CSL Vifor

EU RISK MANAGEMENT PLAN FOR TAVNEOS® (AVACOPAN)

RMP version to be assessed as part of this application:

RMP Version Number:	2.1
Data Lock Point for this RMP:	5 January 2024
Date of Final Sign-off:	25 September 2024
Rationale for Submitting an Updated RMP:	EU PASS Avacostar updates (protocol Version 3 approved by the EC)
Summary of Significant Changes in this RMP:	Section SI, SVII.3.1 and respective summary updated to reflect up-to-date scientific evidence SIII and SV updated per up-to-date exposure figures Part III and Annex 2 update per EU PASS status change Annex 3 EU PASS protocol provided
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QPPV Name:	Juergen Zorn, EU QPPV
QPPV Oversight Declaration:	The content of this RMP has been reviewed and approved by Vifor QPPV. The electronic signature is available on file.

Following the acquisition of Vifor Pharma by CSL on 9 August 2022, Vifor Pharma is now operating under the brand CSL Vifor and is a dedicated business unit of CSL. The Vifor Pharma legal entities will continue to use the Vifor Pharma entity names until the appropriate legal and regulatory approvals are obtained.

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LIST OF ABBREVIATIONS

AAV	ANCA-associated vasculitis
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANCA	anti-neutrophil cytoplasmic autoantibody
APAC	Asia Pacific
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BVAS	Birmingham Vasculitis Activity Score
C5aR	complement 5a receptor
CI	confidence interval
C_{max}	maximum concentration
CPK	creatine phosphokinase
CSR	Clinical Study Report
ECG	electrocardiogram
EEA	European Economic Area
EU	European Union
EULAR	European League Against Rheumatism
GC	glucocorticoid
GPA	granulomatosis with polyangiitis (Wegener's)
ISS	Integrated Safety Summary
IV	intravenous(ly)
MPA	microscopic polyangiitis
MPO	myeloperoxidase
PASS	Post-Authorisation Safety Study
PK	pharmacokinetic
PR3	proteinase 3
PT	preferred term
RMP	Risk Management Plan
SAE	serious adverse event

SmPC	Summary of Product Characteristics
TCC	terminal complement complex
TEAE	treatment-emergent adverse event
UK	United Kingdom
US	United States

PART I: PRODUCT OVERVIEW

Table 1 Product Overview

Active Substance(s) (INN or Common Name):	Avacopan (also known as CCX168)
Pharmacotherapeutic Group(s) (ATC Code):	Complement inhibitors, ATC code: L04AJ05
MAH or Applicant:	Vifor Fresenius Medical Care Renal Pharma France
Medicinal Products to Which this RMP Refers:	Avacopan
Invented Name(s) in the EEA:	Tavneos
Marketing Authorisation Procedure:	Centralised
Brief Description of the Product:	Chemical Class: Antagonist of the complement 5a receptor 1 (known as C5aR1 or CD88) Summary of mode of action: Avacopan specifically and selectively binds to the C5aR1 (or CD88), competitively inhibiting the interaction between C5aR1 and the anaphylatoxin C5a. C5a and C5aR1 play a central role in the pathogenesis of ANCA-associated vasculitis. C5a activates vascular endothelial cells, promoting their retraction and increased permeability. The interaction between neutrophils and C5a generated through activation of the alternative complement pathway is critical to vascular inflammation and organ damage in ANCA-associated vasculitis. By antagonising C5aR1, avacopan inhibits many of the pro-inflammatory effects of C5a, which include neutrophil activation, migration, and decreases adherence to sites of small blood vessel inflammation, vascular endothelial cell retraction and increased permeability. Avacopan does not decrease the formation of the membrane attack complex (C5b-9) or TCC, which is important in fighting infections with encapsulated bacteria such as Neisseria meningitidis. Important information about its composition: Not applicable.
Hyperlink to Product Information:	Tavneos (avacopan) Product Information
Indication(s) in the EEA:	Current: Tavneos, in combination with a rituximab or cyclophosphamide regimen, is indicated for the treatment of adult patients with severe, active GPA or MPA.
Dosage in the EEA:	Current: The recommended dose is 30 mg avacopan (3 hard capsules of 10 mg each) taken orally twice daily, morning and evening, with food.
Pharmaceutical Form(s) and Strengths:	Current: 10 mg hard capsules for oral use Capsules with yellow body and light orange cap with “CCX168” in black ink. Capsule size: 0 (22 mm x 8 mm)

Is/Will the Product be Subject to Additional Monitoring in the EU?	Yes

Notes: ANCA=Anti-neutrophil cytoplasmic autoantibody; ATC=Anatomical Therapeutic Chemical; C5aR=Complement 5a receptor; EEA=European Economic Area; GPA=Granulomatosis with polyangiitis; INN=International Non-proprietary Name; MAH=Marketing Authorisation Holder; MPA=Microscopic polyangiitis; RMP=Risk Management Plan; TCC=Terminal complement complex.

PART II: SAFETY SPECIFICATION

SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

SI.1 Epidemiology of the Disease

Indication

Tavneos, in combination with a rituximab or cyclophosphamide regimen, is indicated for the treatment of adult patients with severe, active GPA or MPA.

GPA (previously named Wegener's granulomatosis) and MPA are characterised by inflammation of small blood vessels, elevated levels of circulating auto-antibodies against the neutrophil-expressed antigens myeloperoxidase (MPO) and/or proteinase 3 (PR3), collectively known as ANCA, and by complement activation and C5a production. Similarities in pathology, clinical symptoms, natural history, presence of ANCA and response to therapy form a rationale basis for classifying GPA and MPA together as forms of ANCA-associated vasculitis (AAV) [1], and for the established practice of studying these diseases together and for the highly overlapping treatment and monitoring recommendations. For example, the European League Against Rheumatism (EULAR) recommendations for the management of AAV [2] do not distinguish between GPA or MPA for treatment or monitoring.

The third form of AAV, eosinophilic GPA (formerly Churg-Strauss syndrome), has a distinct pathophysiology, clinical course and a different treatment paradigm. As patients with eosinophilic GPA were not included in the avacopan clinical development programme, and as avacopan is not currently indicated for eosinophilic GPA, this condition is not considered further in this document and where the term AAV is used it refers to GPA and MPA only.

SI.1.1 Incidence and Prevalence

There is considerable geographical variation in the incidence of GPA and MPA but median overall incidence of GPA and MPA is approximately 9 and 5.9 per million people per year, respectively [3].

GPA is considered an orphan disease in the EU with a prevalence between 86.8 and 198 per million people. MPA is an orphan disease in the EU with a prevalence between 16.3 and 61.9 per million people [3].

SI.1.2 Demographics of the Target Population (Age, Sex, Race/Ethnic Origin)

The peak age of onset of AAV is between 50 to 70 years of age [4]. AAV is very rare in childhood. GPA has slightly higher incidence in men compared to women in European studies (male:female ratio range 1.07-1.48); the opposite is true in most European studies of MPA [5]. At diagnosis GPA patients tend to be younger than MPA patients [6] and

although renal involvement is equally common in both GPA and MPA, more MPA patients have renal limited disease. AAV is observed worldwide without clear differences by race/ethnic origin [7]. A recent UK study has confirmed no difference in incidence of AAV between Indo-Asians and Caucasians [8].

SI.1.3 Risk Factors for the Disease

Both genetic and environmental factors contribute to the development of AAV. The strongest genetic associations are with the major histocompatibility complex Class II, PR3 and MPO [9].

Infectious agents have long been suspected as important in the pathogenesis of disease in at least a subset of patients. Data are strongest for nasal carriage of Staphylococcus aureus playing a role in relapse of GPA [10].

AAV secondary to certain drugs, for example levamisole and propylthiouracil is well described [11].

Other non-infectious exposures such as silica [12] dust and cigarette smoking have also been associated with an increased risk of AAV, although their role is far from certain [12].

SI.1.4 Main Existing Treatment Options

AAV is a severe and relapsing disease. In the era before effective therapies were available, reported mortality was 90% within 2 years of disease onset [13]. Outcomes are much improved after the introduction of potent immunosuppressive regimens. These have evolved over time with the goal of improving efficacy while reducing treatment-related morbidity.

European recommendations for the management of AAV developed by EULAR were last updated in 2022 [2]. These recommendations reflect well the way AAV is currently managed in European specialist centres. The relevant sections are those that describe the management of patients with the presence of organ-threatening or life-threatening manifestations. This particular patient population is relevant because it is similar to the population recruited during the avacopan clinical development programme and to the population described in the avacopan Summary of Product Characteristics (SmPC).

Existing treatment options for this population can be considered in 2 parts: an induction part utilising intensive immunosuppression to induce remission, using either rituximab or cyclophosphamide, in combination with glucocorticoids (GCs), and a maintenance phase designed to prevent further flares, using either rituximab, azathioprine or methotrexate as an alternative. Maintenance therapy is generally continued for 24-48 months, and both induction and maintenance therapy are adapted to specific characteristics of the individual patient.

For induction of remission, treatment with GCs at a starting dose of 50-75 mg prednisone equivalent depending on body weight with stepwise reduction and achieving a target of 5 mg by 4-5 months.

As per EULAR recommendations for the management of AAV, avacopan may be considered for induction of remission in GPA or MPA, as part of a strategy to substantially reduce exposure to GCs.

While receiving potent immunosuppression, participants will also receive Pneumocystis Jirovecii pneumonia prophylaxis, usually with trimethoprim-sulphamethoxazole, and while receiving GCs prophylaxis against gastritis and osteoporosis is usually given according to local practice.

Flares may occur at any time and are treated by re-initiating induction treatment, adapted according to the initial response.

Despite improvements over time, current standard of care treatment regimens are still associated with incomplete rates of remission and significant flare rates, as well as substantial morbidity. These are described in the next section.

SI.1.5 Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity

The clinical course of GPA and MPA is variable in terms of organ systems involved, severity (life-threatening, organ system threatening, or localised), response to induction therapy, and frequency of relapse following successful induction therapy. Patients have higher risk of acute and long-term mortality and organ damage accumulates over time because of active vasculitis and effects of therapies [14].

For most patients, AAV is now a relapsing, remitting long-term condition characterised both by acute morbidity related to disease flares and acute complications of treatment and by accumulated damage related complications of both the disease itself and to long-term immunosuppression and GC use.

Therefore, important aspects of natural history of AAV in patients receiving standard of care treatment prior to the availability of avacopan include:

1. Response to AAV therapy: response to therapy is still incomplete and often not sustained. With current standard of care therapy successful remission induction (Birmingham Vasculitis Activity Score (BVAS) of 0) along with stopping of GC treatment can be achieved in only approximately 60% of AAV patients at 6 months [15,16]. A proportion of patients (29.4%) had uncontrolled disease or had relapsed so were likely to be still receiving GCs and 5.5% were still receiving GCs despite a BVAS of 0 [16]. In a longer-term follow-up of patients (12 months) in one of these clinical trials, RAVE [17], only 39% in the rituximab group and 33% in the cyclophosphamide group were still in complete remission without GC at 18 months. A recent real-world

retrospective study in 4 European countries has confirmed these same findings that under 60% of patients achieve and maintain remission over 12 months [18]. A long-term follow-up study demonstrated the importance of achieving and sustaining remission in AAV [19]. Remission status at 6 months predicted long-term outcomes of death and end-stage kidney disease with late remission (after 3 months but by 6 months), relapsing disease (remission by 3 months but relapse by 6 months), as well as refractory disease (no remission by 6 months) all having worse long-term outcomes compared to those who achieved and sustained remission [20]. In real-world practice in Europe [19] response to induction therapy in incident AAV patients is still incomplete with only 43.4%, 61.4% and 58.8% having a full response at 3, 6 and 12 months respectively.

2. Acute mortality risks: AAV leads to increased risk of mortality especially in the first year and patients with GPA have a 9-fold increased mortality risk in the first year of disease compared to healthy controls, attributed to infection, vasculitis, and renal failure [19]. It is estimated that 11% of patients die within the first year after diagnosis [21,22]. This early mortality risk is related to both active vasculitis and the toxicity associated with standard of care treatment [21]: it is estimated that 59% of the first year mortality is related to the medications used with infection being the most important cause of death.

3. End-stage renal failure: renal involvement is common in GPA and MPA and patients with renal involvement have a worse prognosis than patients without renal involvement [23], and 23% of patients who require dialysis at time of diagnosis die within 6 months [24]. As early as 6 months after diagnosis, 8% of patients require long-term dialysis therapy for end-stage renal failure [25].

4. Relapse: relapse is still common and overall risk of relapse in a long-term follow-up study was 38% at 5 years [26]. Risk factors include PR3 antibody status, prior relapse as well as after changes in AAV therapy. Severity of relapse varies but can be severe; treatment will include [2] increased GC dose for minor relapse and full treatment as with incident phase for more severe relapses. Thus the acute risks of active vasculitis and its treatment are related to patients who relapse and have greater exposure to GCs [27] with attendant increased chronic tissue and organ damage [17].

5. Chronic damage and GC-related adverse events (AEs): GPA and MPA patients accumulate organ damage from a combination of vasculitis activity and GC AEs. In this context, patients typically receive 0.5 to 1 g intravenous (IV) GCs, followed by oral GCs, 1 mg/kg/day, tapered according to local practice and treatment response. Chronic GC use is associated with an increased risk of new-onset/worsening of diabetes mellitus, hypertension, osteoporosis, avascular necrosis of bone, glaucoma, cataracts, psychiatric disorders, and other debilitating side effects [21,25]. In a study with 779 rheumatoid arthritis patients, a dose-dependent increase in death including cardiovascular mortality was associated with long-term use GC treatment [28]. Cumulative organ damage in GPA and MPA has been assessed in long-term follow-up

studies utilising the Vasculitis Damage Index [25]. The Vasculitis Damage Index assesses vasculitis related and treatment-related damage accumulating over time. This study followed over 600 GPA and MPA patients for up to 7 years and found the frequency of damage including potentially treatment-related damage, rose over time ($p<0.01$). The most commonly reported items of treatment-related damage were hypertension (41.5%), osteoporosis (14.1%), malignancy (12.6%) and diabetes (10.4%). This study [25] also observed one-third of patients have more than or equal to 5 items of damage and demonstrated that this long-term vasculitis damage was associated with cumulative GC use ($p=0.016$). This is significant serious morbidity and translates into the significantly increased mortality risk in GPA and MPA according to standard of care, with a hazard ratio of 2.41 (95% confidence interval (CI), 1.74-3.34) compared to age and sex matched control.

6. Impaired patient experience, fatigue and reduced functional status: from the time of initial diagnosis, GPA and MPA patients have impaired quality of life [29]. This severe impairment of quality of life is associated with fatigue, and impaired physical and mental functioning [30,31.32]. A more recent study, a longitudinal survey study [31] of 50 AAV patients confirmed frequent and severe fatigue, anxiety and depression and an adverse impact on everyday function and employment. In addition, AAV patients report difficulties in making plans both short-term social engagements and long-term life planning [32]. A major cause of the adverse patient reported experience in GPA and MPA relates to the impact of GCs. This longitudinal survey study [33] examined patient views about GCs in 50 AAV patients and observed patients acknowledged their effectiveness for remission induction but also described significant adverse emotional, physical and social effects. Patients described the significant emotional impact (mania or euphoria, anxiety, mood swings) of GCs plus changes in appearance (weight gain, change in facial features, comments by partners and friends), change in appetite, diabetes, skin changes, muscle strength reduction which all affect personality and impact life and work [34].

SI.2 Important Comorbidities

Since GPA and MPA often affect elderly patients, comorbidities associated with increasing age, e.g., cardiovascular disease, including hypertension and ischaemic heart disease, are frequently observed. In a recent real-world study of AAV patients [18], two-thirds of incident patients and over 80% of relapsing patients had at least 1 comorbidity with the most common being hypertension, diabetes, chronic obstructive pulmonary disease and coronary arterial disease.

Patients then develop additional comorbidities as they live with AAV and compared to control patients of age and sex AAV patients develop more osteoporosis, venous thromboembolism, thyroid disease and diabetes mellitus [35].

Treatment for AAV also confers significant risk for comorbidity. Infection is the most common AE associated with therapy [19,34,35,36]. Several studies have shown that use of GC therapy is associated with increased risk of infection [36,37,38].

