EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 November 2021
EMA/708044/2021 Corr [1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tavneos

International non-proprietary name: avacopan

Procedure No. EMEA/H/C/005523/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

[1] 19.07.2023

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List of abbreviations

AAV	ANCA-associated vasculitis
AIS	Aggregate improvement score
ANCA	Anti-neutrophil cytoplasmic antibody
AUC	Area under concentration-time curve
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics classification system
BID	Twice-a-day
BVAS	Birmingham Vasculitis Activity Score
C5a	Complement 5a
C5aR	Complement 5a receptor, also called CD88
C_{max}	Maximum concentration
CEP	Certificate of suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human use
CPP	Critical process parameter
CV	Coefficient of variation
CWS	Cumulative worsening score
CYP	Cytochrome P450
DDI	Drug-drug interaction
DoE	Design of experiments
DSC	Differential scanning calorimetry
DVS	Dynamic vapour sorption
EC	European Commission
EU	European Union
eGFR	Estimated glomerular filtration rate
EQ-5D-5L	EuroQuality of Life-5 domains-5 levels
EULAR	European League Against Rheumatism
EULAR-ERA/EDTA	European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association
GM	Geometric mean
GC	Gas chromatography
GC-MS	Gas chromatography mass spectrometry
GPA	Granulomatosis with polyangiitis
GTI	Glucocorticoid toxicity index
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
IC_{50}	Concentration associated with 50% inhibition
ICP-MS	Inductively coupled plasma mass spectrometry
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IV	Intravenous(ly)
IR	Infrared
KF	Karl Fischer titration
LDPE	Low density polyethylene
LSM	Least squares mean
NMR	Nuclear magnetic resonance
M1	Mono-hydroxylated CCX168-M1, the main metabolite of avacopan

MAH	Marketing authorisation holder
MS	Mass spectrometry
MCP-1	Monocyte chemoattractant protein-1
MDR-1	Multi-drug resistance gene 1
MPA	Microscopic polyangiitis
MPO	Myeloperoxidase
OAT	Organic anion transporter
OATP	Organic anion transporter polypeptide
OCT	Organic cation transporter
PDE	Permitted daily exposure
PEG	Polyethylene glycol
Ph. Eur	European Pharmacopoeia
PK	Pharmacokinetics
PR3	Proteinase 3
QD	Once-a-day
QTPP	Quality target product profile
RH	Relative Humidity
SAE	Serious adverse event
SEM	Standard error of the mean
SF-36v2	Medical Outcomes Survey Short Form 36 version 2
SmPC	Summary of product characteristics
SOC	System organ class
TEAE	Treatment-emergent adverse event(s)
t_{max}	Time of maximum concentration
TSE	Transmissible Spongiform Encephalopathy
UACR	Urinary albumin:creatinine ratio
ULN	Upper limit of normal
UV	Ultraviolet
VAS	Visual analogue scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Vifor Fresenius Medical Care Renal Pharma France submitted on 9 October 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Tavneos, through the centralised procedure falling within the Article 3(1) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 12 December 2019.

Tavneos, was designated as an orphan medicinal product on 19 November 2014 in the following conditions: "Treatment of granulomatosis with polyangiitis" (EU/3/14/1373) and "Treatment of microscopic polyangiitis'' (EU/3/14/1372).

The applicant applied for the following indication: "Tavneos is indicated for the treatment of adult patients with granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA)."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0103/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0103/2020 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance avacopan contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

PRIME assistance

ChemoCentryx obtained priority medicines (PRIME) designation for avacopan (CCX168) in treatment of patients with GPA or MPA on 26 May 2016.

A Conditional Marketing Authorisation (CMA) was submitted to EMA by the applicant ChemoCentryx based on the Phase 2 data (studies CL002_168 and CL003_168). Given the near-term availability of the pivotal Phase 3 data, ChemoCentryx decided to withdraw the CMA on 22 January 2019 and refocused efforts on completion of the Phase 3 ANCA associated vasculitis study.

The Phase 3 trial CL010_168 has been completed (last patient last visit: November 2019) and the resulting data provides the basis to establish benefit/risk in support of the current MAA.

ChemoCentryx and Vifor Fresenius Medical Care Renal Pharma France (VFMCRP) have established contractual agreements enabling VFMCRP to be the applicant for the MAA of avacopan in EU Member States and certain other countries. Vifor Fresenius Medical Care Renal Pharma France (VFMCRP) is now the applicant for avacopan hard capsules. Avacopan is currently not in a PRIME scheme.

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
21 July 2016	EMEA/H/SA/3340/1/2016/PA/SME/III EMEA/H/SA/3340/2/2016/PA/SME/III	Kerstin Wickström, Brigitte Blöchl Daum
26 January 2017	EMEA/H/SA/3340/1/FU/1/2016/PA/SME/PR/III EMEA/H/SA/3340/2/FU/1/2016/PA/SME/PR/III	Kerstin Wickström, Kolbeinn Gudmundsson.

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- Selection of starting materials. Setting specifications and controls with regards to GMP-starting materials, GMP-intermediates, drug substance and drug product. Plans for completing the evaluation of the syntheses of the GMP-Starting Materials for the presence of potential genotoxic impurities. Sponsor's plans for commercialisation and locations of production.
- Species selection and design for the lifespan carcinogenicity assessment, and acceptability to complete the studies post-approval. Sufficiency of completed preclinical safety studies to support initiation of a Phase 3 clinical trial. Acceptability that GLP Segment 1 and 2 (FEED and EFD) reproductive toxicology studies may be completed during Phase 3 clinical development. Proposal to characterise the cardiovascular safety profile.
- Whether the design of clinical trial CL002_168 (including patient population and exposure, endpoints, analysis plan, safety database, background therapy, etc.) together with proposed commitments for further quality, nonclinical and clinical development could be sufficient to support an application for conditional marketing authorisation (CMA).
- Design of the proposed Phase 3 clinical trial CL010_168, specifically inclusion and exclusion

criteria, dose regimen, primary efficacy endpoint, secondary efficacy endpoints and the safety endpoints, and statistical analysis approach and sample size.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Outi Mäki-Ikola

The application was received by the EMA on	9 October 2020
The procedure started on	29 October 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 January 2021
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	18 January 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	2 February 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 February 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 May 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	29 June 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 July 2021
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	22 July 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	17 August 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	29 September 2021
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	12 October 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tavneos on	11 November 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Tavneos was proposed by the applicant for *"treatment of adult patients with granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA)"*.

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a multisystem autoimmune condition that occurs due to production of anti-neutrophil cytoplasmic antibodies. The disease is characterised by generalised inflammation of small to medium sized blood vessels that can affect many different organ systems but commonly involves the kidneys. The two main forms of the disease are granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).

GPA can affect any organ or tissue but has a predilection for the upper and lower respiratory tracts and the kidneys, with >75% of patients having renal involvement that is associated with progressive glomerular nephritis. GPA is most commonly associated with ANCA positivity by immunofluorescence and positive testing for the proteinase 3 (PR3)-antigen. MPA can be distinguished from other forms of small vessel vasculitides by the absence of granuloma formation, and by the predominance of perinuclear ANCA staining by immunofluorescence and positive testing for the myeloperoxidase (MPO) antigen. If left untreated, 80% of patients with GPA or MPA die within 2 years of disease onset and mortality is higher for patients with renal involvement.

2.1.2. Epidemiology

ANCA-associated vasculitis (AAVs) are classified as orphan diseases, with an incidence of about 20 per million population per year estimated for Europe and North America; there is a slight male preponderance and incidence rate increases with age. Annual reported incidence rates for ANCA-associated glomerulonephritis in Europe are between 1.2 and 1.3 per 100,000 adults, with a similar incidence seen in Japan, as described in the scientific literature.

2.1.3. Aetiology and pathogenesis

AAV are characterised by the production of circulating autoantibodies against the neutrophil-expressed antigens myeloperoxidase (MPO) and proteinase 3 (PR3) and involve complement activation and C5a production. The applicant stated that central role of C5a and its receptor C5aR has been proposed in the pathogenesis of ANCA-associated vasculitis, as per the published literature, and that C5a primes neutrophils and enhances ANCA-induced neutrophil activation. Neutrophils activate the alternative complement pathway through endogenous properdin secretion and neutrophils also release C5a when stimulated by inflammatory cytokines such as tumour necrosis factor α. The C5a, acting on C5aR, has been reported to be a potent neutrophil chemoattractant and agonist, which triggers homotypic neutrophil aggregation via interactions of the tumour necrosis factor activated αMβ2 (Mac-1)-integrins with intercellular adhesion molecule-3 or inactivated complement fragment 3b on bystander neutrophils. Deformability is important for non-activated neutrophils for unperturbed movement through small blood vessels such as in the glomeruli. The C5a decreases neutrophil deformability, particularly in the presence of ANCA. ANCA bound to endothelial-adherent neutrophils activate the classical complement pathway, and lastly, C5a activates endothelial cells, promoting retraction and increased permeability.

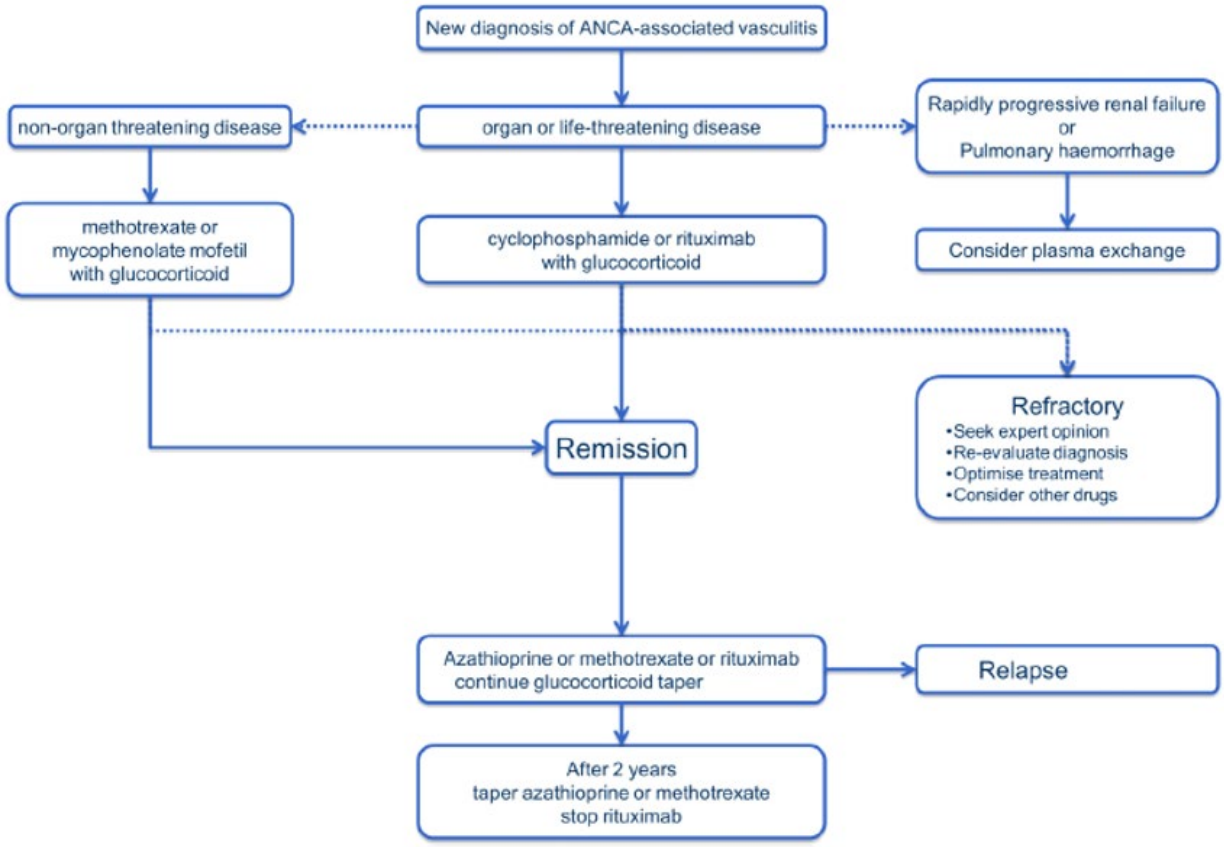
2.1.4. Clinical presentation, diagnosis and prognosis

Patients with all forms of AAV commonly present with upper respiratory tract symptoms such as sinusitis, dyspnoea, rhinitis, nasal polyps and conductive deafness. Renal involvement is present in the majority of patients with MPA and GPA and is asymptomatic until advanced renal failure occurs. According to the EULAR recommendations, a diagnosis should be supported by a biopsy from affected organ.

2.1.5. Management

A treatment algorithm guiding the management of ANCA-associated vasculitis based on the European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations is presented below.

Algorithm for the Management of New ANCA-Associated Vasculitis



Source: Yates et al, 2016.

Cyclophosphamide plus glucocorticoids or rituximab plus glucocorticoids are currently considered the standard of care for ANCA-associated vasculitis. Cyclophosphamide plus glucocorticoids or rituximab plus glucocorticoids are considered the standard of care induction therapy for organ or life-threatening AAV. Patients typically receive 0.5 to 1 g IV glucocorticoids, followed by oral glucocorticoids, 1 mg/kg/day, tapered according to local practice and treatment response. Chronic glucocorticoid 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. Cyclophosphamide is given for 3-6 months with variable remission rates

depending on the definition used. Patients are often switched from cyclophosphamide to azathioprine, mycophenolate mofetil, or methotrexate due to toxicity concerns with long-term cyclophosphamide use.

Rituximab, an anti-CD20 chimeric monoclonal antibody which depletes B lymphocytes, in combination with glucocorticoids, was shown to be non-inferior to cyclophosphamide plus glucocorticoids in inducing remission in AAV in two randomised controlled trials. Rituximab plus a glucocorticoid has been approved for treatment of patients with GPA or MPA.

Maintenance treatment includes immunosuppressive drugs such as azathioprine, mycophenolate mofetil, or methotrexate. Glucocorticoid treatment is also often used during maintenance. Adjuvant treatment includes plasmapheresis in patients with severe progressive renal failure.

Due to the serious side effects associated with current therapies, including glucocorticoids, there is a major unmet medical need in AAV. There is need for safer, convenient therapeutic agents that are able to rapidly bring disease activity under control, and that can safely maintain remission.

About the product

Avacopan (previously known as CCX168) is proposed to selectively inhibit the binding of complement 5a (C5a) to the C5a receptor (C5aR, also called CD88): C5a is a terminal component of the complement cascade. Avacopan is being developed as new, orally administered, first in class C5aR antagonist treatment for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

The recommended dose of Tavneos is 30 mg avacopan (3 hard capsules of 10 mg each) taken orally twice daily.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 10 mg of avacopan as active substance.

Other ingredients are:

Capsule contents: macrogolglycerol hydroxystearate, macrogol (4000)

Capsule shell: gelatin, red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171) and polysorbate 80.

Printing ink: black iron oxide (E172), shellac, potassium hydroxide

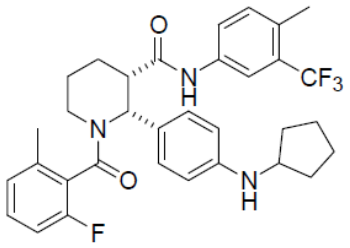
The product is available in high density polyethylene (HDPE) bottles with child-resistant closures and induction seals as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

General information

The chemical name of avacopan is (2*R*,3*S*)-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-*N*-[4-methyl-3(trifluoromethyl)phenyl]piperidine-3-carboxamide corresponding to the molecular formula $C_{33}H_{35}F_4N_3O_2$. It has a relative molecular mass of 581.64 g/mol and the following structure:



Active substance structure

The chemical structure of avacopan was inferred from the route of synthesis and elucidated by a combination of elemental analysis, infrared spectroscopy, ultraviolet spectroscopy, NMR spectroscopy, mass spectrometry, and specific optical rotation. Single crystal x-ray diffractometry was used for definitive structure determination.

