approval to the Sponsor. All correspondence with the IEC should be retained in the Investigator File.

Should the study be terminated early for any reason, the Investigator will be responsible for informing the IEC of the early termination.

10.4 Patient Information and Consent

An ICF must be signed by the patient (or the patient's legally authorised representative) before his or her participation in the study, according to local requirements. The medical file for each patient should document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed ICF must be provided to the patient or the patient's legally authorised representative. If applicable, it will be provided in a certified translation of the local language. All signed and dated ICFs must remain in each patient's study file and must be available for verification by study monitors at any time. Patients may withdraw consent at any time, with no effect on the patient's medical care or access to treatment.

The ICF should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate. For any updated or revised ICFs, the medical file for each patient should document the informed consent process and that written informed consent was obtained for the updated/revised ICF for continued participation in the study.

As outlined in Section 9.2.4, participants in the non-avacopan group who start avacopan during the follow-up period may re-enrol in the avacopan group if the study eligibility criteria are fulfilled and the recruitment period is still open. These participants will have to re-sign an informed consent at the time of re-enrolment.

In case the patient agrees to also share his/her data with the UKIVAS registry, the patient will provide informed consent signing the UKIVAS ICF to allow the PASS to share his/her data with the UKIVAS according to local governance rules where applicable.

10.5 Patient Insurance

As this PASS uses data from patients treated according to routine clinical practice at the discretion of the Investigator and according to the existing treatment guidelines, no risks beyond regular therapy exists for the patient, so that there is no additional hazard arising from study participation. As no study related risks exist, there is no need for an additional protection of the patient by a specific patient insurance. The general regulations of medical law and the professional indemnity insurance of the Investigators and the institutions involved, respectively, provide sufficient protection for both patient and Investigator.

10.6 Confidentiality

General Data Protection Regulation legislation will be followed in addition to country-specific regulations on the protection of individuals with regard to the processing of personal data.

In order to maintain patient confidentiality, each patient will be assigned a unique patient identifier (patient ID) upon study enrolment. For patients re-enrolling the study as described in Section 9.2.4, a new patient identification number will be attributed at the time of re-enrolment. For each of these participants, the new identification number will be linked in the dataset to their previous patient identification number.

The patient identifier will be used in place of patient name for the purpose of data analysis and reporting. The participating centres will keep record of list of patient ID and corresponding patient. Medical record numbers or other local reference identifiers will not be collected in the eCRF. All parties will ensure the protection of patient personal data and will not include patient names, initials and/or date of birth on any study forms, reports, publications, or in any other disclosures. In accordance with local regulations in each of the participating countries, patients will be informed about data handling procedures and asked for their consent. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data.

11. MANAGEMENT AND REPORTING OF AEs/ADRs

Reports of AEs/reactions will be summarised in the study report, where applicable.

11.1 Definition

An AE is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product [17].

The AE may be:

- A new illness
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An effect of the study medication
- Any combination of one or more of these factors
- An effect related to lack of drug effect
- An effect related to drug interactions
- An effect related to medication errors
- An effect related to off-label use
- An effect related to overdose, drug abuse (use for nonclinical reasons) or drug misuse, drug dependency
- An effect related to pre-existing condition improved (unexpected therapeutic or clinical benefits are observed)

As mentioned above no causal relationship with a study medication is implied by the use of the term “AE”.

An ADR is any AE suspected as having a reasonable causal relationship to the studied drug. It is defined as a response to a drug, which is noxious and unintended and may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors. The phrase “responses to” a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

An AE is serious if it:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation (see exceptions below)
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is medically important

Death is usually the outcome of an underlying clinical event that causes it. Hence, it is the cause of death that should be regarded as the SAE. The one exception to this rule is "sudden death" where no cause has been established. In this instance, "sudden death" should be regarded as the AE and "fatal" as its reason for being "serious".

Life-threatening: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an AE which hypothetically might have caused death if it were more severe.

Hospitalisation: Any AE leading to hospitalisation or prolongation of hospitalisation will be automatically considered as serious, UNLESS at least one of the following exceptions is met:

- The admission results in either a hospital stay of less than 24 hours or does not result in an overnight stay
- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study)
- The admission is not associated with an AE (i.e., social hospitalisation for purposes of respite care)

However, it should be noted that invasive treatment during any hospitalisation may fulfil the criteria of 'medically important' and as such may be reportable as an SAE dependant on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Medically important events either refer to or might be indicative of a serious disease state. Such reports warrant special attention because of their possible association with serious disease state and may lead to more decisive action than reports on other terms. Medically important events may jeopardise the patient and may require intervention to prevent another serious condition.

11.2 Drug Exposure Before or During Pregnancy or Lactation

Drug exposure before or during pregnancy, where the embryo or foetus may have been exposed to avacopan (through maternal exposure), will be followed up in order to collect information on the outcome of the pregnancy and development of the child after birth.