New-onset GC-associated diabetes develops in 8.2% of patients, half within the first 2 months. Other GC-associated AEs are common: 2.5% of patients develop fractures, 2.5% develop peptic ulcers, 2% develop cataracts, and 0.4% develop avascular necrosis of the hip [19].

SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

SII.1 Toxicity

Key safety findings from the nonclinical toxicology programme of avacopan (CCX168) with relevance to human usage are summarised below in Table 2.

Table 2 Key Nonclinical Safety Findings - Toxicity

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Single-dose Toxicity	
In rats (PC0381_168_a), single doses of avacopan up to 100 mg/kg produced no remarkable effects. The NOAEL was considered to be 100 mg/kg.	No special risk for humans based on the single-dose toxicity study in rats.
Repeat-Dose Toxicity	
Orally administered avacopan was well tolerated in 4-week studies up to the highest doses tested (100 mg/kg in rats (PC0384_168) and 50 mg/kg in cynomolgus monkeys (PC0385_168)). There were no significant toxicological findings of concern in these studies. Due to non-formed/liquid faeces attributable to the vehicle, monkeys received supportive care starting on Day 11 of the dosing phase. In additional studies of 13 weeks duration in rats (PC0356_168) and 20 weeks in cynomolgus monkeys (PC0357_168), no toxicology findings were noted at doses up to 100 mg/kg/day in rats and 30 mg/kg/day in monkeys. Avacopan was also well tolerated in the 13-week hamster study at dose levels up to 100 mg/kg/day and 1,000 mg/kg/day (administered as 500 mg/kg BID). The NOAEL was 1,000 mg/kg/day (500 mg/kg BID), however, the highest exposures were achieved with 100 mg/kg/day, without adverse findings (PC0677_168). Finally, in chronic studies in rats (PC0655_168) and cynomolgus monkeys (PC0654_168), no adverse effects were observed at doses up to 200 and 45 mg/kg/day, respectively. The NOAEL in the 26-week rat study (PC0655_168) was 200 mg/kg/day, ≤15-fold clinical exposure based on AUC. There were a few clinical pathology changes at ≥100 mg/kg/day which were small in magnitude, reversible, inconsistent between sexes and not considered adverse. In the 44-week study in monkeys (PC0654_168), avacopan was generally well tolerated and the NOAEL was 30/45 mg/kg/day, ≤4.6-fold clinical exposure based on AUC. The observed clinical signs, which included emesis, vomitus, non-formed faeces and/or liquid faeces, and a transient reduction in body weight were attributable to the vehicle. Metabolite CCX168-M1 (which has been identified in humans) (further referred to as M1) was present in samples collected in the rat 13-week (PC0356_168) and 26-week study (PC0655_168), and the monkey 20-week (PC0357_168) and 44-week study (PC0654_168) at relatively high levels indicating that this metabolite was qualified in the toxicology studies.	No special risk for humans based on conventional studies of repeat-dose toxicity in rats and monkeys for up to 26 and 44 weeks, respectively.

Table 2 Key Nonclinical Safety Findings - Toxicity (Cont'd)

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Reproductive/Developmental Toxicity	
There was no evidence of histopathological alterations to the male or female reproductive system in rats or monkeys in toxicology studies. Fertility and Early Embryonic Development: In a male and female hamster fertility study (PC0670_168), avacopan at oral doses of 10, 30, 100, and 1,000 mg/kg/day (1,000 mg/kg/day administered as 500 mg/kg BID) produced no effects on male or female fertility; the NOAEL for fertility was 1,000 mg/kg/day, 6.8-fold clinical exposure based on AUC. Embryo-foetal Development: In a hamster embryo-foetal developmental toxicity study (PC0671_168), oral doses of 10, 30, 100, and 1,000 mg/kg/day avacopan were given from GD 6 to 12 (1,000 mg/kg/day administered as 500 mg/kg BID). No adverse gross external, soft tissue, or skeletal foetal abnormalities were caused by once daily doses up to 100 mg/kg or twice daily doses of 500 mg/kg. In the foetuses of pregnant hamsters given avacopan 500 mg/kg twice daily, there was an increase in the number of litters and foetuses with skeletal variations, principally short thoracolumbar supernumerary ribs. The maternal NOAEL was 1,000 mg/kg/day (500 mg/kg BID), 5.3-fold clinical exposure based on AUC and the developmental NOAEL 100 mg/kg/day, 5.3-fold clinical exposure based on AUC. In a rabbit embryo-foetal developmental toxicity study, oral doses of 10, 30, and 200 mg/kg/day avacopan were given from GD 6 to 18 (PC0672_168). The maternal NOAEL was 30 mg/kg due to maternal toxicity findings of adverse clinical observations and abortions at 200 mg/kg/day. No test article-related gross external, soft tissue, or skeletal foetal alterations (malformations or variations) were observed at any dose and, thus, the developmental NOAEL was 200 mg/kg, 0.60-fold clinical exposure based on AUC. Pre- and Post-natal Development: Avacopan was orally administered to female hamsters at doses of 10, 30, 100, and 1,000 mg/kg/day (1,000 mg/kg/day administered as 500 mg/kg BID) from GD 6 to Day 20 postpartum (PC0673_168). There were no adverse findings in either the F0 dams or the F1 offspring. The maternal NOAEL was 1,000 mg/kg/day (500 mg/kg BID). The NOAEL for reproduction in the dams, and for viability, growth, and reproduction in the F1 generation hamsters was also 1,000 mg/kg/day (500 mg/kg BID), 6.3-fold clinical exposure based on the highest observed AUC. Avacopan was detected in the plasma of the nursing offspring which suggests that avacopan is likely excreted into the milk of lactating dams.	No special risk for humans based on conventional reproductive toxicology studies in hamsters and rabbits. Avacopan is not recommended during pregnancy and in women of childbearing potential not using contraception. It is likely that avacopan is excreted in the milk of nursing dams.

Table 2 Key Nonclinical Safety Findings - Toxicity (Cont'd)

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Genotoxicity	
There was no evidence of genotoxicity in either the bacterial mutagenicity (Ames test; PC0378_168) or mouse lymphoma assays (PC0379_168). Furthermore, avacopan was negative in the rat bone marrow micronucleus assay following 2 consecutive daily oral doses up to a dose limit of 2,000 mg/kg/day (PC0320_168). In each of these assays, cells were also exposed to M1 indicating this metabolite is unlikely to pose a genotoxic risk. In addition, the minor human metabolite M6 was also negative in the Ames assay (PC0320_168).	Based on nonclinical studies to date, avacopan is not considered to be genotoxic.
Carcinogenicity	
The carcinogenic potential of avacopan was evaluated in 2-year studies in both rats and hamsters (i.e., with life-time dosing). In male rats, a slightly increased incidence in C-cell adenomas, a finding which is known to occur spontaneously in aged rats [39], was noted at the highest dose tested, this increase being not statistically significant and the incidence within the historical control range. No neoplasias were noted in female rats. It should be stressed that the rat is not a pharmacologically relevant species (i.e., avacopan is not active at the rat C5a receptor) and, more importantly, avacopan was not carcinogenic in hamsters, the pharmacologically relevant animal species (PC0674_168 and PC0675_168).	No special risk for humans based on conventional studies of repeat-dose toxicity in rats and monkeys for up to 26 and 44 weeks, respectively, and 2-year studies in rats and hamsters.

Notes: AUC=Area under concentration-time curve; BID=Twice a day; GD=Gestation day; NOAEL=No observed adverse effect level.

SII.2 Safety Pharmacology

Key safety findings from safety pharmacology studies are presented in Table 3 below.

Table 3 Key Nonclinical Safety Findings - Safety Pharmacology

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Cardiovascular System (Including Potential Effect on the QT Interval)	
In vitro data indicate that avacopan and its metabolite M1 do not inhibit hERG ionic conductance at therapeutic concentrations (PC0380_168 and PC0490_168a). IC_{50} values were >2.3 µM for avacopan and >3.0 µM for its metabolite M1, the limits of solubility for both compounds. The projected cardiovascular safety margins (hERG IC_{50}/C_{max}, unbound values in human) for avacopan and M1 are >3,800-fold and >14,000-fold, respectively. Accordingly, a very low risk of pro-arrhythmic/torsadogenic effects is predicted for avacopan and M1. Single oral administration of avacopan at doses of 5, 15, and 50 mg/kg produced no biologically significant effect on heart rate, haemodynamic parameters, ECG morphology, or cardiac rhythm in awake, telemetered, male monkeys (PC0377_168). The NOAEL was considered to be 50 mg/kg. No evidence of ECG alterations was seen in the monkey 4-week (PC0385_168), 20-week (PC0357_168), or 44-week (PC0654_168) general toxicology studies, where mean plasma levels as high as 2,470 ng/ml (avacopan) and 573 ng/ml (M1) were achieved.	Based on nonclinical studies, there is no evidence of a cardiovascular effect.
Nervous System	
No effects were seen upon neurobehavioural parameters or body temperature in male rats that received a single oral administration of vehicle or avacopan at nominal doses of 0 (vehicle), 5, 25, or 100 mg/kg (PC0375_168). Dose formulation analysis indicated that the actual doses evaluated were 3.5, 19, and 73 mg/kg in this study. The NOAEL was considered to be 73 mg/kg.	No special risk to humans based on nonclinical neuropharmacological safety study in rats.
Respiratory System	
Male rats were given single oral doses of avacopan (nominal doses of 5, 25, and 100 mg/kg) or vehicle (PC0376_168_a). Dose formulation analysis indicated that the actual doses evaluated were 3.5, 19, and 73 mg/kg. Administration of avacopan was not associated with any biologically significant or dose-dependent effect upon respiratory rate, tidal volume, or minute volume up to a nominal dose of 100 mg/kg. The NOAEL was considered to be 73 mg/kg. These results are consistent with those observed in the 44-week monkey toxicology study (PC0654_168) where no effect upon respiratory behaviour or pulse oximetry was evident.	No special risk to humans based on nonclinical respiratory safety study in rats or the 44-week cynomolgus monkey toxicology study where no effect upon respiratory behaviour or pulse oximetry was evident.

Table 3 Key Nonclinical Safety Findings - Safety Pharmacology (Cont'd)

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Renal System	
In male rats, a single oral administration of avacopan at doses up to 100 mg/kg had no clear effect upon electrolytes, urine volume, water consumption, plasma creatinine, or the other urinary parameters measured in this study (total protein, specific gravity, osmolality, pH, creatinine, and urea nitrogen) (PC0485_168). Based upon the results of the study, NOAEL for effect on renal function was considered to be 100 mg/kg.	No special risk for humans based on conventional studies of repeat-dose toxicity in rats and monkeys for up to 26 and 44 weeks, respectively. No special risk for humans based on a renal safety pharmacology study in rats.

Notes: ECG=Electrocardiogram; hERG=Human ether-á-go-go-related gene; IC_{50}=Concentration associated with 50% inhibition; NOAEL=No observed adverse effect level.

SII.3 Other Toxicity-related Information or Data

Other key safety findings from nonclinical studies are presented in Table 4 below.

Table 4 Key Nonclinical Safety Findings - Other Toxicity-related Information or Data

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Other Toxicity-related Information or Data	
Immunotoxicity	
No evidence for an effect on TDAR induced by KLH was seen in the rat (PC0496_168). In the 44-week monkey study (PC0654_168), avacopan had no effect on TDAR and immunophenotypic analyses did not reveal any avacopan-related effects.	Based on nonclinical studies, there is no evidence for immunotoxic potential.
Phototoxicity	
Avacopan absorbs light between 290 and 370 nm, but was not phototoxic in the mouse fibroblast 3T3 neutral red uptake in vitro assay at concentrations up to 10 µg/ml (PC0663_168).	Based on nonclinical studies, there is no evidence for phototoxic potential.
Pharmacokinetic Drug Interactions Mediated by CYP450 Enzymes and Drug Transporters	
CYP3A4 plays a significant role in avacopan clearance and in the formation and clearance of metabolite M1 (PC0373_168; PC0711_168). The CYP inhibition characteristics of avacopan and metabolite M1 were assessed by determination of their ability to inhibit metabolism of specific probe substrates for seven major CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) in human liver microsomes (PC0360_168, PC0489_168, PC0710_168). Avacopan displayed negligible direct inhibition of the CYP enzymes tested. Similarly, metabolite M1 displayed negligible direct inhibition of the CYP enzymes tested except for CYP2C9, which was inhibited weakly (IC_{50}=4.7 µM).	Results from nonclinical studies pointed to a potential interaction of avacopan with drugs that are substrates, inducers or inhibitors of CYP3A4, and a low probability of metabolite M1 interaction with drugs metabolised by CYP2C9. Clinically relevant drug-drug interactions are unlikely when avacopan is co-administered with drugs that are substrates or inhibitors of transporters. A clinical study (CL008_168) addressed the potential drug-drug interactions of avacopan and M1 (see Section SVII.1.1).

Table 4 Key Nonclinical Safety Findings - Other Toxicity-related Information or Data (Cont'd)

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Both avacopan and metabolite M1 displayed some degree of CYP3A4 time-dependent inhibition (PC0622_168; PC0634_168). The kinetic constants for avacopan CYP3A4 time-dependent inhibition were K_{inact}=0.0659 min^{-1} and K_I=4.47 µM. For metabolite M1, the kinetic constants were K_{inact}=0.0402 min^{-1} and K_I=11.7 µM.	
The CYP induction potential of avacopan was evaluated through a human hepatocyte induction assay, and found negligible induction of CYP1A2 and CYP2B6, and modest induction of CYP3A4 relative to positive control rifampicin (PC0635_168a). CYP3A4 mRNA expression was increased by avacopan but CYP3A4 enzyme activity decreased with increasing avacopan concentration.	
Avacopan is not a substrate of drug transporters OATP1B1, OATP1B3, MDR1/P-gp or BCRP; and M1 is not a substrate of OATP1B1, OATP1B3 or BCRP but is a substrate of MDR1/P-gp. Since clinical Study CL008_168 showed that itraconazole (an inhibitor of CYP3A4 as well as P-gp and BCRP) only weakly increased the exposure of M1, P-gp does not create a drug-drug interaction issue for M1 (PC0712_168).	
Avacopan and M1 do not substantially inhibit any of the nine tested drug transporters (BCRP, MDR1/P-gp, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT2).	

Notes: BCRP=Breast cancer resistance protein; CYP=Cytochrome P450; IC_{50}=Concentration associated with 50% inhibition; KLH=Keyhole limpet haemocyanin; MATE=Multidrug and toxin extrusion; MDR1/P-gp=Multidrug resistance protein 1/ P-glycoprotein; OAT=Organic anion transporter; OATP=Organic anion transporter polypeptide; OCT=Organic cation transporter; TDAR=T-cell dependent antibody response.

SIII CLINICAL TRIAL EXPOSURE

SIII.1 Cumulative Subject Exposure

SIII.1.1 Number of Subjects Exposed Altogether and for Specific Periods of Time

The number of subjects included in the avacopan clinical development programme as of 5 January 2024 is presented by study in Table 5. Overall, 1,266 subjects have been included, 981 of whom have received at least 1 dose of avacopan (not counting subjects in blinded ongoing studies).

A total of 440 subjects, of whom 239 received avacopan, have been included in adequate and well-controlled studies in AAV. The safety in these subjects form the basis for the safety profile described in this document.

Table 5 Summary of Subjects Included by Study in the Avacopan Clinical Programme

Study Number	Total Number of Subjects	Total Number of Subjects Receiving Avacopan
Clinical Pharmacology		
CL001_168 (Phase 1, healthy subjects)	48	35
CL004_168 (Phase 1, healthy subjects)	6	6
CL007_168 (Phase 1, healthy subjects)	16	16
CL008_168 (Phase 1, healthy subjects)	32	32
CL013_168 (Phase 1, healthy subjects)	24	24
CL014_168 (Phase 1, healthy subjects)	58	29
CCX1101 (Phase 1, healthy subjects)	80	64
CL019_168 (Phase 1, healthy subjects)	31	31
CL020_168 (Phase 1, healthy subjects)	32	32
Subtotal	**327**	**269**
Adequate and Well-Controlled Studies		
CL002_168 (Phase 2, AAV)	67	44
CL003_168 (Phase 2, AAV)	42	29
CL010_168 (Phase 3, AAV)	331	166
Subtotal	**440**	**239**
Studies in Other Indications		
CL005_168 (Phase 2, IgAN)	7	7
CL011_168 (Phase 2, C3G)	57	56
Subtotal	**64**	**63**

Table 5 Summary of Subjects Included by Study in the Avacopan Clinical Programme (Cont'd)

Study Number	Total Number of Subjects	Total Number of Subjects Receiving Avacopan
Other Studies		
CL016_168 (Phase 2, HS)	435	410
Subtotal	**435**	**410**
Total	**1,266**	**981**

Notes: For details regarding the data pooling strategy, refer to the Integrated Summary of Safety Statistical Analysis Plan.
AAV=ANCA-associated vasculitis; ANCA=Anti-neutrophil cytoplasmic autoantibody; C3G=Complement 3 glomerulopathy; HS=Hidradenitis suppurativa; IgAN=IgA nephropathy.
Source: Section 2.7.4.