The solid-state properties of the active substance were measured by differential scanning calorimetry (DSC), dynamic vapour sorption (DVS) and particle size distribution.

The active substance is a white to pale yellow non-hygroscopic crystalline solid. It is practically insoluble in aqueous media across the physiological pH range. The manufacturing process ensures that the most stable polymorphic form is isolated. Due to the low aqueous solubility, the finished product is a solid solution within a capsule in which avacopan is present in amorphous form.

Avacopan exhibits stereoisomerism due to the presence of 2 chiral centres (2*R*,3*S* configuration). Enantiomeric purity is controlled routinely by chiral HPLC.

Manufacture, characterisation and process controls

Avacopan is synthesised convergently in several steps using well defined starting materials with acceptable specifications. The starting materials were defined in line with scientific advice provided by CHMP. The process ensures the correct absolute and relative stereochemistry around the piperidine ring.

Several critical steps were identified during development and investigated by extensive uni- and multi-variate experiments. Certain steps were optimised through extensive design of experiments (DoE) studies. Critical process parameters (CPPs) were identified and optimised following a further DoE study. However, no design spaces are claimed.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. Changes introduced have been presented in sufficient detail and have been justified.

The primary contact materials comply with EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance (visual inspection), identity (FTIR, HPLC), assay (HPLC), impurities (HPLC), enantiomeric impurity (chiral HPLC), residual solvents (GC), elemental impurities (ICP-MS), water content (KF) and residue on ignition (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. Elemental and solvent impurities are controlled according to accepted ICH limits.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 12 pilot to production scale batches of the active substance from the intended commercial manufacturer are provided. The results are within the specifications and consistent from batch to batch. Supportive data from 4 batches from a different manufacturer used earlier in development, using a different synthetic route, also complied with the specifications in place at the time.

Stability

Stability data from 6 production scale batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 36 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, assay, impurities (including the enantiomer) and water content. The analytical methods used were the same as for release and were stability indicating. All tested attributes remained within their specifications and no trends were observed.

Forced degradation studies were conducted in order to demonstrate the stability indicating nature of the analytical procedures. Samples were exposed to aqueous acid, base or peroxide or extreme temperature (solid state). Photostability testing following the ICH guideline Q1B was also performed. Extensive degradation was observed under all 3 aqueous conditions. Slight degradation was observed on exposure to extreme heat or light.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months at not more than 25ºC in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is a size 0 hard capsule containing 10 mg avacopan as active substance. The capsules are light orange/yellow opaque bicolour printed with "CCX168" in black ink with a clear gelatin sealing band. Qualitative composition is listed in SmPC and section 2.2.1

The aim of development was an immediate release oral dosage form able to meet clinical, safety, quality and commercial requirements. A quality target product profile (QTPP) was defined according to ICH Q8 and formed the basis of development work.

Formulation development and development of manufacturing process have been discussed. Drug product manufactured by from previous suppliers and was used to supply the Phase 2 clinical trials. In 2016, the drug product formulation, manufacturing process, and supporting analytical methods were transferred to a new manufacturer for the manufacture of the Phase 3 clinical supplies and in preparation for commercialisation.

The active substance is practically insoluble in aqueous media, irrespective of pH, but highly permeable and is thus considered a BCS class 2 molecule. Therefore, a solubility enhancing formulation was needed in order to provide acceptable bioavailability.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report. The relative amounts of active substance and excipients was set in order to ensure the active substance is fully dissolved during formulation and storage.

The size 0 gelatine capsule is quite big, and the posology generally requires 6 capsules to be ingested per day. Therefore, the CHMP recommended further work in order to develop a formulation with an increased active substance load [REC 001]. This would reduce the need for patients to swallow so many large capsules daily and improve compliance.

Dissolution method development was conducted in parallel with formulation and process development. The specification was set in line with clinical batch data.

Discriminatory power was investigated using formulations with different excipient ratios (to reduce solubility) or containing a proportion of crystalline active substance. Incomplete dissolution was observed in these formulations, indicating that the method is suitably discriminatory.

The manufacturing process was designed to dissolve the active substance in a heated molten excipient solution Critical process parameters (CPPs) were identified and ranges were established to ensure complete dissolution of avacopan into the fill solution.

The primary packaging is an HDPE bottle with child-resistant closure and induction seal. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 4 main steps: melting and dissolution of the capsule contents; encapsulation; drying; packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated on 3 consecutive production scale batches of finished product. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The CPPs including mixing temperature and time are sufficiently controlled and reported. The IPCs are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form including appearance (visual), identification (HPLC, UV), assay (HPLC), related substances (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (HPLC) and water content (Ph. Eur.).

The limits for impurities have been appropriately justified. The discriminatory power of the dissolution method has been demonstrated.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, no additional for elemental impurities are deemed necessary.

A risk assessment concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The applicant tested several batches of finished product and of active substance for common low molecular weight nitrosamines using an appropriately sensitive, validated GC-MS/MS method which did not detect any nitrosamine impurities. Based on the information provided, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 14 pilot to production scale batches from the proposed commercial manufacturer, along with 6 pilot scale batches from manufacturers used earlier in development, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market, through traditional final product release testing.

Stability of the product

Stability data from 9 pilot to production batches of finished product stored for up to 36 months under long term conditions (25ºC / 60% RH), for up to 36 months under intermediate conditions (30ºC / 65% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging representative of that proposed for marketing.

Samples were tested for appearance, assay, degradation products, dissolution and water content. All attributes remained within their specification and no significant changes were observed, other than a small increase in water under accelerated conditions.

In addition, samples were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No change was observed for capsules stored within the HDPE bottle. However, capsules stored outside the bottle underwent some degradation, with an increase in impurities and a decrease in assay. The finished product is more photosensitive than the active substance and should thus be stored in its container.

An in-use stability study was conducted on samples stored under either long term or accelerated conditions. At the start of the study, the bottles had been stored sealed for 9 months under long term conditions. Bottles were opened daily and tested at regular intervals for up to 180 days. No significant trends were observed, other than an increase in water under accelerated conditions.

Based on available stability data, the proposed shelf-life of 3 years and stored within the HDPE bottle in order to protect from light, as stated in the SmPC (section 6.3 and 6.4) is acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

No other excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertains to the development of a more patient-friendly formulation with a higher active substance load. This point is put forward and agreed as a recommendation for future quality development.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant is recommended to develop a more patient-friendly formulation with a higher active substance load in order to reduce the number of large capsules to be swallowed daily.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamics

In vitro
The antagonistic properties of avacopan and/or the metabolite CCX168-M1 were evaluated in chemotaxis assays, ligand binding assays, and calcium mobilisation assays. In a myeloid human cell line, avacopan functionally inhibits C5a-mediated chemotaxis with an IC_{50} of 0.92 nM. Additionally, avacopan displaces ^{125}I-C5a from hC5aR with an IC_{50} of 0.45 nM. When tested on freshly isolated human neutrophils, avacopan inhibits the C5a-mediated increase in cytoplasmic calcium levels with an IC_{50} of 0.2 nM.

Avacopan was evaluated for its ability to inhibit C5a-mediated effects on neutrophils in freshly isolated human whole blood. First, in a C5a-mediated neutrophil migration assay in whole blood, avacopan produced 50% inhibition (IC_{50}) at a concentration of 1.7 nM; 90% inhibition required an avacopan concentration of 15.4 nM. Second, in a C5a-mediated upregulation assay of the adhesion molecule CD11b on the surface of neutrophils in freshly isolated whole blood, avacopan treatment made neutrophils two-fold less sensitive to C5a stimulation at a concentration of 4.8 nM; in whole blood, 90% inhibition required an avacopan concentration of 43 nM.

Avacopan also inhibits C5aR in cynomolgus monkeys and hamsters with potencies in a similar range to that observed with human whole blood. However, avacopan possesses moderate potency for rabbit C5aR (IC_{50} ~4 μM) and lacks affinity for mouse or rat C5aR (IC_{50} >10 μM).

One major human metabolite, CCX168-M1, has been identified in human plasma in a Phase I study, (CL001_168). This metabolite is equivalent to avacopan in its potency towards hC5aR. CCX168-M1 has an IC_{50} of 3 nM for inhibition of C5a-mediated whole blood neutrophil chemotaxis and a potency of 7 nM for inhibition of C5a-mediated neutrophil CD11b upregulation in whole blood. Like avacopan, the metabolite CCX168-M1 has comparable potency for cynomolgus monkey, hamster, and human C5aR, moderate potency against rabbit C5aR (IC_{50} ~3 μM) but lacks affinity for mouse or rat C5aR (IC_{50} >10 μM).

In vivo
As avacopan retains little, if any, potency for C5aR expressed by mice or rats, the applicant generated a human C5aR knock-in (hC5aR KI) mouse strain in which the mouse C5aR gene was replaced with the human C5aR gene. The model seems validated by data indicating that the innate immune cells of these hC5aR KI mice respond normally to human (or mouse) C5a and in a highly sensitive manner to avacopan (i.e that the human C5aR in these transgenic mice is fully functional). *In vitro*, avacopan blocks hC5a-mediated chemotaxis of leukocytes freshly isolated from these hC5aR KI mice with an IC_{50} of 13 nM in 100% mouse plasma.

Avacopan has been evaluated in mechanism-based studies in monkeys and in the hC5aR KI mouse model evaluating the effect of avacopan on hC5a-induced neutropenia. *Ex vivo*, the effect of avacopan on C5a-mediated CD11b upregulation on blood leukocytes from the hC5aR KI mouse was evaluated. Finally, avacopan was studied in an ANCA disease model in hC5aR KI mice. In the mechanism-based monkey model, avacopan caused a complete inhibition of hC5a-induced neutropenia at plasma

concentrations of ~230 nM (134 ng/mL) i.e. above the cynomolgus whole blood IC_{90} (162 nM), while concentrations of ~38 nM (22 ng/mL) around the cynomolgus whole blood IC_{50} (18 nM) resulted in ~50% inhibition. Hence, in this model, avacopan can significantly reduce C5a-induced neutropenia in monkeys.

In the hC5aR KI mouse model, an intravenous dose of 20 µg/kg hC5a robustly induced leukopenia (>50% drop from baseline) within one minute after injection. Pre-treatment of these mice with an oral dose of 0.3 mg/kg avacopan resulted in a plasma concentration of approximately 75 nM at one hour which almost completely blocked the C5a-induced leukopenia. A dose of 0.03 mg/kg avacopan, corresponding to a plasma concentration of 15 nM (~9 ng/mL) resulted in a 50% reduction in the C5a-induced leukopenic response.

The amount of avacopan required to hinder C5a-mediated CD11b upregulation on blood leukocytes in plasma was evaluated further with an *ex vivo* assay using hC5aR KI mice. Following an orally administered dose of vehicle or avacopan, blood was collected and stimulated *in vitro* with increasing concentrations of hC5a, resulting in increased CD11b expression on blood neutrophils. The potencies (EC_{50}) of hC5a for CD11b upregulation on neutrophils from vehicle and avacopan-treated mice were compared in the context of the measured avacopan plasma concentration. C5a inhibition was generally proportional to avacopan in this assay. On average, a plasma concentration of 38 nM (~22 ng/mL) avacopan was required to shift the C5a EC_{50} value 10-fold.

ANCA disease is a small vessel vasculitis perpetrated by autoantibodies against neutrophil cytoplasm-expressed proteins such as myeloperoxidase (MPO) and proteinase 3 (PR3). Complement C5a has a critical role in this disease process. In a manner that requires activation of the alternative complement pathway, passive transfer of antibodies to MPO (anti-MPO) induces ANCA necrotising and crescentic glomerulonephritis in mice that closely mimics human disease. In this anti-MPO-induced mouse disease model, antibody-mediated blockade of C5a prevents disease. Moreover, knocking out the C5a receptor makes mice resistant to ANCA disease in this model system. In this ANCA vasculitis mouse model, anti-MPO antibodies were injected intravenously into 10-week old female hC5aR KI mice on Day 0. The mice were dosed orally with 0 (vehicle), 0.1, 1, 10 (2x5) or 37.5 mg/kg avacopan for 7 days. On Day 7, mice were euthanised and kidneys were evaluated histologically for glomeruli containing necrosis and crescents. In addition, serum and urine samples were analysed for indicators of kidney dysfunction. Vehicle-treated mice developed glomerular crescents and necrosis, the primary hallmarks of disease, by Day 7. Mice treated at 10 (2x5) and 37.5 mg/kg/day showed significant reductions in the incidence of glomerular crescent formation and necrosis relative to vehicle-treated mice. At the same dose levels, the mice exhibited significant reductions in indicators of kidney dysfunction, including urinary protein levels and urinary leukocyte and erythrocyte numbers. An avacopan dose of 37.5 mg/kg q.d., reduced the percentage of glomeruli with crescents by 93% on average, and the percentage of glomeruli with necrosis by 100% on average. At 37.5 mg/kg, avacopan mean plasma concentrations range from 4380 ng/mL (at 1 hour) to 276 (at 24 hours). Thus, the effective avacopan plasma concentrations seem to be between 200 and 4000 ng/mL. The mean steady-state trough avacopan plasma concentration at the intended therapeutic dose in humans is ~204 ng/mL. The active dose levels of 10 and 37.5 mg/kg corresponds to HEDs of 0.8 and 3 mg/kg, respectively. Thus, the dose span (HED of 0.0024 to 3 mg/kg) investigated seems relevant to the human recommended dose of 60 mg/day (~1 mg/kg/day).

Secondary pharmacology

Avacopan displays ~10,000-fold or greater selectivity for hC5aR relative to most other chemotactic receptors, and 6,700-fold for CCR5 and 8,000-fold for CCR10. These include CCR1, CCR2, CCR3, CCR4,

CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CCR12, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, CXCR7, C5L2, C3aR, ChemR23, GPR1, and FPR1.

Avacopan was further evaluated against a panel of 55 unrelated receptors and membrane-associated proteins. At 10 µM (~5.8 µg/mL) avacopan showed weak activity on the human Adenosine A2a (42% inhibition) and A3 receptors (33% inhibition), as well as on the sodium channel (site 2).The weak activity of avacopan was observed at exposures >16,000-fold the clinical C_{max} (unbound) for avacopan of 0.349 ng/mL. The metabolite CCX168-M1 was tested against a panel of 17 related chemotactic receptors and a panel of 56 unrelated receptors and membrane-associated proteins. Only weak activity was detected at 10 µM (~6 µg/mL); 53% inhibition at cannabinoid receptor type 1, 64% inhibition at sodium channel (binding site 2), and 51% inhibition at GABA-gated chloride channel. The weak activity of metabolite CCX168-M1 was observed at exposures around 49,000-fold the clinical C_{max} (unbound) for CCX168-M1 of 0.122 ng/mL.

As patients with the indications being pursued who may receive avacopan may also be receiving glucocorticoids as part of their treatment, the ability of avacopan and CCX168-M1 to block the glucocorticoid receptor was evaluated using radio-ligand binding assays. No antagonist activity was observed for either compound in these assays. Furthermore, avacopan and CCX168-M1 were evaluated for their ability to inhibit cellular proliferation of lymphocytes, either alone or together with cyclophosphamide. Neither avacopan nor CCX168-M1 affected the ability of cyclophosphamide to inhibit cellular proliferation; by themselves, avacopan and CCX168-M1 also did not affect cellular proliferation. Neither avacopan nor CCX168-M1 had any activity on 11β-HSD2, an enzyme involved in the metabolism of corticosteroids. Both compounds were thus found to be inactive in these assays, indicating low potential for interference with the biological effects or metabolism of either cyclophosphamide or corticosteroids.