For pregnancies, the following information will be collected: prior pregnancies (including outcome of pregnancy), expected date of delivery, prenatal tests, pregnancy outcome, information on the child (e.g., gender, height, weight), complications, and causal relationship to study drug avacopan (if abnormal outcome).

Individual cases with an abnormal outcome associated with avacopan following exposure before or during pregnancy are classified as serious reports.

This especially refers to:

- Reports of congenital anomalies or developmental delay, in the foetus or the child
- Reports of foetal death and spontaneous abortion
- Reports of suspected adverse reactions in the neonate that are classified as serious

Drug exposure during lactation is not considered an ADR. However, events will be followed up in order to collect information on the drug effects during lactation and development of the child.

11.3 Medical Events of Special Interest

According to the RMP, the following risks were classified as important identified and potential risks of avacopan: liver injury, cardiac disorder, serious infections, and malignancy (see Appendix 3 for definitions) and will be recorded on the appropriate form.

11.4 Laboratory Parameters

Laboratory investigations will be performed according to individual patient need and routine clinical practice.

Not every out-of-range laboratory result qualifies as an AE. A laboratory investigation result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms

- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalaemia) or a change in concomitant therapy

- Presents shift of a parameter from a normal value to a pathological value, or results in a deterioration of Common Terminology Criteria grade, or a further worsening of an already pathological value

- Is clinically significant in the Investigator's judgment

The clinical significance of laboratory data will be evaluated by the treating physician. Only clinically significant changes with causal relationship to avacopan treatment have to be reported as an ADR.

11.5 Documentation

After signing the informed consent, and starting with the first dose of avacopan or non-avacopan SoC induction therapy, all non-serious AEs must be documented on an AE report form of the eCRF within 7 calendar days of awareness, all non-serious ADRs must be documented on the Adverse Event Report Form of the eCRF within 5 calendar days of awareness. All SADRs, SAEs, MESIs and fatal events must be documented and forwarded immediately (within 24 hours of awareness) to the PV staff for processing. Any death (as a primary reason for withdrawal/premature discontinuation and therefore end of study) with or without relation to avacopan and/or any AE leading to fatal outcome must be documented in the eCRF within 24 hours of awareness. The outcome of all reported SAEs (resolution, death, etc.) will be followed up and documented. Where required, physicians might be contacted directly by the PV staff to provide further information.

For each AE, the Investigator must assess and document the seriousness, duration and outcome. If in the avacopan group, causal relationship to avacopan, and action taken with avacopan in response to the event must also be documented.

If a pregnancy occurs during the study, although it is not a SADR, it should be reported within the same time limit as a SADR. The result of a pregnancy should be followed carefully, and any abnormal result of the mother or baby should be reported. Pregnancies are documented in a separate Pregnancy Report Form including prior pregnancies (including outcome of pregnancy), expected date of delivery, prenatal tests, pregnancy outcome, information on the child (e.g., gender, height, weight), complications, and causal relationship of pregnancy outcome (if abnormal) to avacopan.

Special situations of drug interaction, medication abuse, medication misuse, medication overdose, medication errors, unexpected therapeutic or clinical benefit from product use, lactation exposure with the product, lack of efficacy, off-label use, and occupational

exposure, with relationship to avacopan, are to be documented in the eCRF within 5 calendar days of awareness.

All non-serious AEs and special situations have to be documented in the patient's eCRF and source documents. If any situation leads to an SAE, then the event should follow the process of expedited reporting and report the event to Vifor Drug Safety within 24 hours of learning of its occurrence.

In the scope of this study, treatment-emergent ADRs shall be reported from the date/time of first intake of avacopan. Any ADR/SADR/MESI/SAE/fatal event occurring up to 9 weeks after the last dose of avacopan (in case of premature discontinuation) must be documented within the given timelines, even if this period goes beyond the end-of-study participation. ADRs and fatal events are followed up further according to country-specific PV rules.

For any ADR/SADR/MESI/SAE/fatal event occurring after the end of observation/after 9 weeks after last intake (whichever is later) the standard procedures for spontaneous reporting must be followed by the physician.

11.6 Management and Submission to Regulatory Authorities

Reporting of AEs in this study will follow the EMA Guideline on GVP (Module VI Management and reporting of adverse reactions to medicinal products), under non-interventional post-authorisation studies with a design based on primary data collection [13]. Data collection and management for all adverse reactions related to avacopan will be recorded in the PV database, managed, and submitted in line with the appropriate time frames as laid out in the guideline [13].

According to the EMA Guideline on GVP (Module VI Management and reporting of adverse reactions to medicinal products), as this is a combined design including both primary data and secondary use of data, the submission of Individual Case Safety Reports by the Sponsor will be undertaken exclusively for data obtained through primary data collection, following the guidance for primary data in VI.C.1.2.1.1. For AEs identified through secondary use of data (e.g., ADRs occurring prior to signing the informed consent but recorded for the study), the guidance in VI.C.1.2.1.2 applies.