SIII.1.1.1 Clinical Pharmacology Studies

A total of 264 subjects, of whom 206 received at least 1 dose of avacopan were included in Phase 1 clinical pharmacology studies. All of these subjects were healthy volunteers, except for Study CL013_168, in which subjects with mild or moderate impairment of liver function were studied. The avacopan dose given in these studies ranged from 1 mg up to 200 mg (Study CL014_168). The dosing period ranged from 1 day up to 17 days (Study CL008_168).

Pertinent safety information from the clinical pharmacology studies is described for each study individually (see Section 2.7.6). Since these studies included mostly healthy volunteers, the avacopan exposure from these studies is not included with the exposure from the well-controlled studies in AAV.

SIII.1.1.2 Adequate and Well-Controlled Studies

A total of 440 subjects, of whom 239 received avacopan were included in Phase 2 and 3 clinical trials in subjects with AAV. The vast majority of subjects received 30 mg avacopan twice daily in these studies. However, 13 subjects (in Phase 2 Study CL003_168) received 10 mg avacopan twice daily.

Phase 2 Studies in AAV (CL002_168 and CL003_168)

Both Phase 2 studies (CL002_168 and CL003_168) included an 84-day (12-week) treatment period. In the pooled safety population from these 2 studies, the majority of subjects received study drug (avacopan or placebo) for 30 to 183 days. The mean (standard deviation) duration of exposure was 76.2 (19.76) days in the avacopan group (Table 6).

Phase 3 Study in AAV (CL010_168)

The dosing period of Phase 3 Study CL010_168 was 52 weeks. The majority of subjects received avacopan or matching placebo for 184 to 365 days. The mean (standard deviation) exposure was 305.1 (118.36) days in the avacopan group (Table 6).

Table 6 Clinical Trial Exposure to Avacopan in ANCA-Associated Vasculitis from Adequate and Well-Controlled Studies (CL002_168, CL003_168 and CL010_168)

Variable Category/Statistic	CL002_168 and CL003_168 (N=73)	CL010_168 (N=166)	Subject Years
Exposure categories	n (%)	n (%)	
1-29 days	5 (6.8)	8 (4.8)	5.64
30-183 days	67 (91.8)	24 (14.5)	**57.00**
184-365 days	N/A	134 (80.7)	
Total	**72[(1)] (98.6)**	**166 (100)**	**212.31**
Duration of exposure (days)			
n	72	166	
Mean	76.2	305.1	
SD	19.76	118.36	
Minimum	6	4	
Median	84	364	
Maximum	86	391	

1 One subject in Study CL003_168 had missing study drug accountability information and is excluded from the exposure calculation.
Notes: ANCA=Anti-neutrophil cytoplasmic autoantibody; N/A=Not applicable; SD=Standard deviation.
Source: Clinical Study Report CL010_168 Table 14.1.11 and Integrated Safety Summary Table 3.

SIII.1.2 Cumulative Subject Exposure to Avacopan in AAV

The exposure to avacopan—overall and by age and sex—in the pivotal Phase 3 study and the two Phase 2 studies combined is shown in Table 7. Overall, the avacopan exposure was 212.3 subject years in the randomised, controlled clinical trials. Two adolescent subjects were included in the Phase 3 study in the avacopan group. There was good representation of adult subjects across all 4 age groups.

Table 7 Cumulative Subject Exposure to Avacopan in ANCA-Associated Vasculitis from Adequate and Well-Controlled Studies by Age Group and Gender (CL002_168, CL003_168 and CL010_168)

Age Group	Subjects			Subject Years		
	Overall (N=239) n (%)	Male (N=143) n (%)	Female (N=96) n (%)	Overall	Male	Female
12-17 years	2 (0.8%)	0 (0%)	2 (2.1%)	1.41	0.00	1.41
18-50 years	49 (20.5%)	34 (23.8%)	15 (15.6%)	41.97	29.72	12.25
51-64 years	80 (33.5%)	51 (35.7%)	29 (30.2%)	65.35	42.24	23.11
65-74 years	76 (31.8%)	42 (29.4%)	34 (35.4%)	71.40	38.55	32.85
≥75 years	32 (13.4%)	16 (11.2%)	16 (16.7%)	32.19	16.26	15.92
Total (all age groups)	**239[1] (100.0%)**	**143 (100.0%)**	**96 (100.0%)**	**212.31**	**126.77**	**85.54**

1 One subject in Study CL003_168 had missing study drug accountability information and is excluded from the exposure calculation.
Note: ANCA=Anti-neutrophil cytoplasmic autoantibody.
Source: Integrated Safety Summary Table 18.1.

The avacopan exposure by race is shown in Table 8. The majority of exposure was in White subjects.

Table 8 Cumulative Subject Exposure to Avacopan in ANCA-Associated Vasculitis from Adequate and Well-Controlled Studies by Race (CL002_168, CL003_168 and CL010_168)

Racial Group	Subjects (N=239) n (%)	Subject Years
White	207 (86.6%)	180.28
Black	6 (2.5%)	4.90
Asian	17 (7.1%)	19.39
Other	9 (3.8%)	7.74
Total	**239[1] (100.0%)**	**212.31**

1 One subject in Study CL003_168 had missing study drug accountability information and is excluded from the exposure calculation.
Note: ANCA=Anti-neutrophil cytoplasmic autoantibody.
Source: Integrated Safety Summary Table 18.2.

All subjects in the avacopan groups in the two Phase 2 studies and the Phase 3 study in AAV received 30 mg twice daily, except for 13 subjects in Phase 2 Study CL003_168 who received 10 mg twice daily. Two of these 13 subjects discontinued the study early due to AEs (Clinical Study Report (CSR) CL003_168 Table 14.1.2.1).

SIII.1.3 Compassionate Use and Market Access Programmes Exposure

A total of 729 subjects were included in compassionate use and managed access programmes in AAV adult patients out of which 470 were receiving avacopan at the time of this report. One adolescent subject with C3 glomerulonephritis was receiving avacopan through the compassionate use programme.

SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 9 Exclusion Criteria

Criteria	Reason for Exclusion	Missing Information?	Rationale
Patients with any other multisystem autoimmune disease including eosinophilic GPA (Churg Strauss), systemic lupus erythematosus, IgA vasculitis (Henoch Schönlein purpura), rheumatoid vasculitis, Sjögren's disease, anti-glomerular basement membrane disease, or cryoglobulinaemia	Exclusion was in place to enable assessment of the primary efficacy endpoint, which assessed activity in multiple organ systems, without confounding from other autoimmune diseases that could impact the same organ systems	No	Routine risk communication is included in SmPC Section 4.1. Routine risk minimisation measures beyond Product Information include the legal status of the medication (prescription only medication). Treatment with avacopan should be initiated and monitored by healthcare professionals experienced in the diagnosis and treatment of GPA or MPA.
History or presence of any form of cancer within the 5 years prior to screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or cervical carcinoma in situ or breast carcinoma in situ that had been excised or resected completely and was without evidence of local recurrence or metastasis	Safety precaution. There was limited information about the potential carcinogenic risk of avacopan at the time of study initiation	No	To date there is no evidence of an increased risk of malignancy in clinical studies or nonclinical toxicology studies. Throughout the global Phase 3 Advocate study [40,41], malignancies which were attributed to avacopan were not observed. Avacopan is not genotoxic and completed carcinogenicity studies do not indicate any signal or findings related to malignancies. There were also no observations in nonclinical studies of hyperplasia, premalignant or malignant changes noted after 44 weeks in primate, and 26 weeks in rat general toxicity studies. Recent studies have shown that complement components have contributed to regulating the function of the tumour microenvironment and exert immunoregulatory effects under certain conditions [42]. The carcinogenic potential of avacopan was evaluated in 2-year studies in both rats and hamsters (i.e., with life-time dosing). In male rats, a slightly increased incidence in C-cell adenomas, a finding which is known to occur spontaneously in aged rats [39], was noted at the highest dose tested, this increase being not statistically significant and the incidence within the historical control range. Since the studies conducted to date are limited with regards to follow-up time and total exposure to provide any reassurance with regards to the risk for malignancy, considering the mechanism of action, as well as malignancies are included as adverse reactions for eculizumab, this will be included as a potential risk.

Table 9 Exclusion Criteria (Cont'd)

Criteria	Reason for Exclusion	Missing Information?	Rationale
			No neoplasias were noted in female rats. It should be stressed that the rat is not a pharmacologically relevant species (i.e., avacopan is not active at the rat C5a receptor) and, more importantly, avacopan was not carcinogenic in hamsters, the pharmacologically relevant animal species (PC0674_168 and PC0675_168). The information above is included in Section 5.3 of the SmPC (Carcinogenicity studies).
Evidence of tuberculosis based on IGRA, tuberculin PPD skin test, or chest radiography (X-rays or CT scan) done at screening or within 6 weeks prior to screening	Safety precaution. It was unknown at the time of study initiation whether avacopan would increase the risk of tuberculosis reactivation or worsening	No	To date, no cases of tuberculosis have been observed in clinical studies. Routine risk minimisation measures beyond Product Information include the legal status of the medication (prescription only medication).
Patients with positive HBV, HCV, or HIV viral screening test showing evidence of active or chronic viral infection done at screening or within 6 weeks prior to screening	Safety precaution. It was unknown at the time of study initiation whether avacopan would increase the risk of hepatitis B, hepatitis C, or HIV reactivation or worsening	No	To date, no cases of hepatitis B, hepatitis C, or HIV infections have been observed in clinical studies. In the Phase 3 study, 1 case was reported as hepatitis B reactivation during the follow-up period (D391) in the avacopan group considered possibly related to 2 rituximab infusions given prior to the event (D225 and 238). Routine risk minimisation measures beyond Product Information include the legal status of the medication (prescription only medication).
Patients who received a live vaccine within 4 weeks prior to screening	Safety precaution. It was not known at the time of study initiation whether avacopan would increase the risk of infection in patients receiving live vaccines	No	Routine risk minimisation measures beyond Product Information include the legal status of the medication (prescription only medication). Treatment with avacopan should be initiated and monitored by healthcare professionals experienced in the diagnosis and treatment of GPA or MPA.

Table 9 Exclusion Criteria (Cont'd)

Criteria	Reason for Exclusion	Missing Information?	Rationale
White blood cell count <3,500/µl, neutrophil count <1,500/µl, or lymphocyte count <500/µl before start of dosing	Safety precaution. All patients in the avacopan studies received cyclophosphamide or rituximab treatment. Cyclophosphamide and rituximab are both associated with leukopenia	No	Routine risk minimisation measures beyond Product Information include the legal status of the medication (prescription only medication). Treatment with avacopan should be initiated and monitored by healthcare professionals experienced in the diagnosis and treatment of GPA or MPA.
Evidence of severe hepatic disease	Safety precaution	No	At the time of the Phase 3 study initiation, it was unknown whether severe hepatic impairment could have an effect on PK, safety and tolerability of avacopan. Study CL013_168 demonstrates no significant impact on avacopan PK in subjects with mild and moderate hepatic impairment. Routine risk communication regarding hepatic impairment is included in SmPC Section 4.2, Section 4.4 and Section 5.2.
Pregnancy and breastfeeding	Safety precaution	No	The demographics of GPA and MPA, and the risks to pregnancy of the concomitant medications, make it unlikely that avacopan will be prescribed to patients at risk of pregnancy. Avacopan has not been measured in the milk of lactating animals. It is not known whether avacopan or its metabolites are excreted in human milk. However, avacopan was found in the plasma of nursing hamster offspring, thus it is likely that avacopan is excreted in milk. Routine risk communication regarding pregnancy is listed in SmPC Section 4.6 Fertility, Pregnancy and Lactation.

Table 9 Exclusion Criteria (Cont'd)

Criteria	Reason for Exclusion	Missing Information?	Rationale
Patients less than 12 years old	Safety precaution. No data is available for patients below 12 years of age. Limited safety data in 2 adolescent patients in the avacopan arm and 1 in the prednisone arm are available from the Phase 3 study	No	The use of avacopan in the paediatric population is off-label as current data is limited (only 2 subjects were treated with avacopan in the Phase 3 study, one completed the study treatment (365 days) whilst the other was discontinued after 91 days of treatment). To investigate and evaluate the safety and efficacy in the paediatric population, an avacopan Paediatric Investigation Plan was first approved by the EMA on 22-May-2017. Routine risk communication regarding paediatric population is included in the SmPC Section 4.2 and Section 5.1

Notes: CT=Computerised tomography; GPA=Granulomatosis with polyangiitis; HBV=Hepatitis B virus; HCV=Hepatitis C virus; Ig=Immunoglobulin; IGRA=Interferon γ release assay; MPA=Microscopic polyangiitis; PK=Pharmacokinetic; PPD=Purified protein derivative; SmPC=Summary of Product Characteristics.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Table 10 Limitations to ADR Detection

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are rare	A total of 508 subjects were exposed to avacopan during the clinical study programme, (269 in Phase 1 and 73 patients in Phase 2, and 166 patients in Phase 3) who received avacopan in ANCA-associated vasculitis.	The clinical programme was limited in size due to the fact that ANCA-associated vasculitis is an orphan disease, and the database includes subjects from two Phase 2 studies and one Phase 3 study. Therefore, it is theoretically possible that ADRs that are uncommon or rare have not been detected. It is recognised that controlled randomised studies are not feasible for capturing rare ADRs. Post-marketing surveillance will provide additional safety information on rare ADRs, based on larger scale exposure.
Which have a long latency	The length of off-treatment follow-up in the Phase 1 clinical studies in healthy volunteers ranged from 3 to 14 days. The length of follow-up in the Phase 2 studies was 12 weeks and 8 weeks in the Phase 3 study.	It is theoretically possible that it is difficult to detect ADRs with a long latency.

Notes: ADR=Adverse drug reaction; ANCA=Anti-neutrophil cytoplasmic autoantibody.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table 11 Exposure of Special Populations Included or Not in Clinical Study Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	Not included in the clinical development programme.
Patients with Relevant Comorbidities	
Patients with severe hepatic impairment	Patients with severe hepatic impairment were not included in the clinical development programme.
Patients with mild and moderate hepatic impairment	Exposure (PK) was assessed following a single dose of 30 mg avacopan in volunteers with mild or moderate hepatic impairment. No significant change in PK was observed compared to healthy volunteers (Study CL013_168).
Patients with renal impairment	Steady state plasma exposure (AUC) was estimated to be slightly higher (approximately 20%) in ANCA-associated vasculitis subjects with severe renal impairment (eGFR <30 ml/min/1.73 m^2), compared to those with normal/mild renal impairment (eGFR >60 ml/min/1.73 m^2) (CMR_168_POP_PK2). No dose adjustment is required for patients with renal impairment. Avacopan has not been studied in patients with MPA or GPA on renal dialysis or with an eGFR <15 ml/min/1.73 m^2. A total of 251 subjects with an eGFR <60 ml/min/1.73 m^2 received avacopan during the two Phase 2 and one Phase 3 studies (Source: Integrated Safety Summary Table 6.4.1 and 6.4.2).
Patients with cardiovascular impairment	Patients across a broad age range were included in the Phase 2 and 3 clinical studies. 23% of the study population in Study CL010_168 had a baseline condition mapping to the Cardiac Disorders SOC. These primarily included participants reporting a history of arrhythmia and ischaemic heart disease. There was no evidence of an increased cardiovascular risk with avacopan based on the adverse event profile as well as results from an intensive ECG study (CL007_168). Additionally, there was no evidence that avacopan had a clinically significant effect on cardiac electrophysiology based on results from a thorough QT/QTc study (CL014_168).
Immunocompromised patients	In the Phase 2 and 3 studies, avacopan was given as part of immunosuppressive regimens including cyclophosphamide or rituximab in patients with GPA or MPA. In the Phase 2 and 3 studies, avacopan was given concomitantly with either cyclophosphamide or rituximab in patients with GPA or MPA. Cyclophosphamide and rituximab suppress the immune system and cause decreases in lymphocyte counts. Immunocompromised participants were therefore well represented in the avacopan clinical development programme. A total of 239 subjects (person time: 212.31) received avacopan during the Phase 2 and 3 studies (Integrated Safety Summary Table 2 and Table 18.1).
Patients with a disease severity different from inclusion criteria in clinical studies	There is no experience with avacopan in patients with end-stage renal disease (eGFR <15 ml/min/1.73 m^2) in the clinical development programme.
Population with relevant different ethnic origin	A total of 207 of 239 patients (86.6%) who received avacopan in the Phase 2 and 3 studies were White.