Safety pharmacology

Avacopan was tested in the following battery of safety pharmacology assays:

CNS, respiratory and renal systems: Evaluation of behaviour, blood pressure, ECG and respiratory assessments were included in the monkey repeat-dose toxicity studies. No effects on behaviour, respiratory rates, and kidney function were noted in the monkey studies at dose levels up to 30/45 mg/kg/day and avacopan and CCX168-M1 exposures corresponding to ~5.2- and 4.4-fold the clinical AUC, respectively.

Cardiovascular system: 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 4000- and 14000-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 plasma concentration at 4 hrs (approximate T_{max}) post-dose was 1182 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 1845 and 2470 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.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been performed. This is considered acceptable.

2.3.3. Pharmacokinetics

The absorption, clearance, distribution, and metabolism properties of avacopan and its major metabolite CCX168-M1 were evaluated in a series of *in vitro* and *in vivo* studies.

Absorption: Avacopan is highly permeable across the Caco-2 monolayer membrane and is not a substrate of efflux transporters. Following intravenous dosing, avacopan showed moderate total body clearance (30 to 50% of liver blood flow) in mice, rats and dogs. The terminal elimination half-life ranged from approximately 2 hours in mice and rats to 14.2 hours in dogs. Following oral dosing of the crystalline neutral form at 2 mg/kg in a suspension, avacopan was rapidly absorbed in mice and rats with low to moderate bioavailability (17% to 27%). When dosed orally as a solution, bioavailability of 50% to 100% was observed at doses up to 100 mg/kg in rats. Several organic vehicles were explored for rat, rabbit, hamster, and cynomolgus monkey oral pharmacokinetics at several dose levels; the maximum exposure following single oral administration was reached at 100 mg/kg.

Distribution: Both avacopan and its metabolite CCX168-M1 are plasma protein bound reversibly at >99.9% in plasma of mice, rats, hamsters, rabbits, dogs, monkeys and humans over the concentration range of 2.5 to 50 µM. Avacopan is reversibly bound to human albumin and α1-acid glycoprotein (AAG) at >99.9%, while CCX168-M1 is reversibly bound to human albumin and AAG at 99.9% and ~99%, respectively. Avacopan and CCX168-M1 do not selectively partition to red blood cells. The tissue distribution profile of a single oral dose of [^{14}C]-avacopan in rats showed that the radioactivity was rapidly absorbed and extensively distributed into tissues and organs. Distribution profiles were similar in non-pigmented (male) and pigmented (male/female) rats. In non-pigmented male and female rats, the tissues with the highest [^{14}C]-avacopan-related radioactivity concentrations were liver, brown fat, white adipose, adrenal glands, urinary bladder (male), Harderian gland (male), preputial gland (male), pancreas (female) and myocardium (female). In the pigmented (male and female) rats, the tissues with the highest concentrations were liver, brown fat, white adipose, adrenal glands, Harderian gland, pancreas, kidney and renal substructures (male), cecum (female), and small intestine (male). The C_{max} of [^{14}C]-avacopan-derived radioactivity was greater in white adipose than for most other tissues from 8 through 72 hours post dose. Distribution trends in the pigmented uveal tract suggested that [^{14}C]-avacopan-related radioactivity associated with the melanin-containing tissues of the eye; this association was slowly reversible. The total exposure to radioactivity was low to moderate when compared to other non-melanin containing tissues. Radioactivity levels in the skin were similar in pigmented and non-pigmented rats and were measurable through 72 and 336 hours post dose, except in pigmented male rats, where levels were BLQ at 336 hours post dose. The total exposure to radioactivity was moderate when compared to other non-melanin containing tissues. The elimination of radioactivity from pigmented skin and non-pigmented skin occurred at a similar rate, suggesting that there was no apparent selective affinity of [^{14}C]-avacopan-derived radioactivity for integumentary melanin.

Distribution to placenta was not investigated.

Metabolism: When incubated with cryogenically preserved hepatocytes from mice, rats, dogs, and humans, avacopan demonstrated low to moderate intrinsic clearance. In hepatocytes and liver microsomes of several species (mouse, rat, hamster, rabbit, dog, monkey, or human), the most abundant metabolite was CCX168-M1, identified as a product of methyl hydroxylation of avacopan. Several minor metabolites, including CCX168-M6, were also observed, all primarily products of Phase I biotransformation of avacopan.

Definitive *in vivo* metabolite profiling studies with an oral dose of [^{14}C]-avacopan in rats, monkeys, and humans showed that avacopan was the most abundant radioactive component in plasma across these species, while CCX168-M1 was the only major circulating metabolite. This metabolite is equivalent to avacopan in its potency towards hC5aR. In human plasma, avacopan and metabolite CCX168-M1 accounted for 18% and 11.9% of the total plasma radioactivity, respectively. CCX168-M1 is considered qualified as adequate exposure has been achieved in the evaluation of safety pharmacology, general toxicity, genotoxicity and reproductive toxicity studies. This major metabolite was also qualified in the carcinogenicity studies.

Excretion: Mass balance studies were carried out in rats, cynomolgus monkeys, and healthy human subjects, with oral administration of [^{14}C]-avacopan. Results from the rat and human studies showed high total radioactivity recovery (>97% in rats and >86% in humans), while the monkey mass balance was approximately 72% due to complications from diarrhoea caused by PEG-400 in the dosing vehicle. In all three species, the major elimination pathway is 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.

2.3.4. Toxicology

The toxicological profile of avacopan has been evaluated in a set of non-clinical studies including repeat-dose toxicity studies up to 13 weeks in hamsters, up to 26 weeks rats and up to 44 weeks monkeys; *in vitro* and *in vivo* genotoxicity; fertility and early embryonic development (hamster) and embryo-fetal development (EFD) (hamster and rabbit) and pre- and post-natal development (hamster); *in vitro* phototoxicity and *in silico* and *in vitro* impurity qualifying studies. Two-year carcinogenicity studies (hamster and rat) were submitted during the evaluation.

The hamster and Cynomolgus monkey were selected as the main rodent and non-rodent toxicology species as justified by pharmacology and pharmacokinetic data showing that avacopan binds to cynomolgus monkey and hamster C5aR with potencies similar to those seen for human C5aR, and that these species are relevant from a metabolism perspective. Toxicity studies in rats were designed to assess off-target adverse effects.

Single dose toxicity

A single-dose toxicity study in rats showed that oral administration of avacopan up to 100 mg/kg was well tolerated with no significant effects in any of the investigated parameters.

Repeat dose toxicity

Avacopan has been evaluated in repeat-dose toxicity studies in hamsters (up to 13 weeks with 4 weeks recovery), rats (up to 26 weeks with 6 weeks recovery) and monkeys (up to 44 weeks with 6 weeks recovery). No dose-limiting effects or target organ of toxicity were noted in the chronic studies and therefore, the toxicology of avacopan is not considered fully explored. However, the maximum dose levels employed were the maximum feasible dose levels based on dose volume and formulation concentration constraints, and/or formulation tolerability. To further maximise exposure, twice daily dosing was used in all chronic studies. Additionally, a saturated absorption was seen in hamsters and monkeys. Thus, the repeat-dose toxicity profile has been explored to the extent feasible.

Avacopan was well tolerated at doses up to 1000 mg/kg/day in hamsters, 200 mg/kg/day in rats and 45-50 mg/kg/day in monkeys. These doses were associated with maximal systemic exposure following oral administration in each species after optimizing the formulation. Observations in the chronic (26-week and 44-week) toxicology studies were limited to vehicle-related clinical observations of gastrointestinal effects in monkeys and minor clinical pathology effects in rats at doses >100 mg/kg/day, none of which were considered adverse based upon their magnitude, direction of change, reversibility, and absence of any other clinical or microscopic correlate(s).

Genotoxicity

A complete package of genotoxicity studies in agreement with ICH S2(R1) guidance have been performed with avacopan. In the bacterial reverse mutation assay, avacopan did not cause an increase in the mean number of revertants per plate with any tester strains, either in the presence or absence of microsomal activation prepared from Aroclor-induced rat liver. Also, avacopan was found to be negative for inducing forward mutations at the thymidine kinase (TK) locus in L5178Y mouse lymphoma cells. The maximum concentrations evaluated in the *in vitro* studies were limited by solubility and the top dose was ~300 µg/plate in the bacterial reverse mutation assay and 300 µM in the mouse lymphoma test.

In vivo, avacopan was negative in the rat bone marrow micronucleus assay, following two consecutive daily oral doses up to the dose limit of 2000 mg/kg/day. TK analysis, reported in a separate non-GLP study, indicated that avacopan and CCX168-M1 exposure plateaued at the 500 mg/kg dose. Thus, the avacopan and CCX168-M1 AUC exposures up to 95930 ng·h/mL and 13825 ng·h/mL, respectively were evaluated in the study, correlating to 17-fold, and 5-fold, respectively, the clinical AUC. Distribution to the bone marrow was confirmed in the quantitative whole-body autoradiography studies in rat where the [^{14}C]-avacopan derived radioactivity in bone marrow was approximately similar to that in blood.

Carcinogenicity

The carcinogenic potential of avacopan was evaluated in 2-year carcinogenicity studies in rats and hamsters.

In rats, avacopan treatment was generally well tolerated with no dose-limiting effects observed. Given that the TK analysis revealed a saturated exposure, it is agreed that the dose level selection seems appropriate. The study was terminated during Weeks 97 and 92 for males and females, respectively, due to lower survival in the water or vehicle control groups. This is not considered to impact on the assessment of carcinogenic potential as the number of animals evaluated and study duration are sufficient.

A slight increased incidence of focal C-cell hyperplasia in the thyroid was noted in males administered 100 mg/kg/day. The incidences were 11% (6/55), 11% (6/57), 11% (6/57), 12% (7/57) and 19% (11/57) at 0 (vehicle), 0 (water), 10, 30 and 100 mg/kg/day, respectively. In Covance's historical control dataset, the total incidence in male rats was 2.6% (46/1766) with a range of 0.0 to 21.7%.

There were no clear indications on neoplasms of an unusual incidence or nature. A slight increased incidence of benign C-cell adenoma in the thyroid was however noted in males at 100 mg/kg/day. The incidences were 13% (7/55), 11% (6/57), 16% (9/57), 16% (9/57) and 23% (13/57) at 0 (vehicle), 0 (water), 10, 30 and 100 mg/kg/day, respectively. In Covance's historical control dataset, the total incidence thyroid focal C-cell adenomas in male rats was 11% (189/1766) with a range of 2.2 to 25.5%. Thus, the incidence of thyroid focal C-cell adenomas in male rats at 100 mg/kg/day is above the mean total incidence but within the range of the historical controls. In Week 4, the mean $AUC_{0\text{-}24h}$ values for avacopan was 11500, 25600 and 17400 in males at 10, 30 and 100 mg/kg/day, respectively, corresponding to 1.6-, 3.6- and 2.5-fold the clinical AUC exposure. In females, the mean $AUC_{0\text{-}24h}$ values for avacopan was 13600, 33400 and 21400 at 10, 30 and 100 mg/kg/day, respectively corresponding to 1.9-, 4.8- and 3-fold the clinical AUC exposure.

In hamsters, avacopan treatment was also well tolerated with no dose-limiting effects observed. No saturation of avacopan exposure was observed in hamsters at the selected dose levels. However, previous data from the 13-week hamster study indicate saturation of exposure at dose levels above 100 mg/kg/day. Thus, the dose level selection seems appropriate.

The study was terminated during Weeks 98 and 92 for males and females, respectively, due to lower survival in the water or vehicle control groups. This is not considered to impact on the assessment of carcinogenic potential as the number of animals evaluated and study duration are sufficient.

Administration of 30 or 100 mg/kg/day resulted in an increased incidence of mineralisation in the ovaries of females and the majority of findings were of minimal severity degree. The toxicological significance is unknown. The study report mentions that this finding has not been noted in previous long-term studies in hamsters at the test site and is not reported as a common non-neoplastic observation in Syrian hamsters (Kamino et al., 2001, McInnes et al 2015). Mineralisation in ovaries has not been observed in rats (up to 2-years) or monkeys (up to 44 weeks).

Administration of the control article irrespective of the dose of avacopan, resulted in higher incidence and/or severity of pigment in the spleen, mesenteric lymph nodes, liver, colon, and cecum; pigmented macrophages in the liver; cystic glands in the rectum; and chronic progressive nephropathy.

There were no clear indications on neoplasms of an unusual incidence or nature. However, a further discussion is requested on the potential increased incidence of benign adrenal phaeochromocytoma in female hamsters at 100 mg/kg/day. The incidences were 4.6% (3/65), 4.6% (3/65), 0% (0/65), 3.1% (2/65) and 9.2% (6/65) at 0 (vehicle), 0 (water), 10, 30 and 100 mg/kg/day, respectively. In published data from three 2-year hamster studies, benign adrenal phaeochromocytoma was reported in 1.6% (4/250) control females with the highest individual study incidence of 3.3% (2/60). Thus, the incidence at 100 mg/kg/day is outside of this published spontaneous background incidence.

In Week 26, the mean $AUC_{0\text{-}24h}$ values for avacopan was 5560, 21600 and 42000 in males at 10, 30 and 100 mg/kg/day, respectively, corresponding to <1, 3.1- and 6-fold the clinical AUC exposure. In females, the mean $AUC_{0\text{-}24h}$ values for avacopan was 4290, 24500 and 35600 in at 10, 30 and 100 mg/kg/day, respectively corresponding to <1, 3.5- and 5.1-fold the clinical AUC exposure.

Reproduction Toxicity

In the fertility and early embryonic development study in hamsters, there were no significant effects on male or female fertility or early embryonic development parameters when tested up to doses of 1000 mg/kg/day corresponding to 6-fold the expected clinical AUC. In addition, avacopan did not affect reproductive organ weights, or caused macroscopic or histopathological findings in reproductive organs in any of the investigated species in repeat-dose toxicity studies.

Embryo-foetal developmental studies were performed in hamsters and rabbits. In the pivotal hamster study, there were no signs of maternal toxicity, and no alterations in the uterine and ovarian examination. The foetal evaluation revealed no external, visceral or skeletal malformations, but there was a significant increase in the number of litters and foetuses with skeletal variations, principally short thoracolumbar supernumerary ribs, at 1000 mg/kg/day. The applicant is of the opinion that short thoracolumbar supernumerary ribs have been demonstrated to be transient and resolve with further development of the animal. As such, it is unclear why no directed evaluation of the skeleton was included in the pre- and post-natal development study. In the absence of post-natal skeletal data, and any other signs of maternal toxicity (i.e. clinical signs or effects on food consumption or body weight), the skeletal variations cannot be attributed to maternal toxicity and are considered adverse. Thus, the NOAEL for maternal toxicity is 1000 mg/kg/day, corresponding to 5.2-fold the clinical AUC. Based on the increased incidence of supernumerary ribs at 1000 mg/kg/day, the NOAEL for embryo-foetal development is 100 mg/kg/day, corresponding to 5.2-fold the clinical AUC.

In the pivotal rabbit study, maternal toxicity as seen by an increased incidence in abortions and clinical signs were observed at the highest dose tested, 200 mg/kg/day. There were no alterations in the uterine and ovarian examination, and there were no avacopan-related gross external, soft tissue or skeletal foetal alterations (malformations or variations). The NOAEL for maternal toxicity is 30 mg/kg/day, and the NOAEL for embryo-foetal development is 200 mg/kg/day, both NOAELs corresponding to ~0.6-fold clinical AUC exposure.