All AEs/ADRs collected will be recorded and summarised in the interim safety analyses and in the final study report.

All AEs that qualify for reporting according to the applicable reporting requirements for treatment with avacopan will be submitted to the relevant authorities according to EU PV legislation [17,18] and national regulations by the Sponsor; however, all physicians must follow local legal requirements.

All other events for non-avacopan therapeutics must be reported by the primary source to either the manufacturer of that product or to the Competent Authority according to local regulations.

Detailed information on responsibilities as well as handling and processing of AEs are given in the Safety Management Plan (SMP). The SMP is kept in a stand-alone document and listed in Appendix 1. This document is available upon request.

11.7 Evaluation of New Safety Information

Reports of ADRs, fatal events (with or without relation to avacopan), and special situations (with and without ADR) and whenever new important safety information is received, will be processed and entered into the global PV safety database. Vifor shall review all sources of information, including both local PV data and PASS data, on at least a 6-monthly basis while the study is ongoing and any new information that might influence the current important identified or potential risks of avacopan shall be immediately communicated to Competent Authorities of Member States. If a potential safety signal is suspected, an investigation of the suspected potential signal will be performed according to internal SOPs, for further evaluation within the context of benefit/risk.

Reports of AEs/reactions will be summarised in the study report, where applicable. Progress reports and the final study report will be considered and can provide information on the overall benefit/risl for avacopan.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This study will be registered on the publicly accessible database in the EU-PAS register at http://www.encepp.eu/encepp_studies/indexRegister.shtml.

Results will be disclosed in a publicly available database within the standard timelines.

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Appendix 1 List of Stand-Alone Documents

- List of Scientific Committee members
- Scientific Committee Charter
- List of participating centres
- Safety Management Plan
- Statistical Analysis Plan

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

Study title: AvacoStar (Avacopan Post-authorisation Safety Study to evaluate the Incidence of Safety Events of Interest in Patients treated with avacopan for ANCA-associated Vasculitis)

EU PAS Register® number: Study not yet registered
Study reference number (if applicable): CS-AVA-2022-0016

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	9.1
1.1.2 End of data collection[2]	☒	☐	☐	9.1
1.1.3 Progress report(s)	☒	☐	☐	9.7.5
1.1.4 Interim report(s)	☒	☐	☐	9.7.5
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.5; 9.1.1
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.7.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.5.2

Comments:

There is no hypothesis to be tested : this study is observational and is focused on safety data collection.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	11.6
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1.1
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.1.1
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.1
4.2.2 Age and sex	☒	☐	☐	9.2.1.1
4.2.3 Country of origin	☒	☐	☐	9.1
4.2.4 Disease/indication	☒	☐	☐	9.2.1.1
4.2.5 Duration of follow-up	☒	☐	☐	9.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.2
5.3 Is exposure categorised according to time windows?	☒	☐	☐	11.3.2
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	11.3.2
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.1.1

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.1.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.7.3
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	9.7.3

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7.4
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.7.4
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.7.4

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.4

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.2.2
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.2.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.2.2
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.2.2
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.2.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.2.2
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	9.2.2
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.2.2; Annex 3
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	10.6

Comments:

Collection of drugs limited to a restricted list as described in section 9.3.1

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5.2
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.3
10.4 Are stratified analyses included?	☒	☐	☐	11.7.2

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.4
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.3.4

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.7.4; 9.9
12.1.2 Information bias?	☒	☐	☐	9.7.4; 9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.7.4; 9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5; 9.1

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.1; 10.3
13.3 Have data protection requirements been described?	☒	☐	☐	10.6

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☐	☐	☐	12

Comments:

Name of the main author of the protocol: Achim Obergfell,

Date: 18-Jan-2023 | 11:27:35 CET

Signature: DocuSigned by: Achim OBERGFELL
Signer Name: Achim OBERGFELL
Signing Reason: I approve this document
Signing Time: 18-Jan-2023 | 11:27:32 CET
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Appendix 3 Medical Event of Special Interest

MESIs will be identified based on MedDRA preferred terms (PTs) and SMQs. The specific PTs and SMQs used to define MESId are as follows:

Liver Injury

AEs identified by the following SMQ will be considered a liver injury MESI:

- SMQ for drug related hepatic disorders-severe events only (SMQ)

SAEs identified by the following SMQ will be considered a liver injury MESI:

- Liver related investigations, signs, and symptoms (SMQ)

Cardiac Safety

SAEs mapping to the following SOC or identified by any of the following SMQs will be considered a cardiac safety MESI:

- MedDRA SOC Cardiac Disorders
- SMQ for cardiac arrhythmia terms (including bradyarrhythmias and tachyarrhythmias)
- SMQ cardiac failure (broad)

Serious Infections

SAEs mapping to the following SOC will be considered a serious infection MESI:

- MedDRA SOC Infection and Infestations

Malignancy

AEs identified by the following SMQ will be considered a malignancy MESI:

- MedDRA SMQ for malignancies