Table 11 Exposure of Special Populations Included or Not in Clinical Study Development Programmes (Cont'd)

Type of Special Population	Exposure
	A total of 207 White subjects (person time: 180.28 years) and 32 non-white subjects (6 subjects were Black; 17 were Asian and 9 were 'Other') (person time: 32.03 years) received avacopan during the two Phase 2 studies and Phase 3 study (Source: Integrated Safety Summary Table 18.2). Additionally, healthy 50 Japanese adult males and 30 Caucasian adult males were studied in a Phase 1 trial, CCX1101. This study evaluated safety and PK of the study drug in Japanese adult male subjects and investigated the similarity of PK between Japanese and Caucasian subjects. This ethno-bridging PK Study CCX1101 involving Japanese and Caucasian healthy subjects was performed at several doses in Japanese subjects (10, 30 and 100 mg single dose as well as 30 and 50 mg BID for 7 days) and at several corresponding doses in Caucasians (10 and 30 mg single dose as well as 30 mg BID for 7 days). The study concluded that the exposures of avacopan or metabolite M1 were similar between Japanese and Caucasian subjects following administration of a single dose of avacopan. After multiple dosing of 30 mg of avacopan, mean PK parameters of avacopan and metabolite M1 were slightly higher in Japanese subjects than those in Caucasian subjects; however, the ranges of PK parameters of individual subjects in the 2 races roughly overlapped each other. Finally, there were also no clinically significant differences of the safety profile between the Japanese and Caucasian subjects.
Subpopulations with relevant genetic polymorphisms	Not evaluated in the clinical development programme.
Paediatric patients	Paediatric patients less than 2 years of age: The incidence of the target disease (MPA and GPA) is extremely low in the 0 to 27 days and 1 month to 23 months of age paediatric groups. A deferral was granted by the PDCO for paediatric patients less than 18 years of age. Paediatric patients aged 12 years to 17 years: To determine the safety, efficacy, tolerability, PK, and pharmacodynamics of avacopan in adolescents, subjects of this age range have been enrolled into the Phase 3 Study CL010_168. Due to the low prevalence of ANCA-associated vasculitis in paediatric subjects, only 2 adolescent subjects in the avacopan arm have been studied in Phase 3 Study CL010_168. No definitive conclusions could be drawn from these limited data.
Elderly	Elderly subjects with GPA or MPA were included in the Phase 2 and 3 studies. Population PK analysis found no impact from age on the PK of avacopan. Avacopan exposure in elderly subjects (65 to 85 years of age) was similar (<10% difference) to that in adult subjects (<65 years of age). A total of 42 males (person time: 38.55 years) and 34 females (person time: 32.85 years) aged 65-74 years received avacopan during the two Phase 2 and one Phase 3 clinical studies (Integrated Safety Summary Table 18.1). A total of 16 males (person time: 16.26 years) and 16 females (person time: 15.92 years) aged ≥75 years received avacopan during the two Phase 2 and 3 clinical studies (Integrated Safety Summary Table 18.1).

Notes: ANCA=Anti-neutrophil cytoplasmic autoantibody; AUC=Area under the concentration-time curve; BID=Twice per day; ECG=Electrocardiogram; eGFR=Estimated glomerular filtration rate; GPA=Granulomatosis with polyangiitis; MPA=Microscopic polyangiitis; PDCO=Paediatric Committee; PK=Pharmacokinetic; SOC=System organ class.

SV POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

The estimates of post-marketing patient exposure are in part based on unit sales data (e.g., capsules), and in part on observed drug utilisation parameters. Worldwide unit sales are recorded monthly by country and are converted to estimates of person time and when feasible, person count, using region and product specific utilisation parameters and algorithms. These parameters include the average number of mg per administration, average length of treatment, days between administrations, patient turnover rates, market penetration rates, and average revenue per patient. These drug utilisation parameters can change over time to best represent the current patient and market experience.

Post-marketing patient exposure estimates are reported overall and for the following geographic regions: Europe (EU, EEA, European countries outside EU/EEA), North America, Middle East (including Israel), Asia Pacific (APAC).

SV.1.2 Exposure

The cumulative and interval number of patient-years of exposure to avacopan through commercial distribution in Amgen and business partner territories is shown in Table 12 below.

Table 12 Cumulative Exposure from Marketing Experience Until 31 December 2023

Region	Exposure (Units)[1]
	Patient-years
North America	1,538
Europe	814
Middle East	6
APAC	1,793
Total	**4,151**

1 Sales data is available on a monthly basis only, including data from the first to the last day of each month. Therefore the interval exposure presented in this table includes cumulative data until 31 December 2023.

SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATIONS

SVI.1 Potential for Misuse for Illegal Purposes

The potential for misuse of avacopan for illegal purposes is considered low. There are no published reports that the intended mechanism of action, antagonism of C5aR1, is associated with human abuse liability. Based on results from diverse in vitro and in vivo evaluation of avacopan and its major metabolite M1, there is no indication that avacopan is active in the central nervous system.

SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The results of the analysis from the Phase 3 study for potential ADRs occurring in ≥5% of subjects receiving avacopan and >2% higher in the avacopan group compared to the prednisone group are nausea (34 of 164 (20.7%) in the prednisone group and 39 of 166 (23.5%) in the avacopan group), vomiting (21 of 164 (12.8%) in the prednisone group and 25 of 166 (15.1%) in the avacopan group) and headache 23 of 164 (14.0%) in the prednisone group and 34 of 166 (20.5% in the avacopan group). Angioedema (0 of 164 subjects (0.0%) in the prednisone group and 2 of 166 (1.2%) in the avacopan group), and increased blood creatine phosphokinase (CPK) (1 of 164 subjects (0.6%) in the prednisone group and 6 of 166 (3.6%) in the avacopan group) were observed. These adverse reactions are listed in SmPC Section 4.8. The clinical impact of such risks on patients is considered small in relation to the severity of the disease of GPA and MPA and such risks should therefore not be classified as important.

Reason for Not Including as an Identified or Potential Risk in the List of Safety Concerns in the RMP

Clinical Conditions Associated With CPK Elevations such as Rhabdomyolysis

Based on the mechanism of action for avacopan, increased CPK elevations would not be mechanistically plausible nor expected to cause rhabdomyolysis. A total of 7 (4.2%) events in the avacopan arm reported a mild to moderate elevation and reversible blood CPK elevation with the majority considered to be unrelated to avacopan. None of the cases reported were in relation to a concurrent event associated to cardiovascular disorders, however associated to back pain, bone pain, joint pains, muscle spasms, myalgia, fatigue, amylase increase, blood lactate dehydrogenase increase and diarrhoea (Table 13).

Table 13 Subjects Who Had TEAEs of Increased Blood CPK

Treatment Group	Start Date	Severity	Highest CPK CTCAE Grade	TEAEs in Proximity to CPK Elevation	Outcome	Action Taken With Study Drug	Relatedness per Investigator
Prednisone Group							
	Day 28	Moderate	1	Muscle spasms, blepharitis, blood lactate dehydrogenase increased	Resolved Day 92	None	Possibly related
Avacopan Group							
	Day 225	Mild	2	Bone pain, anxiety, rash, ear discomfort	Ongoing	None	Possibly related
	Days 92, 246	Mild, mild	3	Viral upper respiratory tract infection, myalgia, fatigue	Resolved Day 99, resolved Day 261	Study drug interrupted; study drug interrupted	Probably not related, possibly related
	Day 49	Moderate	2	Painful dry nose, joint pains, worse dry cough, painful dry eyes	Resolved Day 141	None	Possibly related
	Day 30	Severe	3	Amylase increased; lipase increased	Ongoing	Study drug discontinued	Probably not related
	Day 93, 276	Mild, mild	1	Back pain	Resolved Day 225, ongoing	None, none	Probably not related, probably not related
	Day 113	Mild	1	Blood lactate dehydrogenase increased, diarrhoea	Ongoing	None	Probably not related

Notes: CPK=Creatine phosphokinase; CTCAE=Common Terminology Criteria of Adverse Event; TEAE=Treatment-emergent adverse event.
Source: Listing 16.2.7.1, Table 14.3.3.12.3.

No increases in blood CPK were reported in either treatment group as a serious adverse event (SAE), and none of the subjects, except for 1 subject in the avacopan group discontinued treatment on Day 189 due to blood CPK increased (Table 14.1.2.2). This subject also had TEAEs of amylase and lipase increases (Listing 16.2.7.1) and was assessed by the Investigator as not related to study medication. No events of rhabdomyolysis or myositis were reported (Listing 16.2.7.1).

Importantly, there was no evidence to suggest an association between CPK increase and cardiac TEAEs. No cardiac AEs were observed at the time of CPK elevations in these subjects. CPK levels can increase with greater physical activity [43,44], which could explain the increases seen in particular in the avacopan group which showed a greater

improvement in physical activity compared with the prednisone group based on the Short Form-36 data (CSR CL010_168 Section 11.4.1.2.3.1).

In the pooled Phase 2 studies, 3 subjects in the avacopan group had TEAEs of blood CPK increased (Integrated Safety Summary (ISS) Table 5.1). None of these TEAEs were serious. First subject in Study CL002_168, had the event on Day 44, which was considered moderate in intensity. The event resolved with no action taken regarding study medication, and was considered not related to avacopan by the Investigator (CSR CL002_168 Listing 16.2.7.1). Second subject in Study CL003_168, had the event on Day 99 (during the avacopan-free follow-up period), which was considered moderate in intensity. The event resolved with no action taken regarding study medication, and was considered not related to avacopan by the Investigator (CSR CL003_168 Listing 16.2.7.1). Third subject in Study CL002_168, had the event on Day 15, which was considered mild in intensity. The event resolved with no action taken regarding study medication, and was considered not related to avacopan by the Investigator (CSR CL002_168 Listing 16.2.7.1).

Upon examination of laboratory data in Study CL002_168, first subject mentioned above, had a Grade 3 CPK abnormality on Day 43 which returned to normal on Day 71 (CSR CL002_168 Listing 16.2.8.1), with no interruption of avacopan treatment. This subject had an AE of mild muscle spasms in the same timeframe as the CPK elevation (CSR CL002_168 Listing 16.2.7.1). One subject in Phase 2 Study CL003_168 with a high baseline CPK, had a Grade 3 CPK on Day 85 (CSR CL003_168 Listing 16.2.8.1). This elevated CPK value persisted until the end of the 12-week follow-up period, while not taking any avacopan. This subject had an AE of mild musculoskeletal pain in the same timeframe as the CPK elevation (CSR CL003_168 Listing 16.2.7.1).

In summary, although there appeared to be a higher subject incidence of increased CPK in subjects receiving avacopan in Phase 2, none of the events were serious. Two of the events appeared to be temporally related to mild musculoskeletal TEAEs. Additionally, the event of blood CPK increased was captured as an ADR.

White Blood Cell Count Decrease

White blood cell count decrease was an event of interest. Based on a thorough analysis of the incidence of white blood cell count decreases, including neutropenia and lymphopenia, there did not appear to be an increased risk with avacopan treatment. Preferred terms (PTs) included agranulocytosis, bone marrow failure, bone marrow toxicity, febrile neutropenia, leukopenia, lymphopenia, neutropenia, pancytopenia, neutropenic sepsis, lymphocyte count decreased, neutrophil count decreased, and white blood cell count decreased. In the Phase 3 trial, the subject incidence for any TEAE associated with low white blood cell count was 29 (23.8%) in the prednisone group and 31 (18.7%) in the avacopan group. The subject incidence in reported events of lymphopenia was 18 (11.0%) in the prednisone group and 6 (3.6%) in the avacopan group. There was no difference between the 2 groups for the reported event of neutropenia which was 4 (2.4%) in both groups. The overall subject incidence of low white blood cell count AEs was 41 of 200 subjects (19.3%) in the

prednisone group and 35 of 239 subjects (15.4%) in the avacopan group, with a difference in incidence of -3.9% (95% CI -10.9, 3.1). The distribution of low white blood cell count AEs was similar for the integrated analysis and the Phase 3 study analysis.

Neutropenia is considered as an ADR and further described in the SmPC further detailing a subject who was diagnosed with agranulocytosis based on a bone marrow biopsy revealing central neutropenia. The event resolved spontaneously with no interventions done. The event of serious infections is considered in the safety specification, see Section SVII for further details.

Cellulitis

In the Phase 3 Study CL010_168, there were 4 subjects with TEAEs of cellulitis in the avacopan group (CSR CL010_168 Table 14.3.1.1.1 and Listing 16.2.7.1). Two of these TEAEs occurred during the follow-up period when avacopan was not given (CSR CL010_168 Listing 16.2.7.1). All 4 were considered mild, 3 of 4 were not considered related to avacopan, and all 4 events resolved (CSR CL010_168 Listing 16.2.7.1). Even though no cases of cellulitis were reported in the prednisone group, there were 2 subjects with an abscess (a subject with subcutaneous abscess and a subject with breast abscess) and 1 subject with wound infection pseudomonas in the prednisone group (CSR CL010_168 Listing 16.2.7.1). Also, the overall incidence of infections was lower in the avacopan group compared to the prednisone group (CSR CL010_168 Table 14.3.1.1.1). Therefore, cellulitis was not considered an ADR.

Worsening GPA

GPA is one of several PTs that captures AAV disease activity (including ANCA positive vasculitis and MPA). In the Phase 3 Study CL010_168, there was a higher number of ANCA positive vasculitis in the prednisone group (46 events in 34 subjects (20.7%)) compared to the avacopan group (30 events in 26 subjects (15.7%)) (CSR CL010_168 Table 14.3.1.1.2), supportive of the efficacy results. When all PTs referring to vasculitis worsening were combined, i.e., ANCA positive vasculitis/GPA/MPA, the incidence was higher in the prednisone group 23 (12.2%) compared to the avacopan group 17 (7.2%). In light of these findings, and the efficacy data from this study, GPA was not considered an ADR.

Mild to Moderate Hepatic Impairment

A Phase 1 (CL013-168) study to test the safety and PK of avacopan in patients with mild and moderate hepatic impairment (cohorts of 8 patients each with moderate impairment, mild impairment, or healthy controls; a single dose of 30 mg avacopan followed by 18 days of observation and PK sampling) was conducted. The PK results suggest that in patients with mild to moderate hepatic impairment, the hepatic condition has no pharmacokinetically relevant impact on avacopan exposure (e.g., geometric mean ratios for both the C_{max} and AUC_{last} were within the range of 0.8-1.25). No SAEs were reported during this study. As a result, no dose adjustment was necessary for patients with mild to

moderate hepatic impairment. Patients with severe hepatic impairment were not included in Phase 3 study because of the low prevalence of severe hepatic impairment in the intended indications for avacopan and the difficulty in recruiting patients with severe hepatic impairment. Mild and moderate hepatic impairment did not show pharmacokinetically relevant effects on the C_{max} and $AUC_{0\text{-}inf}$ of active metabolite M1 compared to healthy matched controls. The magnitude of the changes in the C_{max} and AUC of avacopan and metabolite M1 (well within 2-fold) suggests that no avacopan dosage adjustment is necessary for patients with mild to moderate hepatic impairment. The single dose of avacopan was well tolerated in all subjects.