In the pre- and post-natal development hamster study, oral administration of up to 1000 mg/kg/day avacopan was given from gestation day 6 to lactation day 20. Treatment was generally well-tolerated in female hamsters during the gestation and lactation periods. No deaths, clinical signs, body weight or food consumption differences, gross lesions or changes in organ weights were attributed to avacopan. In the F1 generation, there were no findings considered avacopan-related in any of the parameters evaluated with exception of the male sexual maturation. There was a small statistically significant increase in the preputial separation day values for the male F1 generation offspring at 30, 100 and 1000 mg/kg/day in comparison with the control group values. The effect may indicate a general developmental delay, however, the body weight at the time of preputial separation was similar in all study groups indicating that such explanation is unlikely. In general, preputial separation is known to be androgen dependent and consequently delays could potentially indicate an estrogenic or anti-androgenic effect.

On the basis of these data, the maternal NOAEL was 1000 mg/kg/day, corresponding to ~4-fold clinical AUC exposure.

Toxicokinetic data

The toxicokinetic characteristics of avacopan and its metabolites were determined in the pivotal reproductive toxicity studies.

Local Tolerance

No local tolerance studies were submitted which is acceptable. The intended route of administration of avacopan is oral and local tolerance has been adequately evaluated within the performed non-clinical studies. Vehicle-related clinical observations of gastrointestinal effects were observed in monkeys and in rabbits. This is not considered a concern in the clinical situation.

Other toxicity studies

Phototoxicity: Avacopan absorbs light within the range of natural sunlight (290 to 700 nm) with a peak MEC of 2989 L mol^{-1} cm^{-1} at 290 nm. The study report concludes that avacopan has potential to be photoreactive between 290 and 370 nm. In rat QWBA studies, [^{14}C] avacopan-derived material was widely distributed following an oral dose. Distribution trends in the pigmented uveal tract suggested that [^{14}C]-avacopan-related radioactivity associated with the melanin-containing tissues of the eye; this association was slowly reversible. The total exposure to radioactivity was low to moderate when compared to other non-melanin containing tissues. Radioactivity levels in the skin were similar in pigmented and non-pigmented rats.
Based on criteria established in ICH S10, further experimental evaluation of phototoxicity potential is warranted and the applicant has performed an *in vitro* phototoxicity study concluded as negative. However, the Atlas Xenon lamp used emits light wavelengths in the 300 to 800 nm range corresponding to a range noted for all sunlight approximating emitters listed in the OECD guidance, while avacopan shows a peak absorption at 290 nm. However, given that avacopan levels in the skin were considered moderate and comparable to other tissues and declined at a rate similar to non-melanin containing tissues and that no adverse reactions in skin are reported in the phase 3 clinical trial, further testing is not warranted. In addition, UVB-induced phototoxicity is rarely a concern for pharmaceuticals with systemic exposure since UVB minimally penetrates beyond the epidermis as noted in ICH S10.

In conclusion, the testing strategy is considered acceptable and it can be concluded that avacopan is considered as negative for phototoxic potential under the conditions tested.

Immunotoxicity: The potential immunotoxicity of avacopan has been evaluated by standard assessments in repeat-dose toxicology studies and by evaluation of T-cell dependent antibody responses induced by KLH in rats and monkeys. However, as avacopan has no activity on the rat C5aR, the rat study data are not considered informative. In addition, immunophenotyping of peripheral blood was included in the 44-week monkey study.

In monkeys, avacopan had no effect on T-cell dependent antibody responses or on relative or absolute values for peripheral blood immunophenotyping (total T lymphocytes, helper T lymphocytes, cytotoxic T lymphocytes, B lymphocytes, or natural killer cells). In monkey repeat-dose studies, there were no observed histopathological changes in lymphoid organs or alterations in clinical pathology parameters.

Dependence: No drug dependence studies were submitted. This is considered as acceptable as avacopan has a limited distribution to CNS and there was no evidence of CNS effects in safety pharmacology or toxicology studies. The intended mechanism of action, antagonism of the C5aR is also not suggesting abuse liability.

Metabolites: In humans, metabolite CCX168-M1 was characterised as a major metabolite (~12 % of total plasma radioactivity). This metabolite is equivalent to avacopan in its potency towards hC5aR. Metabolite CCX168-M1 is also a metabolite in all non-clinical species and adequate exposure of CCX168-M1 has been achieved in the evaluation of safety pharmacology, general toxicity, genotoxicity and reproductive toxicity studies. Carcinogenicity studies have been performed in hamsters and rats.

Impurities: Impurities have been evaluated in accordance with ICH M7.

In vitro, the drug substance intermediate and one impurity did not induce bacterial reverse mutations in the presence or absence of metabolic activation with rat liver S9 and are thus considered non-mutagenic.

From a non-clinical perspective, no new or additional risks have been identified.

2.3.5. Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (INN/Invented Name): Avacopan					
CAS-number (if available): 1346623-17-3					
PBT screening		Result			**Conclusion**
Bioaccumulation potential log K_{ow}	OECD117 OECD123	≥4.9 at pH 6-9 7.00-7.12 at pH 5-9			Potential PBT (Y)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	7.00-7.12 at pH 5-9			B
	BCF	<2000 L/kg			not B
Persistence	DT50 or ready biodegradability	Not readily biodegradable DT50 >180 days			P vP
Toxicity	NOEC or CMR				T/not T
PBT-statement:	The compound is considered as vP				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, refined based on prevalence	0.0078	µg/L			>0.01 threshold (N)
Other concerns (e.g. chemical class)	NA	NA			(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Ready Biodegradability Test	OECD TG301B	Biodegradation -2.7% after 29 days			Not readily biodegradable in sludge
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Pfalz $DT_{50,\ water}$ = 1.25 days $DT_{50,\ sediment}$ = 95.2 days $DT_{50,\ whole\ system}$ = 56 days Humsterbach $DT_{50,\ water}$ = 0.85 days $DT_{50,\ sediment}$ >10000 days $DT_{50,\ whole\ system}$ >10000 days >10% shifting to sediment			vP in water-sediment systems
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	664	L/kg	%lipids; 4.4% at test start 3.8% at Day 20 3.6% at end of depuration phase 3.8% as overall mean

Avacopan has a $PEC_{surface\ water}$ value of 0.0078 µg/L (phase I calculation using a prevalence based Fpen of 0.00026 representing the orphan disease indications) and does therefore not trigger a

standard Phase IIA risk assessment. The log K_{OW} of avacopan was determined to ≥4.9 (OECD TG117), and to 6.98-7.12 (OECD123) at environmental relevant pH values triggering a PBT hazard assessment (log K_{OW} ≥4.5).
A stepwise PBT assessment has been provided. With regards to persistence, avacopan does not demonstrate a readily biodegradation profile in activated sludge according to OECD TG301B indicating a certain degree of persistence. The degradation and distribution of avacopan in two water-sediment systems under aerobic conditions was investigated according to test guideline OECD 308. The avacopan degradation rates (DT_{50}) in the sediment and in the total system of one of the two water-sediment systems are higher than the threshold value of 180 days for the half-life in water-sediment systems, as defined as very persistent criterion by ECHA. Thus, avacopan is very persistent (vP) in water-sediment systems. Regarding bioaccumulation, a bioconcentration study in rainbow trout was conducted according to OECD 305. The steady-state and lipid-normalised growth-corrected kinetic bioconcentration factors (BCF_{SS} and BCF_{klg}) of avacopan were in maximum 664 L/kg and hence below the bioaccumulation criterion (B) of 2000 L/kg according to ECHA. Thus, avacopan is not considered bioaccumulative. Consequently, avacopan has not to be classified as a PBT substance, since the criteria bioaccumulative (B) and vB are not fulfilled.
In summary, avacopan $PEC_{surfacewater}$ value is below the action limit of 0.01 µg/L. Avacopan is considered as vP but is not a PBT substance. Considering the rarity of the indications, the environmental exposure will be negligible.

2.3.6. Discussion on non-clinical aspects

The non-clinical characteristics of avacopan has been characterised in pharmacology, pharmacokinetic and toxicology studies in agreement with relevant guidelines.

Pharmacology: Avacopan has been developed as a selective antagonist of the complement 5a receptor (C5aR) thereby inhibiting the binding of complement 5a (C5a), a terminal component of the complement cascade, to the C5aR.

In vitro, the antagonistic properties of avacopan and its major human metabolite CCX168-M1 were evaluated in chemotaxis assays, ligand binding assays, and calcium mobilisation assays. In these studies, avacopan and CCX168-M1 were found to be potent antagonists of human, hamster, and monkey C5aR, moderately potent against rabbit C5aR, but to be non- or minimally active against mouse, rat or rabbit C5aR.

In vivo, avacopan caused a dose-dependent inhibition of hC5a-induced neutropenia in monkeys and in hC5aR KI mice at plasma concentrations of relevance for the clinical situation. In the ANCA disease model in hC5aR KI mice, avacopan caused dose-dependent and significant reductions in the incidence of glomerular crescent formation and necrosis relative to vehicle-treated mice, and significant reductions in indicators of kidney dysfunction, including urinary protein levels and urinary leukocyte and erythrocyte numbers. Overall, *in vitro* and in *vivo* primary pharmacology data support the intended clinical use. Moreover, the *in vivo* models and the avacopan dose ranges studied are considered relevant for the clinical situation.

Regarding the proposed mechanism of action in SmPC section 5.1, the included statements have been supported by data.

Based on the secondary pharmacology screens, the data indicate a low potential for off-target effects of both avacopan and the metabolite CCX168-M1.

Evaluation of effects on CNS, respiratory and renal systems was performed in rats. As avacopan lacks affinity for the rat C5aR, the potential safety pharmacology effects of C5aR antagonism are not

considered evaluated in these rat studies. However, as avacopan and its metabolite CCX168-M1 have similar pharmacological activity on human and cynomolgus monkey C5aR, and as safety pharmacology parameters including evaluation of behaviour, blood pressure, ECG and respiratory assessments were included in the monkey repeat-dose toxicity studies, these data supplement the results from the rat pharmacology studies. In short, no avacopan-related effects were observed in any of these parameters at the dose levels tested. Based on the *in vitro* hERG 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 heart rate and electrocardiographic parameters (P, PR, QRS, QT and QTc intervals, and R amplitude) following single oral doses up to 50 mg/kg although a slight reduction in blood pressure was observed. At the highest dose tested (50 mg/kg), the mean avacopan plasma concentration at 4 hrs (approximate T_{max}) post-dose was 1182 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 repeat-dose monkey studies at exposures represent 5.2- to 7.0-fold (avacopan), and 4.4- to 4.6-fold (CCX168-M1) the clinical AUC.

Overall, 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. However, it should also be noted that supra-therapeutic exposures have not been evaluated *in vivo*.

Pharmacokinetics: Distribution of avacopan to placenta was not investigated. In addition, excretion into milk has not been evaluated. However, based on data from the hamster PPND study, avacopan is considered likely excreted in maternal milk.

Toxicology: The toxicology study package is acceptable and has been performed according to relevant guidelines. The selection of the main toxicology species, hamster and Cynomolgus monkeys is justified based on pharmacology and pharmacokinetic data.

In chronic studies, no dose-limiting effects or target organ of toxicity were noted and therefore, the toxicology of avacopan is not considered fully explored. However, the repeat-dose toxicity profile has been explored to the extent feasible. Exposures of avacopan reached in the pivotal toxicology studies exceeded the expected exposures reached with 30 mg b.i.d. in humans. The AUC exposure margins relative to the human AUC exposure are approximately 4, 15 and 4 in hamsters, rats and monkeys, respectively.

Questions on species selection, study designs, and timing of carcinogenicity studies were discussed in scientific advices given by CHMP in 2016 (EMEA/H/SA/3340/1/2016/PA/SME/III and EMEA/H/SA/3340/2/2016/PA/SME/III). The species selection (hamster and rat) and the carcinogenicity study designs were endorsed. Regarding the proposal to submit these data post-approval, CHMP clarified that from a risk point of view, it may be acceptable to have the rodent carcinogenicity data available post-approval. However, since safety advantages compared to current therapies are targeted, conducting carcinogenicity testing before an approval would provide further support.

The two-year carcinogenicity studies in rats and hamsters have been submitted as part of the responses to the CHMP's request and showed that the life-time treatment of avacopan was generally well tolerated in both species. There were also no clear indications on neoplasms of an unusual incidence or nature in neither species. However, a slight increased incidence of benign C-cell adenoma in the thyroid was noted in male rats. The finding is likely to be of low toxicological significance but is presented in SmPC section 5.3.

In the pre- and post-natal development hamster study, oral administration of up to 1000 mg/kg/day avacopan was given from gestation day 6 to lactation day 20. Treatment was generally well-tolerated in female hamsters during the gestation and lactation periods. No deaths, clinical signs, body weight or food consumption differences, gross lesions or changes in organ weights were attributed to avacopan.

In the F1 generation, there were no findings considered avacopan-related in any of the parameters evaluated with exception of the male sexual maturation. There was a small statistically significant increase in the preputial separation day values for the male F1 generation offspring at 30, 100 and 1000 mg/kg/day in comparison with the control group values. The effect may indicate a general developmental delay, however, the body weight at the time of preputial separation was similar in all study groups. In general, preputial separation is known to be androgen dependent and consequently delays could potentially indicate an estrogenic or anti-androgenic effect. As requested, a further discussion on the delayed preputial separation has been provided. The applicant is of the opinion that this is a chance event. It is agreed that there is no evidence for any oestrogenic or anti-androgenic effect of avacopan observed by evaluation of standard parameters throughout the provided study package. However, such effects could potentially be subtle and transient.

Historical background data has been provided and show that the mean preputial separation values in vehicle controls and treatment groups were above those obtained in any treatment group in the avacopan PPND study, indicating that the day of preputial separation in hamsters is highly variable or potentially that the historical controls are not fully relevant to the hamsters included in the avacopan study. Moreover, the historical data also show a higher within group variation than in the avacopan PPND study. While it is possible that the particularly small variability of the age of preputial separation in the control group may be a confounding factor, it is also noted that the overall variability in the avacopan-treated groups were smaller than the historical controls. Given these apparent differences between the avacopan study data and the historical control data, it is concluded that the within study control groups are considered the most relevant. After a further clarification, the CHMP concluded that the delayed preputial separation observed at or above dose levels of 30 mg/kg/day in comparison with the control groups is considered possibly related to avacopan administration. The finding is likely to be of low toxicological significance but is described in SmPC section 4.6 and 5.3. On the basis of these data, the maternal NOAEL was 1000 mg/kg/day, corresponding to ~4-fold clinical AUC exposure. The developmental NOAEL in male and female hamsters was 10 and 1000 mg/kg/day, respectively.

2.3.7. Conclusion on the non-clinical aspects

Overall, the submitted non-clinical pharmacology, pharmacokinetic and toxicology data is adequate. No post-marketing investigations were considered necessary by the CHMP.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID; Phase	Location of Study Report	Main Study Objectives	Study Title/Design	Test Product; Dosing Regimen; Route of Administration	Target Study Population	Duration of Treatment	Study Status; Type of Report
CL001_168 Phase 1	5.3.3.1	Safety and tolerability; pharmacokinetic and pharmacodynamic profiles	A Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of CCX168 in Healthy Male and Female Subjects	Avacopan or placebo; Period 1: 1, 3, 10, 30, and 100 mg, single dose; Period 2: 1, 3, and 10 mg once daily for 7 days; 30 and 50 mg twice daily for 7 days; Oral	48 healthy subjects	Period 1: 1 day; Period 2: 7 days	Completed; Full
CL004_168 Phase 1	5.3.2.2	Mass balance	An Open-Label, Phase 1 Study in Healthy Volunteers to Evaluate the Mass Balance Recovery and Metabolic Disposition of a Single Oral Dose of [^{14}C]CCX168	100 mg avacopan single dose containing 400 µCi of [^{14}C]avacopan; Oral	6 healthy male subjects	1 day	Completed; Full
CL007_168 Phase 1	5.3.3.4	Food effect	An Open-Label, Phase 1 Study in Healthy Volunteers to Evaluate the Pharmacokinetic Food Effect and Cardiac Safety of CCX168	Period 1: 30 mg avacopan single dose, fed or fasted; Period 2: 30 mg avacopan single dose, fed or fasted; Period 3: 3 mg avacopan single dose, fasted; Period 4: 100 mg avacopan single dose followed by 100 mg avacopan twice daily for 5 days, followed by 100 mg single dose for 1 day, fasted; Oral	16 healthy subjects	Period 1, 2, 3: 1 days Period 4: 7 days	Completed; Full
CL008_168 Phase 1	5.3.3.4	Drug-drug interaction	An Open-Label, Phase 1 Study in Healthy Volunteers to Evaluate the Drug-Drug Interaction Potential of CCX168 with Concomitant Medications	Cohort A: Day 1 and Day 13: single oral doses of 2 mg midazolam and 200 mg celecoxib; Day 3 to 18: avacopan 30 mg orally twice daily; Day 16 to 19: once daily oral dose 200 mg itraconazole; Day 19: single morning oral dose avacopan 30 mg Cohort B: Day 1 and 14: avacopan 30 mg orally once daily Day 4 to 17: 600 mg rifampin orally once daily	32 Healthy Subjects (16 in each Cohort)	19 days	Completed; Full
CL013_168 Phase 1	5.3.3.3	Hepatic impairment	An Open-Label, Phase 1 Study To Evaluate The Single-Dose Pharmacokinetics Of Avacopan (CCX168) In Male And Female Subjects With Mild Or Moderate Hepatic Impairment	30 mg single dose; Oral	24; (8) Healthy Subjects; (8) subjects with mild, and (8) with moderate hepatic impairment	1 day	Completed; Full

Study ID; Phase	Location of Study Report	Main Study Objectives	Study Title/Design	Test Product; Dosing Regimen; Route of Administration	Target Study Population	Duration of Treatment	Study Status; Type of Report
CL014_168 Phase 1	5.3.5.4	Thorough QT	A Multiple-Dose, Randomized, Double-Blind, Placebo-Controlled, Active-Comparator, Parallel Study to Investigate the Effect of Avacopan at Therapeutic and Supratherapeutic Doses on the QT/QTc Interval in Healthy Subjects	Cohort 1: Avacopan 30 mg twice daily for 7 days, 100 mg twice daily for 7 days; Cohort 2: Moxifloxacin and placebo; Oral	58 Healthy Subjects (29 in each Cohort)	14 days	Completed; Full
CCX1101 Phase 1	5.3.3.1	Ethno-bridging	A Phase I Clinical Study of CCX168 in Healthy Adult Japanese and Caucasian Male Subjects; Randomized, single-blind, placebo-controlled	Avacopan or placebo; 10, 30, or 100 single dose; 30 or 50 mg twice daily for 7 days; Oral	80 healthy adult Japanese or Caucasian male subjects; 10 subjects per cohort	7 days	Completed; Full
CL002_168 Phase 2	5.3.5.1	Safety and efficacy; pharmacokinetic profile	A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis on Background Cyclophosphamide or Rituximab Treatment	STEP 1, two dose groups Placebo + 60 mg starting dose prednisone once daily Avacopan 30 mg twice daily + 20 mg starting dose prednisone STEP 2, two dose groups Placebo + 60 mg starting dose prednisone once daily Avacopan 30 mg twice daily	67 subjects with ANCA-associated vasculitis	12 weeks	Completed; Full
				STEP 3, three dose groups Placebo + 60 mg starting dose prednisone once daily Avacopan 30 mg twice daily + 20 mg starting dose prednisone once daily Avacopan 30 mg twice daily All subjects received cyclophosphamide or rituximab. 12-week dosing period; 12-week follow-up period; Oral			
CL003_168 Phase 2	5.3.5.1	Safety and tolerability; pharmacokinetic profile	A Randomized, Double-Blind, Placebo-Controlled, Dose Assessment Phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis	Three dose groups: Placebo Avacopan 10 mg twice daily Avacopan 30 mg twice daily All subjects received 60 mg prednisone starting dose once daily + cyclophosphamide or rituximab. 12-week dosing period; 12-week follow-up period; Oral	42 subjects with ANCA-associated vasculitis	12 weeks	Completed; Full

Study ID; Phase	Location of Study Report	Main Study Objectives	Study Title/Design	Test Product; Dosing Regimen; Route of Administration	Target Study Population	Duration of Treatment	Study Status; Type of Report
CL010_168 Phase 3	5.3.5.1	Safety and efficacy; pharmacokinetic profile	A Randomized, Double-Blind, Active-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of CCX168 (Avacopan) in Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Treated Concomitantly with Rituximab or Cyclophosphamide/Azathioprine	Two dose groups: Placebo + 60 mg starting dose prednisone once daily. Avacopan 30 mg twice daily. All subjects received cyclophosphamide or rituximab. 52-week dosing period; 8-week follow-up period Oral	300 subjects with ANCA-associated vasculitis	52 weeks	Completed; Full

2.4.2. Pharmacokinetics

The pharmacokinetic data has been gathered from studies performed in healthy subjects and in the target population. Avacopan is extensively metabolised and the most abundant metabolite in plasma is M1, which showed similar potency against the C5a receptor (C5aR) compared to avacopan. In the mass balance study, avacopan and M1 accounted for 18% and 12% of the total plasma radioactivity, respectively. As the protein binding is high (>99.9%) for both avacopan and M1 (Study PC0632_168), relative contribution to the *in vivo* pharmacological effect of avacopan and M1 is difficult to conclude. Consequently, in terms of guideline requirements, both avacopan and M1 are considered to be major pharmacologically active moieties. Avacopan and metabolite M1 concentrations in human plasma and urine samples were analysed by validated LC-MS/MS methods.

Population PK analysis was based on data obtained from a total of seven clinical studies (Phase 1 studies CCX1101, CL013_168, CL007_168 and CL008_168, Phase 2 studies CL002_168 and CL003_168, and Phase 3 study CL010_168). A total of 368 subjects were included in the model development with 232 subjects with ANCA-associated vasculitis and 136 subjects in the Phase 1 studies.

Two three-compartment models with linear clearance were found to each best describe the PK of avacopan and metabolite M1 in subjects with ANCA-associated vasculitis as well as in healthy subjects in Phase 1 studies treated with avacopan doses up to 100 mg BID. Overall, the population PK model of avacopan included food effect on all absorption parameters, body weight as scaling factor on systemic and peripheral PK parameters, renal and hepatic biomarkers (i.e., eGFR and ALT, respectively) and age on CL/F and serum albumin on Vc/F. In addition, the effects of health status were also evaluated on absorption duration and lag time, and on CL/F and Vc/F. The effect of health status on CL/F and Vc/F was evaluated. The effect of covariates on CL/F and Vc/F are described below. The PK models were used to predict full individual avacopan and M1 concentration-time profiles, which were subsequently used in non-compartmental analysis to derive individual Cmax, AUC and Cavg values.

Absorption

The absolute bioavailability of avacopan is unknown, and it is uncertain whether avacopan is a high or low permeable compound. Regarding solubility, avacopan is practically insoluble (less than 10 µg/mL) across a wide range of conditions (pH 1.1-12.0, SGF and FaSSIF). Consequently, avacopan is formulated in a solubility enhancing formulation (50/50 Cremophor RH40 /PEG-4000 capsule). The final formulation was used in the clinical Phase II (CL002_168; CL003_168) and III (CL010_168) studies in AAV patients. The same formulation was also used in six Phase I studies e.g. CL001_168

FIH; CL007_168 food effect / cardiac safety; CL008_168 drug-drug interaction; CL013_168 hepatic impairment; CCX1101 ethnobridging; CL014_168 thorough QT. Based on the poor solubility, avacopan is a BCS 2 or 4 compound.

Avacopan pharmacokinetics profile is approximately dose linear, with a dose-proportional increase in systemic exposure in the dose range of 10 to 30 mg and a slightly more than dose-proportional increase in the dose range 30 to 100 mg. Across studies performed during fasting conditions, absorption occurred with median Tmax at approximately 2 hours. Administration of a high-fat, high-calorie meal increased avacopan AUC by approximately 70% compared to administration under fasted conditions in study CL007_168. Cmax was more comparable, with only an 8% increase under fed conditions compared to fasted. Tmax was delayed by approximately 3 hours. The AUC of M1 under fed conditions was comparable to when administered under fasted conditions while Cmax was approximately 50 % lower under fed administration relative to fasted. A similar food effect on avacopan PK (fed/fasted AUC ratio 2.1) was also observed in the ethnobridging study (CCX1101) with Japanese subjects given a 30 mg single-dose avacopan with a low fat meal except that T_{max} was delayed to a lesser extent by only 1 hour in the fed state. Metabolite M1 AUC in Study CCX1101 stayed the same in the fed state while its C_{max} decreased about 40%.

The result from the food interaction study CL007_168 is presented below:

Summary of Statistical Comparisons of Plasma avacopan

	Treatment A (Test)		Treatment B (Reference)			Confidence Intervals	
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	90% Confidence	Intra-subject CV%
AUC_{0-t} (ng*hr/mL)	1410.4	16	826.33	16	170.68	151.09 - 192.81	19.77
AUC_{0-inf} (ng*hr/mL)	1646.0	16	959.23	14	171.60	147.12 - 200.15	23.23
C_{max} (ng/mL)	128.1	16	118.6	16	107.98	92.05 - 126.67	26.06
T_{max} (hr)	5.379	16	2.286	16	235.29	208.37 - 262.21	25.79
Treatment A = 30 mg CCX168 (3 x 10 mg capsules) – fed (test) Treatment B = 30 mg CCX168 (3 x 10 mg capsules) – fasted (reference)							

Summary of Statistical Comparisons of Plasma M1

	Treatment A (Test)		Treatment B (Reference)			Confidence Intervals	
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	90% Confidence	Intra-subject CV%
AUC_{0-t} (ng*hr/mL)	513.29	16	588.95	16	87.15	83.10 - 91.40	7.65
AUC_{0-inf} (ng*hr/mL)	609.74	16	683.11	16	89.26	85.66 - 93.00	6.61
C_{max} (ng/mL)	20.33	16	41.37	16	49.15	44.81 - 53.91	14.94
T_{max} (hr)	6.410	16	2.880	16	222.54	191.70 - 253.37	30.70
Treatment A = 30 mg CCX168 (3 x 10 mg capsules) – fed (test). Treatment B = 30 mg CCX168 (3 x 10 mg capsules) – fasted (reference).							

Distribution

Mean V_z/F was in the range of 3,000 to 11,000 L following a single oral dose of 30 mg avacopan in healthy subjects in Studies CL001_168, CCX1101, CL007_168 and CL013_168. Both avacopan and M1 were protein bound at >99.9% in plasma over the concentration range of 2.5 – 50 µM. Avacopan steady state Cmax at the proposed clinical dose is approximately 0.3 µM. Based on both *in vivo* and *in*

vitro data, blood-to-plasma ratios were less than 1, suggesting that both compounds have limited penetration into red blood cells.

Elimination

Liver metabolism, followed by biliary and renal excretion of the metabolites, is the primary route of elimination for the absorbed avacopan, while biliary and renal excretion of the unchanged parent drug plays a negligible role. The results from the mass balance study indicate that avacopan was the primary component present in plasma, accounting for approximately 18% of the total radioactivity. There was one major metabolite in plasma, M1, which accounted for approximately 12% of the dose. The metabolic pathway responsible for conversion of avacopan into M1 was studied using human liver microsomes and was found to be mainly mediated by CYP3A4 and to a lesser degree by CYP2C19 and CYP2D6. In healthy subjects, the steady state was achieved after approximately 5 days of twice daily dosing. The ratio of steady state AUC0-τ vs single-dose AUCinf is in the range of 1.5 – 2.2, suggesting a modest degree of time-dependent PK.

According to population PK analysis the typical apparent oral clearance (CL/F) of avacopan is 13.1 - 21.1 L/h at the therapeutic dose of 30 mg b.i.d. The median terminal elimination half-life of avacopan is 21 days. In ANCA-associated vasculitis subjects receiving twice daily 30 mg avacopan for 52 weeks (CL010_168), steady-state trough plasma concentrations of avacopan and metabolite M1 appear to be reached by Week 13.

Based on the ADME study, approximately 87% of the radioactive dose was recovered in the excreta within 14 days, with faeces as the primary route of elimination, accounting for 77% of the dose, and urine as the secondary route, accounting for 9.5% of the dose. In faeces, unchanged avacopan accounted for approximately 7% of total radioactivity. The remainder of the dose was excreted as metabolites, with M1 as the most abundant metabolite in faeces, accounting for approximately 7% of the dose. Approximately 0.02% of the dose was excreted unchanged in urine. Several metabolites were detected in urine, but none accounted for more than 3% of the total dose.

Special populations

Regarding renally impaired patients, the applicant has not performed a dedicated renal impairment study. The applicant refers to the mass balance study where approximately 0.02% of the dose was excreted unchanged in urine. The effect of renal impairment was evaluated in the population PK analysis where 237 patients with renal impairment, over the range of mild to severe impairment, were included. Based on the population PK analysis results, avacopan CL/F decreased modestly with moderate renal impairment (RI) and moderately with severe renal impairment: Subjects with moderate RI (eGFR of 30-60 mL/min/1.73 m^2) and severe RI (eGFR of 15-30 mL/min/1.73 m^2) are expected to have 33%-15% and 47%-33% lower CL/F values a typical subject with eGFR of 94 mL/min/1.73 m^2. Based on the estimate of eGFR effect on CL/F of M1, moderate (eGFR=30-60 ml/min/1.73 m^2) and severe (eGFR=15-30 ml/min/1.73 m^2) renal impairment would decrease the clearance of M1 by 10-24% and 24-35%, respectively.

In a study in subjects with hepatic impairment there was only a minor effect on *total* concentrations of avacopan and M1 in subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. The effect on *unbound* concentrations could not be evaluated due to the very high plasma protein binding. Subjects with severe hepatic impairment were not included in the study.

No clinically relevant effects on avacopan PK due to gender, race, old age or weight are expected.

Pharmacokinetic interaction studies

The *in vitro* results indicate that CYP3A4 metabolism is an important elimination pathway. This was confirmed *in vivo* in study CL008_168 where co-administration of the strong CYP3A4 inhibitor itraconazole resulted in a 2-fold increase in avacopan AUC. *In vivo*, upon co-administration with multiple doses of rifampicin (enzyme inducer), avacopan AUC and Cmax were significantly reduced. Avacopan AUC decreased by 93% and Cmax by 79% respectively.

The *in vitro* results indicate a possible CYP3A4 time dependent inhibition. No induction is seen for 1A2 and 2B6 in the relevant concentration range of avacopan. For 3A4 borderline induction is seen in the concentration range relevant for induction of systemically expressed enzymes (up to 0.2 µM) and inconclusive results at concentrations relevant for intestinal. The net effect is described *in vivo* where avacopan was administered concomitantly with a CYP3A4 substrate (midazolam). Avacopan increased midazolam AUC approximately 1.8-fold which suggests that avacopan is a weak inhibitor of CYP3A4 *in vivo*. An *in vivo* study has been performed where avacopan was administered concomitantly with a CYP2C9 substrate (celecoxib). The effect of avacopan on celecoxib was small and mainly related to Cmax. The CYP2C9 inhibitory potential of avacopan is thus considered to be minor. Further, the celecoxib *in vivo* interaction study showing no effect supports that avacopan is not a PXR-inducer *in vivo*.