Drug-Drug Interactions

Additionally, the drug-drug interaction study findings in Study CL008_168 were not considered important for inclusion in the list of safety concerns in the RMP (see SmPC Section 4.5). Co-administration of the strong CYP3A4 enzyme inducer, rifampicin, resulted in a reduction of systemic exposure of avacopan, which may result in a loss of efficacy of avacopan. Co-administration of avacopan with multiple doses of rifampicin resulted in a decrease in AUC and C_{max} by approximately 93% and 79%, respectively. Co-administration of the strong CYP3A4 enzyme inhibitor, itraconazole, resulted in an increase of systemic exposure of avacopan. Co-administration of avacopan with multiple doses of itraconazole resulted in an increase in AUC and C_{max} by approximately 119% and 87%, respectively. Co-administration with potent CYP3A4 inducers such as rifampicin may reduce the avacopan exposure, which is not a safety concern, *per se*. Co-administration with potent CYP3A4 inhibitors such as itraconazole only modestly increase (~2-fold) the avacopan exposure. This does not pose an important safety risk, because the safety margins from the toxicology studies are 4.6 to 15-fold.

Off-Label Use

Theoretically, the potential risk of off-label use is considered to be moderate. The proposed indication is treatment of adult patients with GPA or MPA. Conditions in which the possibility of off-label use could arise include the following:

- Use in children or adolescents with GPA or MPA; risk is regarded as low, reflecting the rarity of disease in this age group. The SmPC includes wording to restrict the indication to adults with GPA or MPA. Routine risk communication is included in SmPC Section 4.1, Section 4.2, and Section 5.1.

- Use in diseases other than GPA or MPA; risk is regarded as low to moderate, the latter reflecting increasing recognition that the complement system is active in multiple diseases that have a high unmet medical need. The SmPC includes wording to restrict the indication to adults with GPA or MPA. Routine risk communication is included in SmPC Section 4.1.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: Liver Injury

Benefit/risk impact: The risk of liver dysfunction requires liver enzyme test monitoring. Patients with AAV are often taking multiple medications, including medication such as trimethoprim plus sulfamethoxazole that may cause idiosyncratic drug-induced liver injury. AE PTs associated with hepatic system abnormalities have been reported with avacopan treatment. All subjects with an event of hepatic abnormalities were predefined and analysed. The adverse reaction includes the following reports of TEAEs (regardless of the causal relationship) listed in descending frequency: hepatic enzyme increased, hepatic function abnormal, alanine aminotransferase (ALT) increased, blood bilirubin increased, liver function test increased, aspartate aminotransferase (AST) increased, transaminases increased, drug-induced liver injury, hepatitis cholestatic, hepatocellular injury, and liver function test abnormal.

In the Phase 3 clinical trial, a total of 19 subjects (11.6%) in the prednisone group and 22 subjects (13.3%) in the avacopan group had a hepatic test AE in the study. Study medication was paused or discontinued permanently due to hepatic test abnormalities in 5 subjects (3.0%) in the prednisone group and 9 subjects (5.4%) in the avacopan group (CSR CL010_168 Table 14.3.1.10.2). Serious hepatic test AEs were reported in 6 subjects (3.7%) in the prednisone group and 9 subjects (5.4%) in the avacopan group. One subject received avacopan and had an SAE of hepatocellular injury. The event occurred on Study CL010-168 Day 37 in a subject who concomitantly received bactrim (co-trimoxazole). Medication with avacopan and bactrim was discontinued. The subject's liver enzymes decreased. On Day 40, the subject had mild pancreatic insufficiency and was treated with creon and resolved. This was not considered related to study drug. On Day 43, the subject had a positive rechallenge with avacopan. On Day 51, avacopan was discontinued. Day 85, liver function tests normalised. The event resolved. The subject was diagnosed with asymptomatic hepatitis with cytolysis and anicteric cholestasis without hepatocellular insufficiency.

A summary of the pooled Phase 2 studies of TEAEs associated with hepatic enzyme elevations is presented in ISS Table 9.2. The incidence of these events was similar in the 2 treatment groups: 3 (out of 36) subjects (8.3%) in the prednisone group and 6 (out of 73) subjects (8.2%) in the avacopan group. One subject receiving avacopan had an SAE of hepatic enzyme increased (ISS Table 5.2). This event occurred in Study CL002_168 in a subject with a medical history of alcohol abuse, who received avacopan, cyclophosphamide, sulfamethoxazole/trimethoprim (co-trimoxazole), amoxicillin clavulanate, pantoprazole, and GCs, and had an increase in ALT, AST, alkaline phosphatase, total bilirubin, and amylase after approximately 3 weeks on treatment. Avacopan and all other medications except GCs were stopped. No rechallenge of avacopan was carried out in this subject after dechallenge of study medication. The AE resolved. A narrative of this case is provided in CSR CL002_168 Section 14.3.3.2.

Based on central laboratory data, there were no Grade 3 increases in ALT or AST in the Phase 2 studies (ISS Table 10.1).

A summary of an integrated analysis of the subject incidence of liver function test AEs in the Phase 2 and 3 studies is shown in ISS Table 14.1. The overall subject incidence of liver function test AEs was 22 of 200 subjects (10.8%) in the prednisone group and 28 of 239 subjects (12.0%) in the avacopan group, with a difference in incidence of 1.2% (95% CI -4.8, 7.2). The distribution of liver function test AEs was similar for the integrated analysis and the Phase 3 study analysis (CSR CL010_168 Table 14.3.1.10.1).

A summary of an integrated analysis of the subject incidence of hepatic test SAEs in the Phase 2 and 3 studies is shown in ISS Table 18.3. The overall subject incidence of hepatic test SAEs was 6 of 200 subjects (2.8%) in the prednisone group and 10 of 239 subjects (4.4%) in the avacopan group, with a difference in incidence of 1.7% (95% CI -1.8, 5.1). The distribution of hepatic test SAEs was similar for the integrated analysis and the Phase 3 study analysis (6 of 164 subjects (3.7%) in the prednisone group and 9 of 166 (5.4%) in the avacopan group; CSR CL010_168 Table 29).

Important Potential Risk: Cardiovascular Safety

Benefit/risk impact: The cardiovascular safety requires close monitoring. Patients with AAV have a higher cardiac risk noted to be 6-30% presented as pericarditis, myocardial ischaemia, myocarditis, endocarditis, valvulitis, or conduction defects [45]. This is due to the underlying disorder but also due to the use of immunosuppressive drugs like cyclophosphamide. While there have been reports that the use of GC may help shield the heart from cardiotoxic effects, it remains a vulnerable situation. Patients with AAV treated with methylprednisone followed by immunosuppressors improved the cardiac clinical symptoms and markedly reduced myocardial magnetic resonance imaging contrast enhancements in patients with inflammatory myopathies [46]. Subjects in the Phase 3 study with an event of cardiac disorder were analysed. These AE PTs associated with cardiac disorder have been reported with avacopan treatment and include the following reports of TEAEs (regardless of the causal relationship) listed in descending frequency: acute myocardial infarction, angina pectoris, atrial fibrillation, atrioventricular block first degree, bradycardia, bundle branch block left, cardiac failure, cardiorenal syndrome, cardiovascular insufficiency, congestive cardiomyopathy, ECG QT prolonged, ECG T wave abnormal, extrasystoles, mitral valve incompetence, myocardial ischaemia, palpitations, pericardial effusion, pericarditis, sinus bradycardia, supraventricular extrasystoles, tachycardia, tricuspid valve incompetence, ventricular extrasystoles, and ventricular hypokinaesia.

In the Phase 3 clinical trial, review of the baseline medical history profiles indicated that there were more subjects in the avacopan group with a prior medical history of cardiac failure congestive/cardiac failure/cardiac failure acute/cardiac failure chronic than in the prednisone group (5 subjects (3.0%) versus 1 subject (0.6%), respectively) (CSR CL010_168 Table 14.1.6.1 page 31). All 4 subjects who had TEAEs of cardiac failure had

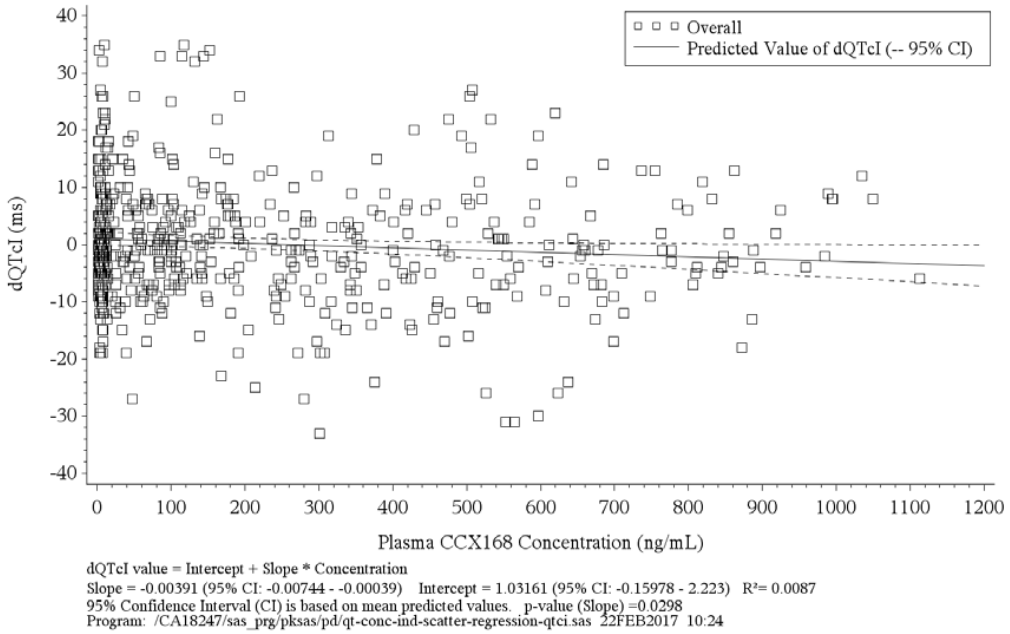
a medical history of cardiovascular disease (CSR CL010_168 Listing 16.2.4.2). All 4 subjects recovered from the event and completed the study (CSR CL010_168 Listing 16.2.7.1). Two of the events were reported as SAEs. These are discussed in Section 2.5.2. Of note, the incidence of serious major cardiovascular events (defined as nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death) was higher in the prednisone group (3 subjects) compared with the avacopan group (1 subject) (CSR CL010_168 Listing 16.2.7.1). Also, the incidence of peripheral oedema, as a possible manifestation of cardiac failure was higher in the prednisone versus the avacopan group (24.4% versus 21.1%, respectively) (CSR CL010_168 Table 14.3.1.1.2). There was no evidence that avacopan had a deleterious effect on cardiac electrophysiology based on results from a thorough QT/QTc study (CSR CL014_168).

One of the prospectively defined main objectives of the Phase 1 Study CL007_168 was to evaluate the cardiac safety of avacopan, at doses ranging from a sub-therapeutic dose of 3 mg avacopan up to supra-therapeutic doses of 100 mg avacopan twice daily. This was done by intensive ECG acquisitions and analysis in the study. The therapeutic dose regimen for treatment of patients with AAV is 30 mg twice daily. A maximum concentration (C_{max}) in the plasma of 262 ng/ml was observed at steady state with this dosing regimen (CSR CL008_168 Table 14.2.1.3.3).

The relationship between plasma avacopan concentrations and QTcI in Study CL007_168 is shown in Figure 1.

Results from this intensive ECG study showed that there was no evidence of a detrimental effect of avacopan on QTcI.

Figure 1 **Linear Model Evaluation of Avacopan in Study CL007_168: Change from Baseline in QTcI (dQTcI) Versus Time-Matched Plasma Avacopan Concentrations (Scatterplot)**



Note: CI=Confidence interval.
Source: Clinical Study Report CL007_168 Figure 11-6.

Results from the cardiodynamic analysis did not show a positive correlation between concentrations of avacopan, CCX168-M1, or avacopan plus CCX168-M1 and QTcI, and other ECG parameters across a broad plasma concentration range of avacopan and CCX168-M1 (see CSR CL007_168).

Plasma concentrations of avacopan up to 1,110 ng/ml were measured in Study CL007_168 (Figure 1). The mean C_{max} (on Day 7 of 100 mg avacopan given twice daily) was 840 ng/ml (CSR CL007_168 Table 14.2.1.1.9), which was 3.2-fold higher than the C_{max} of 262 ng/ml on Day 15 of dosing at the therapeutic dose of 30 mg avacopan twice daily (from Study CL008_168). The avacopan plasma C_{max} of 840 ng/ml was also 1.7-fold higher than the worst-case clinical scenario where avacopan might be dosed concomitantly with a potent CYP3A4 inhibitor such as itraconazole (489 ng/ml; CSR CL008_168 Table 14.2.1.3.4). There was a 2.3-fold margin between the CCX168-M1 C_{max} for the supra-therapeutic dose of 100 mg avacopan twice daily (218 ng/ml; CSR CL007_168 Table 14.2.1.2.9) and the worst-case clinical scenario of CYP3A4 inhibition (94.3 ng/ml; CSR CL008_168 Table 14.2.1.4.4).

Results from the categorical outlier analysis for all subjects in Study CL007_168 indicated that none of the subjects had a QTcI >450 msec during the study. One subject receiving 3 mg avacopan, had changes from baseline in QTcI of 32 msec at Hour 4 and 34 msec at Hour 12 following dosing (CSR CL007_168 Appendix 16.2.6.5.3). One subject receiving 30 mg avacopan, had changes from baseline in QTcI of between 32 and 35 msec at 7 of 9 time points following dosing. No subjects had a change from baseline >60 msec.

Therefore, there were a small number of subjects with a QTc increase from baseline of >30 but ≤60 msec. However, these effects did not indicate an avacopan dose-dependent relationship. Therefore, the results from the categorical analysis suggest no effect on QTc interval with avacopan.

In summary, in light of these data, as well as the findings from the thorough QT/QTc study (CSR CL014_168), which showed no evidence of a cardiac safety signal, there does not appear to be an increased risk of cardiac events with avacopan. However, supra-therapeutic exposures had not been evaluated in vivo. The C5aR is expressed on several other cells than the neutrophils and involved in numerous biological processes and taking into consideration the underlying disease, cardiovascular safety may be seen as an increased risk.

Overall, despite CL014_168 data, there was evidence that showed an imbalance in the avacopan arm from the CL010_168 study. Therefore, close monitoring is required to further evaluate the safety profile for cardiac disorders in patients treated with avacopan.

Important Potential Risk: Serious Infections

In the Phase 3 study CL010_168, the subject incidence of overall infections was lower in the avacopan group (68.1%) compared with the prednisone group (75.6%). Consistent with the Phase 3 study, the system organ classes with the highest subject incidence of TEAEs in the combined avacopan group of the pooled Phase 2 studies were Infections and Infestations (52.1%) (Section 2.7.4). Overall, a lower proportion of subjects had any TEAEs of infection, serious TEAEs of infection, life-threatening TEAEs of infection, and infections resulting in death in the avacopan group compared with the prednisone group. The incidence of severe TEAEs of infection and any TEAE leading to study withdrawal due to TEAEs of infection was similar in the 2 treatment groups. Inhibitors of C5 have been associated with an increased risk of infections with encapsulated bacteria, such as Neisseria meningitidis. Meningococcal infections are included as an uncommon event (≥1/1,000 to <1/100) in the Soliris SmPC. While eculizumab inhibits cleavage of C5 into C5a and C5b and disrupts the subsequent assembly of C5b-9 into the membrane attack complex (that penetrates the bacterial cell wall and causes bacterial lysis), avacopan does not interfere with the formation of C5b and the membrane attack complex or TCC and has no significant impact on this protection against Neisseria infections.

In the Phase 3 study, SAEs of infection were observed in 25 (15.2%) subjects reporting 31 events in the prednisone group and 22 (13.3%) subjects reporting 25 events in the avacopan group (CSR CL010_168 Table 14.3.1.3.3). Serious pneumonia/pneumonia haemophilus/lower respiratory tract infection/pneumonia bacterial/pneumonia cytomegaloviral was reported in 9 subjects (5.5%) in the prednisone group and 9 subjects (5.4%) in the avacopan group. There were 11 subjects (6.7%) with serious opportunistic infections in the prednisone group compared to 6 subjects (3.6%) in the avacopan group. No Neisseria meningitidis infections were reported in the study.