On the transporter side, avacopan showed negligible to weak inhibition of P-gp, BCRP, OATP1B3, OAT3, OCT2, MATE1, MATE2-K, OATP1B1 and OAT1 *in vitro*. Furthermore, avacopan was not a substrate of OATP1B1, OATP1B3, P-gp or BCRP *in vitro. In vitro*, M1 did not inhibit the transporters P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K. Based on *in vitro* data M1 might be a substrate of P-gp. M1 was not a substrate of OATP1B1, OATP1B3 or BCRP *in vitro*.

Pharmacokinetics using human biomaterials

Not applicable.

2.4.3. Pharmacodynamics

The primary PD effects of avacopan were investigated in the Studies CL001_168 and CL002_168. The cardiodynamic effects of avacopan were surveyed in the Study CL007_168 and Study CL014_168.

Mechanism of action

Avacopan selectively inhibits the binding of complement 5a (C5a) to the C5a receptor (C5aR, also called CD88); C5a is a terminal component of the complement cascade. Based on literature data, C5a and its receptor C5aR has a central role in the pathogenesis of ANCA-associated vasculitis; C5a primes neutrophils and enhances ANCA-induced neutrophil activation. Neutrophils activate the alternative complement pathway through endogenous properdin secretion and neutrophils also release C5a when stimulated by inflammatory cytokines such as tumour necrosis factor α. The C5a, acting on C5aR, is a potent neutrophil chemoattractant and agonist, which triggers homotypic neutrophil aggregation via interactions of the tumour necrosis factor activated αMβ2 (Mac-1)-integrins with intercellular adhesion molecule-3 or inactivated complement fragment 3b on bystander neutrophils. Deformability is important for non-activated neutrophils for unperturbed movement through small blood vessels such as in the glomeruli. The C5a decreases neutrophil deformability, particularly in the presence of ANCA. ANCA bound to endothelial-adherent neutrophils activate the classical complement pathway. Lastly, C5a activates endothelial cells, promoting retraction and increased permeability.

Murine models have shown that alternative complement pathway activation is critical to development of MPO ANCA-induced glomerulonephritis. Anti-C5 treatment can prevent this glomerulonephritis, as can depletion of complement using cobra venom factor. Furthermore, complement factor B (an essential factor for alternative pathway activation) knockout mice are protected against development of ANCA-induced glomerulonephritis. Importantly, blocking the C5aR with avacopan prevents the development of ANCA-induced glomerulonephritis in the anti-MPO murine model.

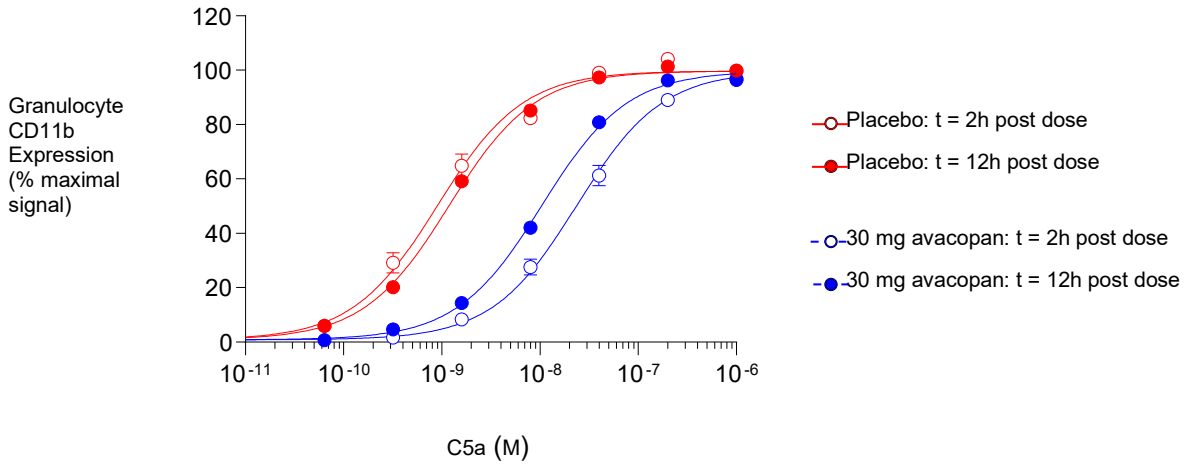
The applicant claimed that plasma C5a was significantly higher in patients with active ANCA vasculitis compared with patients in remission, as described in the literature. The C5a was increased in the plasma and urine of patients with active ANCA vasculitis in another study.

Primary and Secondary pharmacology

Phase I study CL001_168 was a randomised, double-blind, placebo-controlled, two-period study in which 48 subjects received either avacopan or placebo (3:1 ratio) as a single dose and as multiple once daily or twice daily doses. In Period 1, single doses of 1, 3, 10, 30, and 100 mg avacopan were studied; 6 subjects in each dose cohort received avacopan and 2 received placebo, except in cohort 1 in which 5 subjects received avacopan and 3 received placebo. In Period 2, avacopan doses of 1, 3, and 10 mg once daily for 7 days, and 30 and 50 mg twice daily for 7 days, were studied. The effect of avacopan on neutrophil migration and C5a-induced CD11b upregulation was studied. Two functional assays were developed and tested on blood samples. Specifically, blood samples were collected from subjects in the 10, 30, and 100 mg dose cohorts from the single-dose period, and the 30 mg BID dose cohort from the multi-dose period. The relationship between the avacopan plasma concentration and the inhibition of C5aR-dependent upregulation of the integrin CD11b in peripheral blood neutrophils and inhibition of C5aR-dependent neutrophil chemotaxis was determined.

Blood neutrophils from avacopan-treated, but not placebo-treated, subjects were impaired in their ability to functionally respond to exogenously added recombinant C5a, indicating that avacopan effectively blocked C5aR in the treated subjects. The level of blockade correlated strongly with avacopan plasma concentrations. The 30 mg BID dose of avacopan resulted in extended (>12 hour) inhibition of C5aR, indicating that 30 mg BID dose regimen provides around-the-clock coverage of the C5aR, see figure below. Inhibition of C5a-mediated migration of neutrophils in blood taken from these subjects was also observed. Therefore, 30 mg avacopan BID was selected as the dose regimen subsequent clinical trials in patients with ANCA-associated vasculitis.

Inhibition of C5a Receptor in Neutrophils from Subjects treated with Avacopan vs Placebo (Study CL001_168)



The placebo group (in red solid line) showed no shift in the C5a concentration vs. granulocyte CD11b expression curve, whereas the avacopan 30 mg BID group (in blue dashed line) showed a >10-fold shift in the curve at both the 2-hour and 12-hour (trough level) time points.

When investigating secondary pharmacology in the phase I studies Study CL001_168, a slight decrease in mean WBC and neutrophil count was observed more frequently in subjects receiving CCX168 compared to placebo. Adverse events of white blood cell decreased occurred only in the avacopan group. Low White Blood Cell Counts were observed also in the phase II and phase III studies and will be discussed in the Clinical Safety section.

Effect on complement: In phase II study CL002_168, in addition to the samples from treated vasculitis patients, plasma samples (matched for age, gender, and ethnic background) were collected from healthy subjects for use as a control group. The following was measured: Bb, C3a, C5a, sC5b-9 and Properdin. Patients with active AAV (n=66) had higher baseline levels of complement activation products in circulation than healthy controls (n=20). The levels of Bb, C3a and C5a were significantly reduced in patients treated with standard of care but did not return to healthy control levels for C3a and C5a. Decreases were also observed in the group treated with avacopan with low dose prednisone. No changes, considered as statistically significant, occurred in the five complement fragments in avacopan only treated patients. The outcome for plasma sC5b-9 levels (at baseline as compared to healthy controls and during treatment) are provided in the tables below.

Plasma Soluble C5b-9 Levels at Baseline in Subjects with AAV and Healthy Controls

Subjects	Healthy Controls	AAV-All Subjects	AAV-MPO ANCA Positive	AAV-PR3 ANCA Positive
N=	20	66	37	29
GeoMean (ng/mL)	155	241***	243	239
95% CI Lower	136	222	220	207
95% CI Upper	178	262	269	276

Note: Compared to healthy controls: ***p<0.001. No difference between MPO and PR3 positive subjects.

Plasma Soluble C5b-9 Levels in Subjects with AAV at Baseline and During the 12-Week Treatment Period and in Healthy Controls

Plasma sC5b-9 ng/mL												
Time Points	Placebo + FD Prednisone				Avacopan + LD Prednisone				Avacopan + No Prednisone			
	N=	Geo mean	95% CI		N=	Geo mean	95% CI		N=	Geo mean	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper
Pre dose	22	273	238	313	21	225	195	260	22	233	200	271
6 hours	22	262	231	297	19	201	174	232	20	226	194	262
Day 8	21	250	217	289	21	207	175	244	22	215	183	254
Day 29	20	260	223	305	21	205	168	251	20	203	172	239
Day 85	19	255	220	295	20	178	149	213	20	207	170	253

Concentration QT: These relationships were evaluated in studies CL007_168 and CL014_168. Time-matched plasma concentrations of avacopan and metabolite M1, and heart rate assessments were

used in both analyses. Both studies covered the expected therapeutic concentration range. In study CL014_168 the preferred Fridericia's correction factor (correction factor 1/3), ΔQTcF, was used in the analysis, whereas in study CL007_168 an individual correction factor (mean correction factor 0.34), ΔQTcI, was used. Nonetheless, in both studies no apparent trends towards QT prolongation with increased plasma avacopan or M1 plasma concentrations were detected.

The risk of drug-drug interactions between avacopan and other concurrent medications in the intended patient population is considered to be low based on a series of biochemical studies conducted *in vitro*; these studies included assessment of serum protein binding, red blood cell partitioning, hepatocyte metabolism, cytochrome (CYP) inhibition and induction, effects of avacopan on cyclophosphamide metabolic activation, prednisone metabolism, and Caco-2 monolayer permeability.

2.4.4. Discussion on clinical pharmacology

A population PK analysis was performed with a pooled dataset of phase 1, 2 and 3 studies. Due to model complexity, parent compound (avacopan) and the major metabolite (M1) were modelled separately and previously developed structural models were used as the basis for the present model development. Overall, the three-compartment structural models described avacopan and M1 data sufficiently well. The covariate selection was based on visual screening as well as clinical and scientific plausibility. Covariates that were selected to be included in the model was judged statistically significant if the confidence interval for the covariate effect did not include null. The covariate modelling methodology, also called the full covariate approach, is accepted. Avacopan is chiral and has two chiral centres and the applicant has performed analysis of some plasma samples in study CL014_168 using a chiral liquid chromatography with tandem mass spectrometry method and the chiral analysis only detected avacopan and not the enantiomer or any of the diastereomers and suggests no inter-conversion *in vivo*.

The absorption, distribution and elimination characteristics of avacopan and M1 have been sufficiently described.

The applicant did not perform a dedicated renal impairment study, but the effect of renal impairment was evaluated in the population PK analysis which is considered acceptable since 237 patients with renal impairment, over the range of mild to severe impairment, were included in the analysis dataset. The

population PK analysis detected a maximum 47% decrease in avacopan CL/F and 35% decrease in metabolite M1 CL/F due to renal impairment. Thus, the increase in exposure due to renal impairment is not substantial and supports the conclusion that no dose adjustment based on renal function is warranted, as reflected in the SmPC.

Since avacopan is primarily cleared through hepatic metabolism, a hepatic impairment study has been performed. The applicant has presented individual Child Pugh scores for subjects with mild and moderate hepatic impairment and the individuals included in the study are not fully representative of the moderate Child Pugh class and the effect on avacopan could be underestimated in subjects with moderate HI that have effects on albumin, bilirubin and prothrombin time. However, three subjects in the moderate HI group had impairment in serum bilirubin or serum albumin and the plasma exposure were not higher than the healthy control group. This supports that no dose adjustment is necessary in patients with mild and moderate Child-Pugh and the proposed SmPC wording is acceptable.

The *in vitro* results indicate that CYP3A4 metabolism is an important elimination pathway. This was confirmed in study CL008_168 where co-administration of the strong CYP3A4 inhibitor itraconazole resulted in a 2-fold increase in avacopan AUC, which is considered acceptable. Co-administration with

strong CYP3A4 inhibitors is advised to be used with caution. The applicant also discussed non-clinical safety data from the thorough QT-study CL014_168 and exposure-safety data. Taken all together, a doubling of the plasma exposure could be accepted by the CHMP. The suggested SmPC text with the advice of caution and monitoring for potential increase of side effects when concomitant administration of strong CYP3A4 inhibitors is supported.

In vivo, upon co-administration with multiple doses of rifampicin (enzyme inducer), avacopan AUC and Cmax were significantly reduced. Avacopan AUC decreased by 93% and Cmax by 79% respectively. These results indicate that avacopan is strongly affected by enzyme inducers and co-administration of strong CYP3A4 inducers with avacopan should be avoided according to the SmPC which is acceptable.

Avacopan increased midazolam AUC with approx. 81% which suggests that avacopan is a weak inhibitor of CYP3A4 *in vivo*. Nevertheless, avacopan may have clinically relevant effects on CYP3A4 substrates with narrow therapeutic index (e.g. alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus and tacrolimus). Information regarding this risk is appropriately included in section 4.5 of the SmPC.

Literature data indicate that the excipient Cremophor RH40 could inhibit P-gp and literature reports that Cremophor RH40 increased digoxin systemic exposure *in vivo* in humans after an oral dose. The currently observed increase in digoxin exposure of about 22% might not be clinically relevant, but at the same time it is indicative of P-gp inhibition in the intestine, which could be even more pronounced for other P-gp substrates with lower oral bioavailability. A clinically relevant effect of Cremophor RH40 on sensitive P-gp substrates with relatively low bioavailability cannot be excluded. Information regarding the risk of interaction between Cremophor RH40 and sensitive P-gp substrates is included in section 4.5 in the SmPC.

The results of the studies assessing the primary PD effect of avacopan support the proposed hypothesis of mechanism of action, selective inhibition of the binding of complement 5a (C5a) to the C5a receptor. It was shown in the Study CL001_168, that the ability of the neutrophils to functionally respond C5a-induced activation is impaired with simultaneous administration of avacopan. This response was measured by the inhibition of the upregulation of CD11b by the neutrophils. The response correlated with the avacopan plasma concentrations. The results of the second assay investigating the chemotaxis of neutrophils were also supportive indicating trend towards decreased chemotaxis of neutrophils.

The phase 2 study CL003_168 and the phase 3 study CL10_168 included collection of PD markers. Reports of PD markers from these studies are not included in the submission. The PD reports of these studies will be submitted as a post-approval measure.

In both, the healthy controls and in subjects with AAV, avacopan was associated with a decrease in WBC, as discussed in the section on Clinical Safety. Concentration-QTc relationships were evaluated on study CL007_168 and CL014_007 data. Both avacopan and M1 plasma concentrations were included in the evaluations and no statistically significant relationship between plasma concentration and QT prolongation was detected.

Overall, the available pharmacology data are considered adequately described in the SmPC**.**

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology testing concerning PK, PD effects of avacopan is sufficient and results are adequately reflected in the product information. The CHMP considers that the following measure is necessary to address the issues related to pharmacology:

- The phase 2 study CL003_168 and the phase 3 study CL10_168 included collection of PD markers. Reports of PD markers from these studies should be submitted to the CHMP in the post-authorisation phase.