It should be noted that the overall subject incidence in the two Phase 2 and Phase 3 studies for infections was 139 of 200 subjects (67.2%) in the prednisone group and 151 of 239 subjects (64.1%) in the avacopan group. The distribution of infections by PT was similar for the integrated analysis and the Phase 3 study analysis (CSR CL010_168 Table 14.3.1.9).

- Clinical trials and real-world evidence demonstrated that AAV patients are at high risk of infection and this is associated with high mortality in the first year especially in the first year following the start of vasculitis treatment [47]. Patients are receiving high dose GC and/or prolonged low dose GC – standard GC regimes [21] and the use of IV GC [48] have been linked to heightened infection risk so avoiding or using a reduced dose of steroids could be associated with reduced infection risk.

- Cyclophosphamide and rituximab are integral parts of AAV treatment [2] but are immunosuppressants and may therefore increase infection risk. Cyclophosphamide is associated with myelosuppression, infections, urinary tract and renal toxicity as well as cardiotoxicity. Azathioprine is associated with bone marrow suppression, infections and hepatoxicity. Rituximab is associated with infections, neutropenia, thrombocytopenia, infusion related reactions and some cardiac disorders (see SmPC for full details). The RAVE study [17] was performed to determine if rituximab was associated with a lower infection rate but there was no difference, in this regard, when rituximab was compared with cyclophosphamide.

- AAV patients have organ damage from vasculitis (e.g., lung inflammation/ haemorrhage) and multiple medical interventions which may heighten risk of infection [2].

From these clinical data, avoiding or reducing GC use and achieving and maintaining vasculitis control effectively are appropriate clinical strategies to reduce infection risk.

Avacopan confers potential benefits in terms of risk of infection based on:

- Mode of action of avacopan is based on the innate immune response and specifically retains C5b-9 activity, so the membrane attack complex responsible for bacterial lysis is not affected [49,50]. Avacopan does not influence adaptive immunity i.e., lymphocyte count or function or antibody response

- Effective vasculitis control with avacopan would reduce any impact of ongoing organ damage and the need for medical interventions conferring infection risk

- GC dose is much lower or GCs may be avoided with avacopan

Therefore, there is a rationale for considering that patients receiving avacopan would be at lower risk from infections compared to patients receiving GCs only.

No infections caused by Neisseria meningitidis have been observed in all the clinical trials with avacopan. This is consistent with the mechanism of action of avacopan, which would not reduce TCC formation.

- Published literature that shows a liability for Neisseria infections with C5b-9 TCC genetic deficiency but not with C5aR genetic deficiency
- The finding that circulating levels of C5b-9 are unaffected by avacopan treatment
- Published literature that shows a protective effect against meningococcal sepsis with C5aR deficiency
- Therefore, immunisation for Neisseria meningitidis should not be required before starting avacopan treatment. The usual immunisation practices applicable to patients with autoimmune inflammatory rheumatic diseases, which also include AAV, should be followed [51].

The overall exposure-adjusted first incidence rate of all infections in the Phase 2 and 3 studies was 148.5 per 100 subject years in the prednisone group and 139.1 per 100 subject years in the avacopan group, with a difference in rate of -9.4 (95% CI -42.6, 23.7). The overall exposure-adjusted event rate of all infections in the Phase 2 and 3 studies was 166.6 per 100 subject years in the prednisone group and 142.2 per 100 subject years in the avacopan group, with a difference in rate of -24.3 (95% CI -48.5, -0.1). Although the Phase 3 study has demonstrated that avacopan is not associated with additional risk of infection in AAV and steroids are known to cause an increased risk for infections (especially in high doses), one cannot dismiss the similar or closely similar incidence of infections in the avacopan arm.

Overall, considering the seriousness of AAV and the severity of infections, close monitoring is required to further evaluate the safety profile for serious infection in patients with AAV treated with avacopan.

Important Potential Risk: Malignancy

Benefit/risk impact: Based on the data observed in the clinical and nonclinical setting, the incidence of malignancy events did not demonstrate statistical significance, and there were no clinically significant findings among the reported events.

The pivotal Phase 3 Study CL010_168 was a large study with 166 subjects exposed to avacopan for up to 52 weeks. The study also had 8 more weeks of follow-up, so 60 weeks in total. In the Phase 3 study, the incidence of neoplasms was lower in the avacopan compared to the prednisone group (6 subjects (3.6%) versus 16 subjects (9.8%), respectively; see CSR CL010_168 Table 14.3.1.1.1 page 32). None of the neoplasms occurring in the avacopan group in any of the Phase 2 or 3 studies was attributed to avacopan by the Investigators, the Data Monitoring Committee or by the Sponsor (Section 2.7.4).

The carcinogenic potential of avacopan was evaluated in 2-year studies in both rats and hamsters (i.e., with life-time dosing). In male rats, a slightly increased incidence in thyroid C-cell adenomas, a finding which is known to occur spontaneously in aged rats [39], was noted at the highest dose tested (100 mg/kg/day). This increase was not statistically significant and the incidence was within the historical control range. No neoplasias were noted in female rats. This increased incidence was not observed at the 30 mg/kg/day avacopan dose, which in fact had higher plasma avacopan levels than the 100 mg/kg/day group. It should be stressed that the rat is not a pharmacologically relevant species (i.e., avacopan is not active at the rat C5aR) and, more importantly, avacopan was not carcinogenic in hamsters, the pharmacologically relevant animal species (PC0674_168 and PC0675_168).

Recent studies have demonstrated that complement activation within the tumour microenvironment can promote tumour growth. Complement activation may support chronic inflammation, promote an immunosuppressive microenvironment, induce angiogenesis, and activate cancer-related signalling pathways. Several lines of evidence indicate a role for molecules of the complement system in sustained tumour growth and metastasis. C3, C4, or C5aR deficiencies prevent tumour growth in mice, potentially via inhibition of the classical pathway and the generation of C5a, which has a potent inflammatory potential. C5a and C5aR have been found to be often overexpressed in tumours attracting immunosuppressive cells in the tumour microenvironment [52]. These data support an anti-tumourigenic effect of a C5aR inhibitor such as avacopan.

Based on all above remarks, there is an increased amount of recent evidence, from both nonclinical and clinical studies, showing that mechanistically, blockade of C5aR1 could be a molecular target for cancer treatment. Based on this line of nonclinical evidence, advoralimab/IPH 5401, discovered by Innate Pharma, a fully human antibody that specifically binds and blocks C5aR, is currently in Phase 2 clinical development for the treatment of non-small cell lung cancer and hepatocarcinoma [53].

The clinical data, however, is currently limited. Due to the mechanism of action immunomodulatory medicinal products may increase the risk of malignancies.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 14 Important Identified Risk: Liver Injury

Identified Risk	Liver injury
Potential mechanisms	Findings from the mass balance studies and excretion studies in rats and cynomolgus monkeys indicate that avacopan is primarily metabolised in the liver, with little excretion of avacopan in the urine. Avacopan is readily absorbed and extensively distributed following oral administration. The major elimination pathway is extensive metabolism through CYP3A4-mediated oxidation in the liver and the metabolites are primarily excreted into faeces via bile. Hepatic or renal direct excretion of the unchanged avacopan is minimal. CCX168-M1, a monohydroxylation metabolite, is the only major circulating metabolite and is adequately qualified in the monkey, rat, rabbit, and hamster toxicology studies. Avacopan does not have significant DDI risk as a perpetrator but may be susceptible to enhancing the effects of potent CYP3A4 inducers and to a lesser extent of potent CYP3A4 inhibitors. The pathogenesis of liver injury is unknown. Liver injury may be the result of direct toxicity from the administered drug or their metabolites, or injury may result from immune-mediated mechanisms.
Evidence source(s) and strength of evidence	In a small number of cases, hepatic transaminases and bilirubin elevations have been observed in Phase 2 and in Phase 3 studies. These occurred in a background of co-administered drugs, such as trimethoprim/sulfamethoxazole which are known liver toxins, so clear and direct causality with avacopan could not be established. These elevations reversed with withdrawal of study drug (and trimethoprim/sulfamethoxazole).
Characterisation of the risk	
Frequency	**Related Clinical Trial Population:**

	Prednisone (N=200)	**Avacopan (N=239)**	
	Rate[(1)]	**Rate[(1)]**	**Rate Difference**
Any TEAE associated with hepatic abnormalities	12.3	14.7[(1)]	2.3
Any SAE with hepatic abnormalities	3.2	4.9	1.7

1 Incidences based on exposure-adjusted first incidence rate from the Phase 2 and 3 studies combined.
Note: Rate = Incidence per 100 subject years.
Source: Integrated Safety Summary Table 14.2 and Table 18.3.

Data are from the Phase 2 and 3 studies in ANCA-associated vasculitis combined.

Identified Risk	Liver injury		
	Post-marketing Experience		
	Number of Avacopan Related Cases	**Exposure Since International Birth Date to DLP**	**Frequency per 100 Patient-Years**
	125 (non-serious) 106 (serious) 231 (total)	4,151 patient-years	3.0 2.6 5.6
Seriousness/outcomes	**Related Clinical Trial Population:** Any SAE: Avacopan: 4.9 per 100 subject years (10 of 239 subjects had an SAE) Prednisone: 3.2 per 100 subject years (6 of 200 subjects had an SAE) Outcome SAEs in the avacopan group: fatal: 0 of 10 (0%); recovered without sequelae: 10 of 10 (100.0%); hospitalised: 4 of 10 (40.0%) **From Post-marketing Experience (in 4,151 patient-years):** Non-serious cases: 129 cases of which 125 related to avacopan. Outcome (all non-serious events): 47 events were reported as "recovered/resolved", 20 events were reported as "not recovered/not resolved", 14 events were reported as "recovering/resolving", and 52 events were reported as "unknown". Serious cases: 113 cases of which 106 related to avacopan. Outcome (all serious events): 37 events were reported as "recovered/resolved", 19 events were reported as "not recovered/not resolved", 26 events were reported as "recovering/resolving", and 32 events were reported as "unknown". 8 events with fatal outcome		
Severity and nature of risk	**Related Clinical Trial Population:** Severity of SAEs in avacopan group: Severe: 9 of 10 (90.0%) Moderate: 0 of 10 (0%) Mild: 1 of 10 (10.0%) **Post-marketing Experience** In the post-marketing setting it is not always possible to determine the severity of an event due to lack of sufficient information or severity not being reported as such. As a consequence of liver injury, vanishing bile duct syndrome (VBDS) has been reported in the post-marketing setting which is a rare and serious outcome of liver injury [54].		
Background incidence/prevalence	Liver function test increased is common in ANCA-associated vasculitis patients treated with cyclophosphamide/azathioprine plus glucocorticoids or rituximab plus glucocorticoids, without avacopan. For example, ALT increased was reported in 15.15% of subjects in the rituximab group and 22.45% of subjects in the cyclophosphamide group in the RAVE study [17]. AST increased was reported in 11.11% of subjects in the rituximab group and 16.33% of subjects in the cyclophosphamide group in the RAVE study [55]. During the active state of ANCA-associated vasculitis, liver function test abnormalities were detected in 49.4% of patients, receiving no treatment. Willeke et al, 2016 [56] demonstrated that the liver is frequently affected (49.4%) in patients with active GPA when affection is mirrored by liver test abnormalities [57]. Hepatotoxicity may occur with cyclophosphamide and azathioprine, both used for the treatment of ANCA-associated vasculitis [58,59,60]. Also, patients with ANCA-associated vasculitis are commonly treated with drugs such as co-trimoxazole (trimethoprim/sulfamethoxazole) in order to prevent		

Identified Risk	Liver injury
	pneumocystis infections. Co-trimoxazole is a known hepatotoxic drug [61,62,63]. Therefore, liver injury is well documented in patients receiving standard of care treatment for ANCA vasculitis not including avacopan.
Risk factors and risk groups	Common risk factors for hepatotoxicity include [64,65]: • Older age • Female gender • Underlying liver diseases (e.g., hepatitis) • Other comorbidities such as acquired immunodeficiency syndrome • Genetic predisposition involving CYP450, HLA alleles and other drug-processing enzymes • Chronic alcohol consumption • Concomitant use of hepatotoxic medications
Preventability	Early detection and management can decrease the seriousness of the outcomes. Text proposed in prescribing information under Warnings and Precautions (SmPC Section 4.4), where monitoring is required. Depending on the level of the liver enzymes, clinical re-assessment, pausing and discontinuation are described in SmPC Section 4.2.
Impact on the benefit/risk balance of the product	The hepatic disorder TEAEs observed during the clinical development concerned mainly hepatic enzymes increased transient in nature. However, this risk will be characterised further in the ongoing PASS study Avacostar. Overall, the benefits that the patient receives from treatment with avacopan outweigh the risk of liver injury to the patients.
Public health impact	Avacopan is indicated for the treatment of AAV, which is a rare disease. The public health impact is anticipated to be negligible.

Notes: AAV=ANCA-associated vasculitis; ALT=Alanine aminotransferase; ANCA=Anti-neutrophil cytoplasmic autoantibody; AST=Aspartate aminotransferase; DDI=Drug-drug interaction; DLP=Data lock point; GPA=Granulomatosis with polyangiitis; PASS=Post-Authorisation Safety Study; SAE=Serious adverse event; SmPC=Summary of Product Characteristics; TEAE=Treatment-emergent adverse event.

Table 15 Important Potential Risk: Cardiovascular Safety

Potential Risk	Cardiovascular safety
Potential mechanism	The possible mechanism remains unclear: the increased number of events within the Cardiac Disorders SOC did not point to any specific pathological process. Both nonclinical data and clinical studies have eliminated certain potential causes, notably QTc effects. The cardiovascular effects of avacopan and CCX168-M1 were evaluated in vitro and in vivo. In vitro data indicate that avacopan inhibited hERG ionic conductance by 26% at a concentration of 2.3 µM (~1.3 µg/ml), the maximal concentration testable due to solubility constraints. The major human metabolite CCX168-M1 inhibited hERG ionic conductance by 37% at a concentration of 3 µM (~1.8 µg/ml), the maximal concentration of the compound achievable without precipitation. Exposure margins for avacopan and CCX168-M1 of about 4,000- and 14,000-fold, respectively, relative to human C_{max}, free plasma levels. Based on these data, a low risk of pro-arrhythmic/ torsadogenic effects is predicted for avacopan and CCX168-M1. In the telemetry study in conscious monkeys, there were no effects on cardiovascular (blood pressure) and electrocardiographic parameters (P, PR, QRS, QT and QTc intervals, and R amplitude) following single oral doses up to 50 mg/kg, the highest dose tested. At 50 mg/kg, blood pressure values were slightly reduced (≤12%) versus vehicle. This slight effect was not statistically significant and all mean and individual values were within the range of normal biologic variation. At the highest dose tested (50 mg/kg), the mean avacopan

Potential Risk	Cardiovascular safety
	plasma concentration at 4 h (approximate T_{max}) post-dose was 1,182 ng/ml, corresponding to about 3.3-fold the C_{max} at MRHD (349 ng/ml). Additionally, no evidence of electrocardiographic abnormalities was seen in vivo in the 28-day, 20-week, and 44-week repeat-dose monkey studies. Mean plasma levels of 1,845 and 2,470 ng/ml (avacopan) and 573 and 548 ng/ml (CCX168-M1) were achieved in the 20-week and 44-week studies, respectively. These exposures represent 5.2- to 7.0-fold (avacopan), and 4.4- to 4.6-fold (CCX168-M1) the clinical AUC. Taken together, based on the available data avacopan and its major metabolite CCX168-M1 have a low potential for adverse QT-effects at the intended therapeutic exposure.
Evidence source and strength of evidence	Based on the available in vitro and in vivo nonclinical studies, there is no evidence of a cardiovascular effect. However, supra-therapeutic exposures have not been evaluated in vivo. Additionally, results from intensive ECG study showed that there was no evidence of a detrimental effect of avacopan on QTcI (CL007_168). There was no evidence that avacopan had a clinically significant effect on cardiac electrophysiology based on results from a thorough QT/QTc study (CL014_168). Overall, despite CL014_168 data, there was evidence that showed an imbalance in the avacopan arm from the CL010_168 study. Therefore, close monitoring is required to further evaluate the safety profile for cardiac disorders in patients treated with avacopan. The complement 5a receptor is expressed on several other cells than the neutrophils and involved in numerous biological processes and taking into consideration the underlying disease, cardiovascular safety may be seen as an increased risk.
Characterisation of the risk	
Frequency	**Related Clinical Trial (Phase 3 Study) Population**

	Prednisone (N=164)	Avacopan (N=166)	Difference
	N (%)	N (%)	(%)
Any related TEAE associated with Cardiac Disorders (SOC)	2 (1.2)	4 (2.4)	1.2
Any related SAE with Cardiac Disorders (SOC)	0.0	1 (0.6)	0.6

Source: CL010_168; Tables 14.3.1.4.1 and 14.3.1.6.1.