2.5. Clinical efficacy

Summary of Completed Avacopan Clinical Efficacy and Safety Studies in ANCA-Associated Vasculitis

Study Phase	**Study Sites/ Location**	**Study Start/End Enrolment**	**Design Type**	**Study Drug Regimen**	**Subjects Entered /Completed (by Study Arm)**	**Duration**	**Gender Median Age (range)**	**Diagnostic Inclusion Criteria**	**Primary Objectives/ Endpoints**
CL010_168 Phase 3	239 sites; 143 sites enrolled subjects in North America, Europe, Australia, New Zealand, and Japan	15-Mar-2017 to 01-Nov-2019 331 subjects enrolled	Randomised, double-blind, double-dummy, active-controlled	Avacopan and matching placebo: 30 mg avacopan twice daily, orally Prednisone and prednisone-matching placebo: 60 mg prednisone once daily, tapered to 0 by Week 21	Entered Control:165 Avacopan:166 Completed Control: 150 Avacopan: 151	52 weeks of treatment; 8 weeks of follow-up	187 males/ 144 females aged 64.0 (13 to 88) years	GPA, MPA	Safety and tolerability: AE incidence Efficacy: BVAS remission at Week 26; sustained remission to Week 52
CL003_168 Phase 2	47 sites in the USA and Canada	04-Feb-2015 to 19-Jul-2016 42 subjects enrolled	Randomised, double-blind, placebo-controlled	Avacopan and matching placebo: 10 mg or 30 mg avacopan twice daily, orally Prednisone and matching placebo: all groups: 60 mg prednisone once daily, tapered to 0 by Week 21	Entered Control: 13 10 mg avacopan: 13 30 mg avacopan: 16 Completed Control: 13 10 mg avacopan: 12 30 mg avacopan: 15	12 weeks of treatment 12 weeks of follow-up	19 males/ 23 females aged 58.5 (26 to 83) years	GPA, MPA, or renal limited vasculitis	Safety and tolerability: AE incidence Efficacy: BVAS response at Week 12
CL002_168 Phase 2	60 sites in Austria, Belgium, the Czech Republic, Hungary, France, Germany, Ireland, the Netherlands, Poland, Sweden, and the United Kingdom	27-Sep-2011 to 18-Jan-2016 67 subjects enrolled	Randomised, double-blind, double-dummy, placebo-controlled	Avacopan and matching placebo: 30 mg avacopan twice daily, orally Prednisone and matching placebo: 60 mg prednisone once daily, tapered to 0 by Week 21	Entered Control: 23 Avacopan+low-dose prednisone: 22 Avacopan alone: 22 Completed Control: 18 Avacopan+low-dose prednisone: 19 Avacopan alone: 18	12 weeks of treatment 12 weeks of follow-up	47 males/ 20 females aged 59.3 (20 to 82) years	GPA, MPA, or renal limited vasculitis	Efficacy: BVAS response at Week 12 Safety and tolerability: AE incidence

2.5.1. Dose response study

No formal dose-finding studies have been conducted. The avacopan dosing of 30 mg twice a day used in the phase 2 studies is based on the PD results of the study CL001_168 in healthy subjects. A dose of 50 mg b.i.d. for 7 days was also used in study CL001_168, but PD assessment was conducted neither for that higher dose nor for subjects with AAV. However, since the findings of study CL001_168 support the chosen dose, the lack of specific dose-finding studies can be accepted.

2.5.2. Main studies

One Phase 3 clinical trial (CL010_168, ADVOCATE) has been conducted and is considered the pivotal study. Two Phase 2 clinical trials (CL002_168 and CL003_168) were conducted evaluating the efficacy and safety of avacopan for AAV.

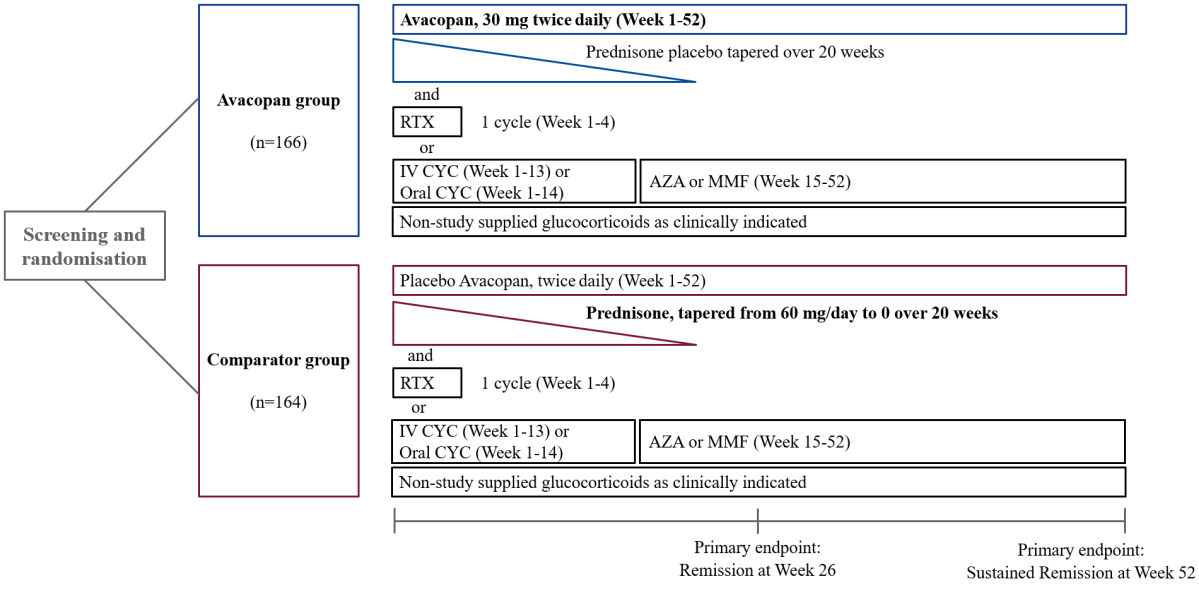
Main study

Study CL010_168: A Randomized, Double-Blind, Active-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of CCX168 (avacopan) in Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Treated Concomitantly with Rituximab or Cyclophosphamide/Azathioprine

Methods

Study CL010_168 was a prospective, randomised, double-blind, double-dummy, active-controlled clinical study assessed the efficacy, safety, and tolerability of avacopan in subjects with newly-diagnosed or relapsing active ANCA-associated vasculitis when administered against a standard background cyclophosphamide or rituximab regimen. The study treatment period was 52 weeks with an 8-week follow-up period. Av overview of the study design is shown below.

Design of Pivotal Phase 3 Study CL010_168



a. AZA = azathioprine; CYC = cyclophosphamide; IV = intravenous; MMF = mycophenolate mofetil; RTX =rituximab

Study Participants

Key inclusion criteria were:

1. Had a clinical diagnosis of GPA (Wegener's) or MPA, consistent with Chapel-Hill Consensus Conference definitions;
2. Aged at least 18 years, with newly-diagnosed or relapsed ANCA-associated vasculitis where treatment with cyclophosphamide or rituximab was needed; where approved, adolescents (12 to 17 years old) may have been enrolled.
3. Tested positive for anti-PR3 or anti-MPO (current or historic) antibodies;
4. Had at least one major item, or at least three minor items, or at least the two renal items of proteinuria and haematuria in the BVAS;
5. Had an eGFR ≥15 mL/minute/1.73 m^2 (using the Modification of Diet in Renal Disease [MDRD] method for adults, and modified Schwartz equation for adolescents) at screening.

Among key exclusion criteria were:

1. Alveolar haemorrhage requiring invasive pulmonary ventilation support anticipated to last beyond the screening period of the study
2. Other known multi-system autoimmune disease including eosinophilic granulomatosis with polyangiitis (Churg-Strauss), systemic lupus erythematosus, immunoglobulin (Ig)A vasculitis (Henoch-Schönlein), rheumatoid vasculitis, Sjögren's syndrome, anti-glomerular basement membrane disease (GBM), or cryoglobulinaemic vasculitis;
3. Required dialysis or plasma exchange within 12 weeks prior to screening;
4. Had been taking an oral daily dose of a glucocorticoid of more than 10 mg prednisone-equivalent for more than 6 weeks continuously prior to the screening visit.

Treatments

Prior to randomisation, subjects were stratified based on standard background treatment (intravenous [IV] cyclophosphamide, oral cyclophosphamide, or IV rituximab), ANCA positivity status, and ANCA-associated vasculitis disease status (newly diagnosed or relapsed disease).

Following stratification, subjects were subsequently randomised using the stratification factors, in a 1:1 ratio to one of two study treatments: avacopan or placebo. Adult subjects were to receive 30 mg avacopan or matching placebo twice per day (BID). For subjects who were 12 to 17 years old, initial avacopan or placebo doses were selected based on body weight and further refined based on avacopan plasma exposure.

Group A (comparator group):

- Avacopan-matching placebo (3 tablets) twice daily orally for 52 weeks (364 days)
- Oral prednisone tapering regimen over 20 weeks (140 days)

The prednisone tapering schedule is presented below.

The Prednisone/Matching Placebo Dose Schedule in Study CL010_168

Study Day	Avacopan	Prednisone			
		Adults		Adolescents	
		≥55 kg	<55 kg	>37 kg	≤37 kg
Daily Prednisone Dose					
Day 1 to 7	0	60 mg	45 mg	45 mg	30 mg
Day 8 to 14	0	45 mg	45 mg	45 mg	30 mg
Day 15 to 21	0	30 mg	30 mg	30 mg	30 mg
Day 22 to 42	0	25 mg	25 mg	25 mg	25 mg
Day 43 to 56	0	20 mg	20 mg	20 mg	20 mg
Day 57 to 70	0	15 mg	15 mg	15 mg	15 mg
Day 71 to 98	0	10 mg	10 mg	10 mg	10 mg
Day 99 to 140	0	5 mg	5 mg	5 mg	5 mg
≥ Day 141	0	0	0	0	0

Group B (avacopan group):

- Avacopan 30 mg (three 10 mg tablets) twice daily orally for 52 weeks (364 days)
- Oral prednisone-matching placebo tapering regimen over 20 weeks (140 days)

Subjects in both Groups A and B also received either IV or oral cyclophosphamide followed by oral azathioprine, or IV rituximab, as follows:

- IV cyclophosphamide 15 mg/kg IV up to 1.2 g maximum was given on Day 1 and also at the Week 2, 4, 7, 10, and 13 study visits.
- Oral cyclophosphamide 2 mg/kg/day (maximum 200 mg/day) was given orally starting on Day 1 and continuing up to the day before Week 15.
- Oral and IV cyclophosphamide dose was adjusted based on the subject's age, eGFR, and WBC count according to protocol-specified criteria
  Note: For subjects in either the oral or IV cyclophosphamide stratum, starting at Week 15, all received oral azathioprine at a starting dose of 1 mg/kg/day, with titration up to a target dose of 2 mg/kg/day at 2 weeks. If azathioprine was not tolerated, mycophenolate mofetil at a target dose of 2 g/day may have been given. If mycophenolate mofetil was not tolerated or not available, enteric coated mycophenolate sodium may have been given at a target dose of 1440 mg/day.
- IV rituximab on Day 1, and then Weeks 1, 2, and 3 at a dose of 375 mg/m2 at each visit for a total of 4 weekly infusions
    - Glucocorticoid pre-medication for the rituximab IV infusions was allowed.

Prior glucocorticoid use of up to 3 g methylprednisolone equivalent IV within the 4 weeks before screening or 10 mg prednisone-equivalent per day oral for not more than 6 continuous weeks was allowed Per Protocol (PP). During the screening period (of up to 14 days), IV glucocorticoids were allowed as long as the cumulative dose did not exceed 3 g methylprednisolone equivalent for both the screening and pre-screening periods. If a subject received oral glucocorticoids during the screening period, the dose needed to be tapered to ≤20 mg prednisone equivalent by Day 1 of the study.

During the treatment period, subjects receiving ≤20 mg prednisone equivalent on Day 1, were tapered to no glucocorticoid use over a 4-week period. In cases of adrenal insufficiency, a prednisone

equivalent dose of ≤10 mg per day could be used. Subjects who experienced relapse during the study could receive IV glucocorticoids (typically 0.5 to 1 g methylprednisolone per day over 3 days) and/or oral glucocorticoids, tapered according to the subject's condition. Glucocorticoid pre-medication for rituximab infusion, typically 100 mg methylprednisolone equivalent IV, was permitted. Subjects who experienced worsening disease during the study that involved a major BVAS item could be treated with IV glucocorticoids (typically 0.5 to 1 g methylprednisolone per day for 3 days) and/or oral glucocorticoids, tapered according to their condition. Worsening of disease not involving a major BVAS item could be treated with a short (≤2 weeks) burst of oral glucocorticoids at a maximum dose of 20 mg prednisone equivalent. Any glucocorticoid use was recorded in the case report form.

Objectives

The primary objective was to evaluate the efficacy of avacopan to induce and sustain remission in subjects with active ANCA-associated vasculitis, when used with cyclophosphamide followed by azathioprine, or with rituximab (non-inferiority vs prednisone).

Outcomes/endpoints

The primary efficacy endpoints were as follows:

1. The proportion of subjects achieving disease remission at Week 26.
   Disease remission at Week 26 was defined as:
    a. Achieving a BVAS of 0 as determined by the Adjudication Committee (AC);
    b. No administration of glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to Week 26;
    c. No BVAS >0 during the 4 weeks prior to Week 26 (if collected for an unscheduled assessment).
2. The proportion of subjects achieving sustained disease remission at Week 52.
   Sustained remission at Week 52 was defined as:
    a. Disease remission at Week 26 as defined above;
    b. Disease remission at Week 52 defined as a BVAS of 0 at Week 52 as determined by the AC and no administration of glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to Week 52;
    c. No disease relapse between Week 26 and Week 52 as determined by the AC.

Please refer to the statistical section for further details on the testing strategy.

Birmingham Vasculitis Activity Score (BVAS) version 3 was used for evaluation of activity of systemic vasculitis for definition of remission, sustained remission, and relapse.

The BVAS has been previously validated. There are 9 organ systems, plus an "Other" category in the BVAS, each of which is given a numerical value according to its perceived clinical relevance as decided by expert consensus. Only symptoms/signs ascribed to the presence of active AAV (GPA or MPA) were to be reported in the standardised form.

One modification was made to the BVAS version 3 for the purpose of this study: For the Week 4 BVAS assessment, disease activity present within the 7 days, instead of 28 days, prior to the visit was to be

recorded. This was done to avoid inclusion of the baseline visit (which could have occurred within the prior 28 days) from the BVAS assessment at Week 4. The "persistent" disease aspect of the BVAS version 3 was not used, since for the purpose of this study, only the presence or absence of disease activity was assessed. The calculation of BVAS was be performed programmatically. A total score was calculated from the individual organ system scores as described below.