Post-marketing Experience

Number of Avacopan Related Cases	Exposure Since International Birth Date to DLP	Frequency per 100 Patient-Years
138 (non-serious)	4,151	3.3
120 (serious)	patient-years	2.9
258 (total)		6.2

Seriousness/outcomes	Outcomes of any related TEAEs in the avacopan group: fatal 0 (0%); leading to discontinuation 2 (1.2%); recovered without sequelae 4 of 4 (100%); hospitalised 1 of 4 (25.0%) **From Post-marketing Experience (in 4,151 patient-years):** Non-serious cases: 141 cases of which 138 related to avacopan. Outcome (all non-serious events): 20 events were reported as "recovered/resolved", 35 events were reported as "not recovered/not resolved",

Potential Risk	Cardiovascular safety
	15 events were reported as “recovering/resolving”, and 73 events were reported as “unknown”. Serious cases: 128 cases of which 120 related to avacopan. Outcome (all serious events): 22 events were reported as “recovered/resolved”, 28 events were reported as “not recovered/not resolved”, 15 events were reported as “recovering/resolving”, and 62 events were reported as “unknown”. 7 events with fatal outcome
Severity and nature of risk	Severity of overall TEAEs in avacopan group in the Phase 3 trial: (n=166) Overall: 26 (15.7%) Fatal: 0 (0.0%) Life-threatening: 1 (0.6%) Severe: 1 (0.6%) Moderate: 13 (7.8%) Mild: 11 (6.6%)
Background incidence/prevalence	Overall, patients with AAV appear at greater risk of CVD [66] and have an increased CVD related mortality due to vascular inflammation and accelerated atherosclerosis [67]. Significantly increased risks of MI and ischaemic stroke have been reported in GPA [68]. A long-term study conducted among AAV patients demonstrated that patients with AAV are at increased risk for any CVD, with a risk more than 3 times higher for CVD overall, and more than 8 times higher for CVA, compared to matched comparator subjects from the same population. Increasing evidence links AAV to cardiovascular disease. In particular, a recent study demonstrated the risk for CVD in AAV patients is around 65% higher than in the general population [69]. In contrast to some previous reports, the risk of CAD in AAV is not significantly higher than the general population when patients with prior CVD events are excluded from the analysis. The risk for CVD in AAV is increased, particularly in the first 2 years following disease occurrence, gradually declining thereafter. For the clinician and patient, active vigilance for any CVD and VTE, and an aggressive treatment of CVD risk factors is recommended, especially in the first years after diagnosis of AAV [70]. The calculated rate for CV events in these patients was 3.4 strokes per 1,000 patient-years and 3.8 heart attacks per 1,000 patient-years, totalling 7.2 CV events per 1,000 patient-years overall. In GPA patients, the overall CV event rate was 7.4 per 1,000 patient-years, while in those with eosinophilic GPA, the rate was 6.8 per 1,000 patient-years. The CV event rate in the general population was totalling 7.2 CV events per 1,000 patient-years overall. In GPA patients, the overall CV event rate was 7.4 patient-years [71]. Cardiac disorders among patients treated with avacopan did not show increased risk [71].
Risk factors and risk groups	The risk for CVD in AAV is increased, particularly in the first 2 years following disease occurrence, gradually declining thereafter. A treatment regimen based on the combination with cyclophosphamide followed by azathioprine may carry an increased risk for cardiac disorders as compared to a regimen based on the combination with rituximab.
Preventability	For the clinician and patient, active vigilance for any CVD, and an aggressive treatment of CVD risk factors is recommended, especially in the first years after diagnosis of AAV.
Impact on the benefit/risk balance of the product	The reported cardiac disorder events were mostly mild to moderate and reversible. However, this risk will be characterised further in the ongoing PASS study. Overall, the benefits that the patient receives from treatment with avacopan outweigh the potential risk to the patients.

Potential Risk	Cardiovascular safety
Public health impact	Avacopan is indicated for the treatment of AAV, which is a rare disease. The public health impact is anticipated to be negligible.

Notes: AAV=ANCA-associated vasculitis; ANCA=Anti-neutrophil cytoplasmic autoantibody; AUC=Area under the concentration-time curve; CAD=Coronary artery disease; CV=Cardiovascular; CVA=Cerebrovascular accident; CVD=Cardiovascular disease; DLP=Data lock point; GPA=Granulomatosis with polyangiitis; hERG=Human ether-á-go-go-related gene; MI=Myocardial infarction; MRHD=Maximum recommended human dose; PASS=Post-Authorisation Safety Study; SAE=Serious adverse event; SOC=System organ class; TEAE=Treatment-emergent adverse event; VTE=Venous thromboembolism.

Table 16 Important Potential Risk: Serious Infections

Potential Risk	Serious infections
Potential mechanism	Complement activation can cause tissue inflammation and injury and complement-inhibitory drugs are effective treatments for several inflammatory diseases. One important role of the complement cascade is to fight serious infectious diseases as part of the body's defence against bacteria and other pathogens, and a major concern regarding inhibition of this system is that it may increase the risk for infection. However, a study by Choudhry et al, 2016 [72] found that antagonism of C5aR1 reduces renal fibrosis in a mouse model of urinary tract infection with Escherichia coli. C5aR1 antagonism was also associated with faster clearance of the infection, potentially related to their finding that C5a reduced bacterial killing by macrophages. Other recent studies have shown that C5a impairs elimination of tumour cells by the immune system [73]. Taken together, these data indicate that C5aR1 inhibition may have benefits for the immune surveillance of malignancy and clearance of infection. Although inhibitors of C5 have been associated with an increased risk of infections with encapsulated bacteria, such as Neisseria meningitidis, there is a scientific rationale that this risk does not apply to C5aR1 inhibitors, such as avacopan. In particular, while C5 inhibitors such as eculizumab act to inhibit the cleavage of C5 into both C5a and C5b, thereby disrupting the assembly of C5b-9 into the membrane attack complex (which penetrates the bacterial cell wall and causes bacterial lysis), avacopan only inhibits downstream effects of C5a and does not significantly affect membrane attack complex formation.
Evidence source and strength of evidence	The risk of infections in AAV is considered high; however, this has yet to be robustly quantified. Studies of infection in AAV report variable risks ranging from 6 to 67% [74]. Based on the available data from Phase 3, the incidence of serious infections was 15.2% in the prednisone group versus 13.3% in the avacopan group. Although the Phase 3 study has demonstrated that avacopan is not associated with additional risk of infection in AAV and steroids are known to cause an increased risk for infections (especially in high doses), one cannot dismiss the similar or closely similar incidence of infections in the avacopan arm. Further, although some of the infections could be attributed to other components of the vasculitis SOC (i.e., cyclophosphamide, rituximab and azathioprine), the number of the avacopan treated subjects in the Phase 3 study that had an infection is still considered high. In addition, given the mechanism of action, it does not seem unexpected that avacopan in itself would increase the risk for infection. Considering the seriousness of AAV and the severity of infections, close monitoring is required to further evaluate the safety profile for serious infection in patients with AAV treated with avacopan.

Potential Risk	Serious infections
Characterisation of the risk	

Frequency

	Prednisone (N=164)	Avacopan (N=166)	Difference
	N (%)	N (%)	(%)
Any related TEAE associated with infection	54 (32.9)	51 (30.7)	-2.2
Any related SAE associated with infection	12 (7.3)	6 (3.6)	-3.7

Source: CL010_168; Table 14.3.1.4.1 and 14.3.1.6.1.

Overall, a lower proportion of subjects had any TEAEs of infection, serious TEAEs of infection, life-threatening TEAEs of infection, and infections resulting in death in the avacopan group compared with the prednisone group. The incidence of severe TEAEs of infection and any TEAE leading to study withdrawal due to TEAEs of infection was similar in the 2 treatment groups.

The most common infection in both treatment groups was nasopharyngitis (30 subjects (18.3%) in the prednisone group and 25 subjects (15.1%) in the avacopan group). Urinary tract infection, bronchitis, and influenza appeared to be more common (≥2% difference) in the prednisone compared with the avacopan group. Gastroenteritis was observed more commonly (≥2% difference) in the avacopan compared with the prednisone group. On first glance, the incidence of pneumonia appeared to be similar in the 2 groups. However, when all subjects with pneumonia/pneumonia bacterial/atypical pneumonia/pneumonia cytomegaloviral/
pneumonia haemophilus/lower respiratory tract infection are considered, there were 22 subjects (13.4%) in the prednisone group and 18 subjects (10.8%) in the avacopan group.

Post-marketing Experience

Number of Avacopan Related Cases	Exposure Since International Birth Date to DLP	Frequency per 100,000 Patient-Years
169 (serious)	4,151 patient-years	4.1

Seriousness/outcomes

	Prednisone (N=164)	Avacopan (N=166)	Difference
	N (%)	N (%)	(%)
Any infection leading to study withdrawal	5 (3.0)	4 (2.4)	-0.6
Any life-threatening infection	2 (1.2)	1 (0.6)	-0.6
Any infection leading to death	2 (1.2)	1 (0.6)	-0.6

Source: CL010_168; Table 14.3.1.9.

From Post-marketing Experience (in 4,151 patient-years):

Serious cases: 186 cases of which 169 related to avacopan.

Outcome: 43 events were reported as “recovered/resolved”, 1 event was reported as “recovered with sequelae”, 20 events were reported as “not recovered/not

Potential Risk	Serious infections
	resolved", 21 events were reported as "recovering/resolving", and 85 events were reported as "unknown". 24 events with fatal outcome
Severity and nature of risk	Severity of overall TEAEs in avacopan group in the Phase 3 trial: (n=166) Overall: 113 (68.1%) Fatal: 1 (0.6%) Life-threatening: 1 (0.6%) Severe: 12 (7.2%) Moderate: 39 (23.5%) Mild: 60 (36.1%)
Background incidence/prevalence	The risk of infections in AAV is considered high; however, this has yet to be robustly quantified. Studies of infection in AAV report variable risks ranging from 6 to 67% [74]. Several studies have analysed the prognostic factors associated with AAV mortality, reporting infections as one of the most important aetiologies, representing up to 66% during the first 12 months [24].
Risk factors and risk groups	Serious active disease remains one of the main causes of death in patients with AAV, especially in the first months of follow-up. It is important to identify predisposing factors such as intensive immunosuppressant treatment, severe renal dysfunction and leukopenia, and stratify treatment according to the disease severity.
Preventability	Text proposed in prescribing information: SmPC Section 4.2, Section 4.4, and Section 4.8.
Impact on the benefit/risk balance of the product	The majority of the reported infections varied between mild to severe but were reversible. However, this risk will be characterised further in the ongoing PASS study. Overall, the benefits that the patient receives from treatment with avacopan outweigh the potential risk to the patients.
Public health impact	Avacopan is indicated for the treatment of AAV, which is a rare disease. The public health impact is anticipated to be negligible.

Notes: AAV=ANCA-associated vasculitis; ANCA=Anti-neutrophil cytoplasmic autoantibody; C5aR=Complement 5a receptor; DLP=Data lock point; PASS=Post-Authorisation Safety Study; SAE=Serious adverse event; SmPC=Summary of Product Characteristics; TEAE=Treatment-emergent adverse event.

Table 17 Important Potential Risk: Malignancy

Potential Risk	Malignancy
Potential mechanism	The complement has been described to have an active role in facilitating cancer-associated processes such as increased proliferation, angiogenesis and migration. Complement factors C3a and C5a have been linked to various aspects of tumour biology. In addition to their recognised role in sustaining chronic inflammation, the anaphylatoxins C3a and C5a also promote a microenvironment that is immunosuppressive for tumour growth, is proangiogenic, and accelerates tumour growth through enhancement of tumour cell migration and subsequent tissue invasion and metastasis. Dysregulation of the complement system has been reported in numerous tumours and increased expression of complement activation fragments in cancer patient specimens correlates with poor patient prognosis. Importantly, genetic or pharmacological targeting of complement has been shown to reduce tumour growth in several cancer nonclinical models, suggesting that complement could be an attractive therapeutic target in anticancer therapy [75]. The link between inflammation and tumour progression is well recognised, and the fact that complement is upregulated in patients with cancer may allow nascent tumours to productively use anaphylatoxin-induced inflammation [76]. Furthermore, C3aR and C5aR1 signal through the PI3K-AKT pathway in an autocrine manner thereby facilitating tumour cell proliferation [77].
Evidence source and strength of evidence	The risk of malignancy is a concern based on the role of the complement system in tumour biology. Additionally, due to eculizumab affecting similar target as avacopan, malignancies are included within the risk profile for eculizimab as an adverse reaction. Furthermore, nonclinical data from mutagenicity and carcinogenicity studies indicate that avacopan was not mutagenic, clastogenic and carcinogenic in pharmacologically relevant animal species (hamster). The Phase 2 and Phase 3 clinical studies mainly excluded subjects with a history or presence of any form of cancer within the 5 years prior to screening. The studies conducted to date were limited with regards to follow-up time and total exposure to provide any substantial assessment to the risk.
Characterisation of the risk	
Frequency	**Phase 3 Clinical Trial Population**

	Prednisone (N=164)	Avacopan (N=166)	Difference
	N (%)	N (%)	(%)
Any related TEAE associated with Neoplasm Benign, Malignant, and Unspecified	3 (1.8)	2 (1.2)	-0.6
Any related SAE associated with Neoplasm Benign, Malignant, and Unspecified	0	0	0

Source: CL010_168; Table 14.3.1.4.1 and table 14.3.1.6.1.

Post-marketing Experience

Number of Avacopan Related Cases	Exposure Since International Birth Date to DLP	Frequency per 10,000 Patient-Years
2 (non-serious) 13 (serious) 15 (total)	4,151 patient-years	4.8 31.3 36.1

Potential Risk	Malignancy
Seriousness/outcomes	**Phase 3 Clinical Trial Population** There were 2 (1.2%) non-serious TEAEs considered related to avacopan, Anogenital warts and skin papilloma both resolved. There were no serious related TEAEs in the avacopan arm associated with neoplasm benign, malignant and unspecified. **From Post-marketing Experience (in 4,151 patient-years):** Non-serious cases: 2 cases of which 2 related to avacopan. Outcome: 0 cases were reported as “recovered/resolved”,0 cases were reported as “not recovered/not resolved”, 0 cases were reported as “recovering/resolving”, and 2 cases were reported as “unknown”. Serious cases: 14 cases of which 13 related to avacopan. Outcome: 2 cases were reported as “recovered/resolved”, 5 cases were reported as “not recovered/not resolved”, 0 cases were reported as “recovering/resolving”, and 7 cases were reported as “unknown”. 0 case reports with fatal outcome
Severity and nature of risk	Severity of overall TEAEs in avacopan group in the Phase 3 trial: (n=166) Overall: 6 (3.6%) Fatal: 0 (0%) Life-threatening: 1 (0.6%) Severe: 0 (0%) Moderate: 2 (1.2%) Mild: 3 (1.8%)
Background incidence/prevalence	The vasculitis encompasses a rare subset of autoimmune diseases. Reports of the concurrent association of malignancies with some forms of vasculitis raise the possibility that patients with certain types of vasculitis may be at increased risk of cancer. Conversely, some forms of vasculitis may be a manifestation of malignancy [78]. There are several potential mechanisms by which an increased malignancy risk may be associated with vasculitis. First, a dysfunctional immune system associated with autoimmunity may increase the risk of certain cancers [79,80]. Cytotoxic drug therapies used for the management of vasculitis, such as CYC, may in turn modulate the subsequent risk of certain cancers [81]. Vasculitis may be a paraneoplastic phenomenon as in the case PAN with HCL [82]. Finally, a coincidental association related to detection bias (patients with vasculitis coming to medical attention and being followed more closely) may contribute to some reports of malignancy in association with vasculitis. Several studies have consistently demonstrated an increased risk of cancer in WG [83-89] and MPA [85,87]. This risk appears in part to be related to cytotoxic medications used for treatment, especially CYC. CYC, a known carcinogen, is an alkylating agent, the active compound of which is phosphoramide mustard, which produces interstrand and intrastrand DNA crosslinks [81]. CYC use has been associated with an increased risk for bladder cancer, acute leukaemia, and skin cancer [81], which are the same types of malignancies reported among patients with WG and MPA exposed to CYC. CYC is an induction agent in the treatment of ANCA-associated vasculitis and studies have found increased risk of bladder cancer in WG and MPA [83-89]. Risk of other cancers, particularly skin cancer and haematologic malignancies is also increased in these patients. There was a prolonged period of latency from CYC exposure to detection of bladder cancer ranging from 7 months to 12 years. The Investigators compared the observed cancers to that expected for the general population using the National Cancer Institute Registry and found a 2.4-fold overall increase in cancer with a 33-fold increase in bladder cancer and 11-fold increase in lymphomas [89]. In a study evaluating bladder toxicity in 145 patients with WG treated with CYC, 7 patients (4.8%) developed bladder cancer [88].

Potential Risk	Malignancy
	Furthermore, incidence of bladder cancer increased with time, with an estimated incidence of 16% over 15 years after CYC exposure [88]. In another cohort of 155 patients with WG, followed for a median of 7 years, 7 patients (4.5%) developed cancer. In this study, a cumulative CYC dose of ≥100 g was associated with a 2-fold increased risk of cystitis or myelodysplastic syndrome compared with WG patients who received lower cumulative doses of CYC [86].
Risk factors and risk groups	Active disease in patients with AAV treated in combination with CYC. It is important to identify predisposing factors such as intensive immunosuppressant treatment and stratify treatment according to the disease severity.
Preventability	Text proposed in prescribing information: Warnings and Precautions SmPC Section 4.4.
Impact on the benefit/risk balance of the product	The reported events of malignancy were predominantly benign and successfully treated. However, this risk will be characterised further in the ongoing PASS study. Overall, the benefits that the patient receives from treatment with avacopan outweigh the potential risk to the patients.
Public health impact	Avacopan is indicated for the treatment of AAV, which is a rare disease. The public health impact is anticipated to be negligible.

Notes: AAV=ANCA-associated vasculitis; ANCA=Anti-neutrophil cytoplasmic autoantibody; C5aR=Complement 5a receptor; CYC=Cyclophosphamide; DLP=Data lock point; HCL=Hairy cell leukaemia; MoA=Mode of action; MPA=Microscopic polyangiitis; PAN=Polyarteritis nodosa; PASS=Post-Authorisation Safety Study; SAE=Serious adverse event; SmPC=Summary of Product Characteristics; TEAE=Treatment-emergent adverse event; WG=Wegener's granulomatosis.

SVII.3.2 Presentation of the Missing Information

Table 18 Missing Information

Missing Information	Evidence Source
None	Not applicable

SVIII SUMMARY OF THE SAFETY CONCERNS

Table 19 Summary of Safety Concerns

Important identified risks	Liver injury
Important potential risks	Cardiovascular safety Serious infections Malignancy
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

All safety information will continue to be monitored in accordance with Good Pharmacovigilance Practices including regular review and evaluation of data.

Routine pharmacovigilance entails evaluation and presentation of adverse events in a Periodic Safety Update Report, collecting data on adverse events of concern.

Findings from routine pharmacovigilance will be communicated to the Agency through appropriate reports and the RMP will be updated upon newly detected findings.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

There are no specific adverse reaction follow-up questionnaires for the other safety concerns listed in this RMP in Table 19.

Other Forms of Routine Pharmacovigilance Activities:

There are no other forms of routine pharmacovigilance activities for the safety concerns listed in this RMP in Table 19.

III.2 Additional Pharmacovigilance Activities

EU PASS Summary

EU PASS study AvacoStar, CS-AVA-2022-0016 (CT.gov: NCT05897684, EU PASS register no: EUPAS 105408): 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)

Rationale and Study Objectives

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. The protocol fulfils the requirements of the EMA to conduct a PASS as a post-marketing commitment.

Primary Objectives:

- To evaluate the incidence of defined medical events of special interest in patients with AAV commencing avacopan.

Secondary Objectives:

- To evaluate the incidence of AEs, AEs leading to discontinuation of therapy, SAEs, ADRs, serious adverse drug reactions, laboratory abnormalities, disease flares as measured by the BVAS, and organ damage as measured by the Vasculitis Damage Index in patients with AAV commencing avacopan.

- To evaluate the background incidence of AEs, medical events of special interest, SAEs, laboratory abnormalities, disease flares as measured by the BVAS, and organ damage as measured by the Vasculitis Damage Index in a similar population of patients with severe, active AAV but not receiving avacopan.

- To compare SAEs and medical events of special interest 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

Observational

This 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 milestone, 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.

Study Population

Adult patients in Europe diagnosed with ANCA-positive 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 standard of care induction therapy, in the opinion of the Investigator.

Milestones

All requested milestones for reporting to the Regulatory Authorities as well as major milestones from study protocol are included in Annex 2.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 20 Ongoing and Planned Additional PV Activities

Study/ Activity Type	Objectives	Safety Concerns Addressed	Status (Planned/ Started)	Milestones (Required by Regulators)	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit/risk)					
N/A	N/A	N/A	N/A	N/A	N/A
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances					
N/A	N/A	N/A	N/A	N/A	N/A
Category 3 - Required additional pharmacovigilance activities (by the competent authority)					
EU PASS AvacoStar Ongoing	Evaluate the long-term (beyond 1 year up to 36 months) safety of avacopan in ANCA vasculitis patients; estimate the incidence rates of medical events of special interest (e.g., liver injury, serious infections, malignancies and cardiovascular events).	All safety concerns for avacopan	Started FPFV 11-Sep-2023	Protocol submission	3 months post EC decision
				Interim reports	Every 24 months (after FPFV)
				Progress reports	To be incorporated in PSURs
				Final report	2H 2031

Notes: ANCA=Anti-neutrophil cytoplasmic autoantibody; EC=European Commission; FPFV=First patient first visit; N/A=Not applicable; PASS=Post-Authorisation Safety Study; PSUR=Perodic Safety Update Report; PV=Pharmacovigilance.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no post-authorisation efficacy studies that are conditions of the marketing authorisation or that are Specific Obligations.

Table 21 Planned and Ongoing Post-Authorisation Efficacy Studies that Are Conditions of the Marketing Authorisation or that are Specific Obligations

Study	Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation					
N/A	N/A	N/A	N/A	N/A	N/A
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances					
N/A	N/A	N/A	N/A	N/A	N/A

Note: N/A=Not applicable.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1 Routine Risk Minimisation Measures

Table 22 Description of Routine Risk Minimisation Measures by Safety Concerns

Safety Concern	Routine Risk Minimisation Activities
Liver Injury	
Routine risk communication	SmPC Section 4.2, Section 4.4, and Section 4.8. PIL Sections 2 and 4
Routine risk minimisation activities recommending specific clinical measures to address the risk	Recommendation for liver function test monitoring, awareness for patients with liver disorders is included in SmPC Section 4.4 and PIL Section 2
Other routine risk minimisation measures beyond the Product Information	
Legal status	Prescription only medicine
Cardiovascular Safety	
Routine risk communication	SmPC Section 4.4 PIL Section 2
Routine risk minimisation activities recommending specific clinical measures to address the risk	Information regarding cardiovascular safety awareness for patients is included in SmPC Section 4.4 and PIL Section 2
Other routine risk minimisation measures beyond the Product Information	
Legal status	Prescription only medicine
Serious Infection	
Routine risk communication	SmPC Section 4.2, Section 4.4 and Section 4.8 PIL Sections 2 and 4
Routine risk minimisation activities recommending specific clinical measures to address the risk	Information regarding seriousness of infection is included in SmPC Section 4.4 and PIL Section 2
Other routine risk minimisation measures beyond the Product Information	
Legal status	Prescription only medicine
Malignancy	
Routine risk communication	SmPC Section 4.4. PIL Section 2
Routine risk minimisation activities recommending specific clinical measures to address the risk	Information regarding malignancy is included in SmPC Section 4.4 and PIL Section 2
Other routine risk minimisation measures beyond the Product Information	
Legal status	Prescription only medicine

Notes: PIL=Patient Information Leaflet; SmPC=Summary of Product Characteristics.
Source: SmPC avacopan (10 mg hard capsules).

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table 23 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risk		
Liver injury	Routine risk minimisation measures: SmPC Section 4.2, Section 4.4, and Section 4.8 PIL Sections 2 and 4 Recommendation for liver function test monitoring, awareness for patients with liver disorders is included in SmPC Section 4.4 and PIL Section 2 Legal status: Prescription only medication Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: EU PASS AvacoStar
Important Potential Risk		
Cardiovascular safety	Routine risk minimisation measures: SmPC Section 4.4 PIL Section 2 Information regarding cardiovascular safety is included in SmPC Section 4.4 and PIL Section 2 Legal status: Prescription only medication Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: EU PASS AvacoStar
Serious infection	Routine risk minimisation measures: SmPC Section 4.2, Section 4.4 and Section 4.8 PIL Sections 2 and 4 Information regarding serious infections is included in SmPC Section 4.4 and PIL Section 2 Legal status: Prescription only medication Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: EU PASS AvacoStar
Malignancy	Routine risk minimisation measures: SmPC Section 4.4 PIL Section 2 Information regarding malignancy is included in SmPC Section 4.4 and PIL Section 2 Legal status: Prescription only medication Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: EU PASS AvacoStar
Missing Information		
None	N/A	N/A

Notes: N/A=Not applicable; PASS=Post-Authorisation Safety Study; PIL=Patient Information Leaflet; SmPC=Summary of Product Characteristics.

PART VI: SUMMARY OF THE RMP

Summary of Risk Management Plan for Tavneos (Avacopan)

This is a summary of the Risk Management Plan (RMP) for Tavneos. The RMP details important risks of Tavneos, how these risks can be minimised, and how more information will be obtained about Tavneos's risks and uncertainties (missing information).

Tavneos's Summary of Product characteristics (SmPC) and its Package Leaflet give essential information to healthcare professionals and patients on how Tavneos should be used.

This summary of the RMP for Tavneos should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report.

Important new concerns or changes to the current ones will be included in updates of Tavneos's RMP.

I The Medicine and What it is Used for

Tavneos, in combination with a rituximab or cyclophosphamide regimen, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) (see SmPC for the full indication). It contains avacopan as the active substance and it is given as 10 mg hard capsules for oral use.

Further information about the evaluation of Tavneos's benefits can be found in Tavneos's European Public Assessment Report, including in its plain-language summary, available on the EMA website, under the medicine's webpage (https://www.ema.europa.eu/en/medicines/human/EPAR/tavneos).

II Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Tavneos, together with measures to minimise such risks and the proposed studies for learning more information about Tavneos's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the Package Leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly

- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that can affect the safe use of Tavneos is not yet available, it is listed under missing information below.

II.A List of Important Risks and Missing Information

Important risks of Tavneos are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tavneos. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Liver injury
Important potential risk	Cardiovascular safety Serious infection Malignancy
Missing information	None

II.B Summary of Important Risks

Important Identified Risk: Liver injury	
Evidence for linking the risk to the medicine	In a small number of cases, hepatic transaminases and bilirubin elevations have been observed in Phase 2 and in Phase 3 studies. These occurred in a background of co-administered drugs, such as trimethoprim/sulfamethoxazole which are known liver toxins, so clear and direct causality with avacopan could not be established. These elevations reversed with withdrawal of study drug (and trimethoprim/sulfamethoxazole).
Risk factors and risk groups	Common risk factors for hepatotoxicity include [64,65]: • Older age • Female gender • Underlying liver diseases (e.g., hepatitis) • Other comorbidities such as acquired immunodeficiency syndrome

	• Genetic predisposition involving CYP450, HLA alleles and other drug-processing enzymes • Chronic alcohol consumption Concomitant use of hepatotoxic medications
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2, Section 4.4, and Section 4.8; PIL Sections 2 and 4 • Recommendation for liver function test monitoring, awareness for patients with liver disorders is included in SmPC Section 4.4 and PIL Section 2 • Legal status: Prescription only medication Additional risk minimisation measures: None

Important Potential Risk: Cardiovascular safety

Evidence for linking the risk to the medicine	Cardiovascular safety is high in patients with AAV. Due to the small number of patients who demonstrated cardiac abnormalities in patients treated with avacopan, careful monitoring is required.
Risk factors and risk groups	AAV patients have a higher risk for cardiovascular disorders. A treatment regimen based on the combination with cyclophosphamide followed by azathioprine may carry an increased risk for cardiac disorders as compared to a regimen based on the combination with rituximab.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4; PIL Section 2 Information regarding cardiac disorder awareness for patients is included in SmPC Section 4.4 and PIL Section 2 Legal status: Prescription only medication Additional risk minimisation measures: None

Important Potential Risk: Serious infection

Evidence for linking the risk to the medicine	The risk of infections in AAV is considered high; however, this has yet to be robustly quantified. Studies of infection in AAV report variable risks ranging from 6 to 67%. Based on the available data from Phase 3, the incidence of serious infections was 15.2% in the prednisone group versus 13.3% in the avacopan group. Considering the seriousness of AAV and the severity of infections, close monitoring is required to further evaluate the safety profile for serious infection in patients with AAV treated with avacopan.
Risk factors and risk groups	Active disease remains one of the main causes of death in patients with AAV, especially in the first months of follow-up. It is important to identify predisposing factors such as intensive immunosuppressant treatment, severe renal dysfunction and leukopenia, and stratify treatment according to the disease severity
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2, Section 4.4 and Section 4.8; PIL Sections 2 and 4 • Information regarding seriousness of infection is included in SmPC Section 4.4 and PIL Section 2 • Legal status: Prescription only medication Additional risk minimisation measures: None

Important Potential Risk: Malignancy

Evidence for linking the risk to the medicine	The risk of malignancy is a concern based on the role of the complement system in tumour biology. Additionally, due to eculizumab affecting similar target as avacopan, malignancies are included within the risk profile for eculizimab as an adverse reaction. Furthermore, nonclinical data from mutagenicity and carcinogenicity studies indicate that avacopan was not mutagenic, clastogenic and carcinogenic in pharmacologically relevant animal species (hamster). The Phase 2 and Phase 3 clinical studies mainly excluded subjects with a history or presence of any form of cancer within the 5 years prior to screening. The studies

	conducted to date were limited with regards to follow-up time and total exposure to provide any substantial assessment to the risk.
Risk factors and risk groups	Active disease in patients with AAV treated in combination with CYC. It is important to identify predisposing factors such as intensive immunosuppressant treatment, and stratify treatment according to the disease severity.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4; PIL Section 2 • Information regarding malignancy is included in SmPC Section 4.4 and PIL Section 2 • Legal status: Prescription only medication Additional risk minimisation measures: None

Notes: AAV=ANCA-associated vasculitis; ANCA=Anti-neutrophil cytoplasmic autoantibody; CYC=Cyclophosphamide; MoA=Mode of action; N/A=Not applicable; PIL=Patient Information Leaflet; SmPC=Summary of Product Characteristics.

Missing Information: None	
Risk minimisation measures	Routine risk minimisation measures: N/A Additional risk minimisation measures: N/A

II.C Post-authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or Specific Obligations of Tavneos.

II.C.2 Other Studies in Post-authorisation Development Plan

Study Category	Study Short Name	Study Full Name	Purpose
3	EU PASS AvacoStar	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)	Evaluate the long-term (beyond 1 year for at least 4 years up to LPLV) safety of avacopan in a real-world cohort in ANCA vasculitis patients; Estimate the incidence rates of medical events of special interest (e.g., liver injury, serious infections, malignancies and cardiovascular events).

Notes: ANCA=Anti-neutrophil cytoplasmic autoantibody; LPLV=Last patient last visit; PASS=Post-Authorisation Safety Study.

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