BVAS Organ Systems, Individual Items and Scoring

BVAS Items and Calculations	
Target Item	**Description**
General subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 3 (max score is 3 regardless if sum is above): Myalgia (1), Arthralgia or arthritis (1), Fever >= 38 (2), Weight loss >=2 kg (2)
Cutaneous subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 6 (max score is 6 regardless if sum is above): Infarct (2), Purpura (2), Ulcer (4), ***Gangrene*** (6), Other skin vasculitis (2)
Mucous membranes/eyes subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 6 (max score is 6 regardless if sum is above): Mouth ulcers / granulomata (2), Genital ulcers (1), Adnexal inflammation (4), Significant proptosis (4), ***Scleritis / Episcleritis*** (2), Conjunctivitis / Blepharitis / Keratitis (1), Blurred vision (3), Sudden visual loss (6), Uveitis (6), ***Retinal changes*** (6)
ENT subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 6 (max score is 6 regardless if sum is above): Bloody nasal discharge / crusts / ulcers / granulomata (4), Paranasal sinus involvement (2), Subglottic stenosis (6), Conductive hearing loss (3), ***Sensorineural hearing loss*** (6)
Chest subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 6 (max score is 6 regardless if sum is above): Wheeze (2), Nodules or cavities (3), Pleural effusion / pleurisy (4), Infiltrate (4), Endobronchial involvement (4), ***Massive haemoptysis / alveolar haemorrhage*** (6), ***Respiratory failure*** (6)
Cardiovascular subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 6 (max score is 6 regardless if sum is above): Loss of pulses (4), Valvular heart disease (4), Pericarditis (3), Ischaemic cardiac pain (4), Cardiomyopathy (6), Congestive cardiac failure (6)
Abdominal subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 9 (max score is 9 regardless if sum is above): Peritonitis (9), Bloody diarrhoea (9), ***Ischaemic abdominal pain*** (6)
Renal subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 12 (max score is 12 regardless if sum is above): Hypertension (4), Proteinuria (4), Haematuria (6), Serum creatinine 125-249 (4), Serum creatinine 250-499 (6), Serum creatinine >=500 (8), ***Rise in serum creatinine >30% or fall in creatinine clearance >25%*** (6)
Nervous system subscore	The following items receive the respective scores provided and the score is the sum of these values but cannot exceed 9 (max score is 9 regardless if sum is above): Headache (1), ***Meningitis*** (3), Organic confusion (3), Seizures (9), ***Cerebrovascular accident*** (9), ***Spinal cord lesion*** (9), ***Cranial nerve palsy*** (6), ***Sensory peripheral neuropathy*** (6), ***Mononeuritis multiplex*** (9)
Other	If RBC casts and/or glomerulonephritis is checked, it should be added to the Renal Organ System with a Score of 6. Haematuria is also in the Renal organ system (also given a score of 6). Only one or the other should be included in the Renal System. If additional Other Items are checked the applicable organ system and whether the item is major or minor is indicated. Minor items are given an score of 2 and Major items are given a Score of 4. The maximum score within an organ system is still applicable.
Total BVAS Score	Sum of all individual scores described above (General + Cutaneous + Mucous membranes / eyes + ENT + Chest + Cardiovascular + Abdominal + Renal + Nervous System)
Note: Major items are indicated in ***bold italics***.	

Secondary efficacy endpoints were as follows (not controlled for type 1 error):

1. Glucocorticoid-induced toxicity as measured by change from baseline over the first 26 weeks in the glucocorticoid toxicity index;
2. BVAS of 0 at Week 4, regardless of whether the subjects received glucocorticoids during this period of time and based on assessment by the blinded AC;
3. Change from baseline over 52 weeks in health-related quality of life as measured by the domains and component scores of the SF-36v2 and EQ-5D-5L Visual Analogue Scale (VAS) and index;

4. Proportion of subjects and time to experiencing a relapse after previously achieving remission at Week 26 in the study; relapse was defined as occurrence of at least one major item in the BVAS, or three or more minor items in the BVAS, or one or two minor items in the BVAS recorded at two consecutive visits, after having achieved remission at Week 26 (BVAS = 0 and no glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks) in the study;
5. In subjects with renal disease at baseline (based in the BVAS renal component), the change in eGFR from baseline over 52 weeks;
6. In subjects with renal disease at baseline (based in the BVAS renal component), the percent change in urinary albumin:creatinine ratio (UACR) from baseline over 52 weeks;
7. In subjects with renal disease at baseline (based in the BVAS renal component), the percent change in urinary monocyte chemoattractant protein 1 (MCP-1):creatinine ratio from baseline over 52 weeks;
8. Change in the Vasculitis Damage Index (VDI) from baseline over 52 weeks, including the Week 26 and Week 52 time points.

Sample size

The proportion of subjects in the prednisone group achieving clinical remission at Week 26 was estimated to be ~60%, a blended proportion of 64% and 53% observed in the rituximab and cyclophosphamide/azathioprine groups, respectively, in the largest prior registration study in ANCA-associated vasculitis. A non-inferiority margin of -20 percentage points was derived for the difference between avacopan and prednisone groups, and a one-sided alpha level of 0.025. This non-inferiority margin was based on a thorough review and meta-analysis of all previous clinical studies conducted in subjects with ANCA-associated vasculitis, as well as precedent. A sample size of 150 subjects per group (300 in total) was estimated to provide more than 90% power for the non-inferiority test. This sample size provided 90% power to detect approximately 18% superiority in the proportion of subjects achieving clinical remission at Week 26 if the control group remission rate was 60%. The proportion of subjects in the prednisone group with sustained remission at Week 52 was estimated to be ~45%, a blended proportion observed in a prior study comparing rituximab and cyclophosphamide/azathioprine in ANCA-associated vasculitis (Specks et al, 2013). A sample size of 150 subjects per group (300 in total) was estimated to provide 85% power to detect approximately 18% superiority if the control group sustained remission rate at Week 52 was 45%.

Randomisation

Randomisation was performed centrally via an IRT system and minimisation algorithm, using the stratification factors: 1) IV rituximab, IV cyclophosphamide, or oral cyclophosphamide use (selection of treatment at the discretion of the Investigator prior to randomisation); 2) anti-PR3 or anti-MPO ANCA-associated vasculitis, and 3) newly-diagnosed or relapsed disease. The study was double-blind, double dummy, i.e., placebo capsules were identical in appearance to the avacopan capsules, and prednisone capsules also had matching placebo capsules.

Blinding (masking)

Randomisation was performed centrally via an IRT system and minimisation algorithm, using the stratification factors: 1) IV rituximab, IV cyclophosphamide, or oral cyclophosphamide use (selection of treatment at the discretion of the Investigator prior to randomisation); 2) anti-PR3 or anti-MPO ANCA-

associated vasculitis, and 3) newly-diagnosed or relapsed disease. The study was double-blind, double dummy, i.e., placebo capsules were identical in appearance to the avacopan capsules, and prednisone capsules also had matching placebo capsules.

Statistical methods

The primary analysis compared the remission rates for the two primary efficacy endpoints for the ITT population based on the stratification variables that were the same factors used in the randomisation and included standard of care immunosuppressant regimen, ANCA positivity, and ANCA-associated vasculitis status. The primary endpoint analyses were based on the adjudicated BVAS remission at Week 26, and adjudicated BVAS sustained remission at Week 52 results. For the purpose of analysis of these endpoints, glucocorticoid use refers to both, study supplied (i.e., the prednisone study medication) and non-study supplied medication (i.e., glucocorticoid use other than the prednisone study medication). The same analyses as described for the Primary Analysis was also conducted for the Per- Protocol population.

For the two primary efficacy endpoints, the proportion of subjects achieving disease remission at Week 26 and sustained disease remission at Week 52, and the two-sided 95% confidence (CIs) for the difference in proportions (avacopan minus prednisone) was estimated for the comparison between the avacopan group and the comparator group. For both the noninferiority and superiority tests, the one-sided P-values are presented. Statistical significance was claimed based on the one-sided type-I error of 0.025. The non-inferiority margin was -20%.

Confidence intervals for the stratified analysis were calculated using inverse-variance stratum weights and Miettinen-Nurminen (score) confidence intervals and for un-stratified analyses Wald confidence limits were used. The Clopper–Pearson exact interval is provided for single proportion data.

For secondary endpoints of glucocorticoid toxicity, analysis of change from baseline was performed in the ITT population using a mixed effects model for repeated measures (MMRM). Separate models for GTI-CWS and GTI-AIS will incorporate treatment group, visit, treatment-by-visit interaction and stratification factors as covariates. The stratification factors will be the same factors as used in the randomisation stratification. In the MMRM model, missing data will not be imputed, using a missing at random (MAR) assumption.

Analysis populations were defined as follows: The Randomised Population included all subjects who provided written informed consent and were randomised in the study. The ITT Population included all subjects who were randomised in the study and who received at least one dose of blinded study drug. The PP Population consisted of all subjects in the ITT population who were compliant with taking avacopan/placebo and who did not have major protocol deviations that could have significantly affected the interpretation of the results. Other protocol deviations, and immunosuppressant use, were imputed as non-remission in the PP population.

The two primary endpoints were first tested for noninferiority and then for superiority according to a prespecified multiplicity procedure. A successful study was to be declared if (at minimum) non-inferiority was achieved for the avacopan group versus the comparator group for remission at Week 26.

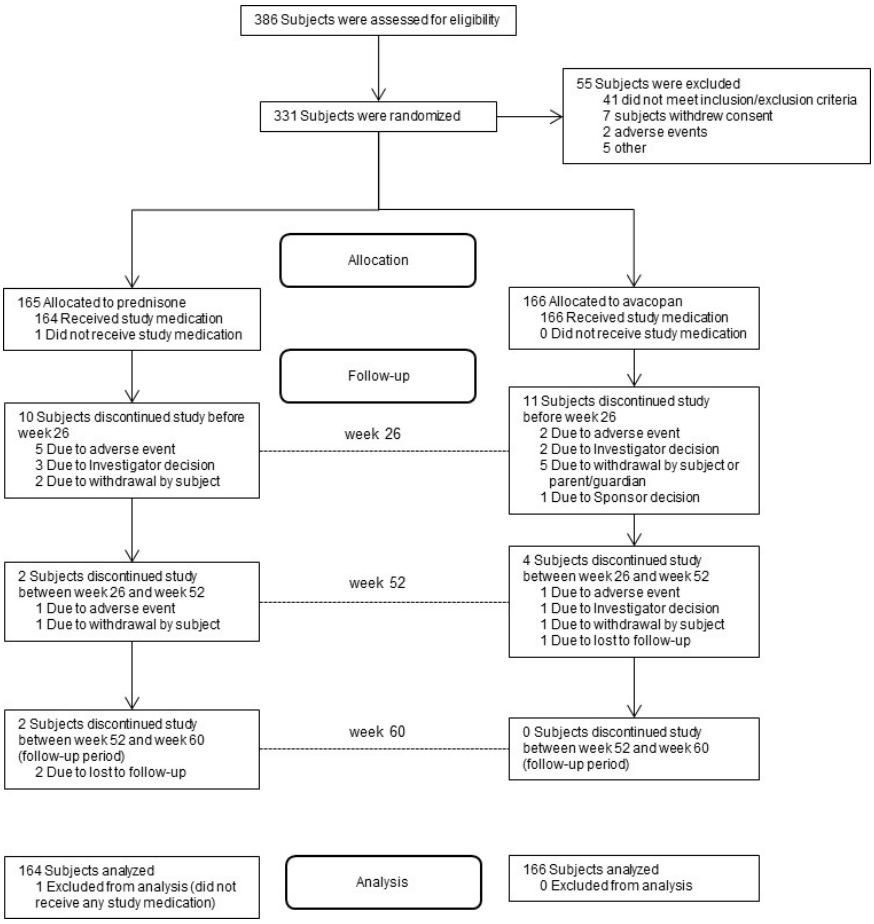
Secondary endpoints were tested in parallel and nominal p-values provided. For the primary endpoints, missing data at Week 26 and Week 52 were imputed as not achieving remission (Week 26) or sustained remission (Week 52), respectively, for the ITT population analyses. Tipping point analyses for missing data Week 26 and Week 52 were provided. No imputation was performed for other time points. No imputation was performed for missing safety endpoints, including safety laboratory values,

vital signs, ECGs, etc. A number of sensitivity analyses were prespecified: Unstratified Analyses, Sensitivity Analyses for High Non-Study Supplied Glucocorticoid Use, Alternative Endpoints, Adjudicated vs Non-Adjudicated Results and Analysis Excluding Japan. No interim analysis for efficacy was performed.

Results

Participant flow

Study CL010_168 Consort Diagram



Subject disposition

Category	Prednisone n (%)	Avacopan n (%)	Total n (%)
Randomised	165 (100)	166 (100)	331 (100)
Safety Population	164 (99.4)	166 (100)	330 (99.7)
ITT Population	164 (99.4)	166 (100)	330 (99.7)
PP Population	161 (97.6)	162 (97.6)	323 (97.6)
Completed Week 26	154 (93.3)	155 (93.4)	309 (93.4)
Completed Week 52	152 (92.1)	151 (91.0)	303 (91.5)
Completed Week 60	150 (90.9)	151 (91.0)	301 (90.9)
Early discontinuation of study treatment (avacopan/placebo)	35 (21.2)	37 (22.3)	72 (21.8)
Sponsor decision	0 (0.0)	2 (1.2)	2 (0.6)
Withdrawal by parent/guardian	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by subject	1 (0.6)	3 (1.8)	4 (1.2)
Lost to follow-up	0 (0.0)	1 (0.6)	1 (0.3)
Adverse event	29 (17.6)	26 (15.7)	55 (16.6)
Investigator decision	4 (2.4)	4 (2.4)	8 (2.4)
Other	1 (0.6)	1 (0.6)	2 (0.6)
Early withdrawal from study	15 (9.1)	15 (9.0)	30 (9.1)
Sponsor decision	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by parent/guardian	0 (0.0)	1 (0.6)	1 (0.3)
Withdrawal by subject	3 (1.8)	6 (3.6)	9 (2.7)
Lost to follow-up	2 (1.2)	1 (0.6)	3 (0.9)
Adverse event	6 (3.6)	3 (1.8)	9 (2.7)
Investigator decision	4 (2.4)	3 (1.8)	7 (2.1)
Other	0 (0.0)	1 (0.6)	1 (0.3)
Death	4 (2.4)	2 (1.2)	6 (1.8)

ITT = intent-to-treat; PP = Per Protocol.

The proportion of subjects with early discontinuation of study treatment was >20 % in both study arms; mostly due to adverse events.

Recruitment

Date first patient enrolled: 15 March 2017

Date last patient completed: 01 November 2019

Conduct of the study

There were four amendments to the original study protocol (dated 28 November 2016). None were considered to affect the reliability of the study results.

Baseline data

Key Baseline and Demographic Characteristics in Study CL010_168 (ITT Population)

Category	Prednisone (N=164)	Avacopan (N=166)
Age (years) at Screening, mean ± SD	60.5 ± 14.50	61.2 ± 14.56
Gender, n (%)		
Male	88 (53.7)	98 (59.0)
Female	76 (46.3)	68 (41.0)
BMI (kg/m^2), mean ± SD	26.78 ± 5.212	26.72 ± 5.997
Race, n (%)		
Asian	15 (9.1)	17 (10.2)
Black or African American	2 (1.2)	3 (1.8)
White	140 (85.4)	138 (83.1)
Other	6 (3.7)	8 (4.8)
Multiple	1 (0.6)	0 (0.0)
ANCA-associated vasculitis status, n (%)		
Newly diagnosed	114 (69.5)	115 (69.3)
Relapsed	50 (30.5)	51 (30.7)
ANCA positivity, n (%)		
Proteinase 3 positive	70 (42.7)	72 (43.4)
Myeloperoxidase positive	94 (57.3)	94 (56.6)
Type of ANCA-associated vasculitis, n (%)		
Granulomatosis with polyangiitis	90 (54.9)	91 (54.8)
Microscopic polyangiitis	74 (45.1)	75 (45.2)
Standard-of-care treatment, n (%)		
Rituximab	107 (65.2)	107 (64.5)
Cyclophosphamide IV	51 (31.1)	51 (30.7)
Cyclophosphamide oral	6 (3.7)	8 (4.8)
Cyclophosphamide IV/oral	57 (34.8)	59 (35.5)
BVAS, mean ± SD	16.2 ± 5.69	16.3 ± 5.87
VDI, mean ± SD	0.7 ± 1.39	0.7 ± 1.54
eGFR (MDRD), mean ± SD	52.9 ± 32.67	50.7 ± 30.96

ITT = intent-to-treat; SD = standard deviation; BMI = body mass index; ANCA = anti-neutrophil cytoplasmic autoantibody; BVAS = Birmingham Vasculitis Activity Score; VDI = Vasculitis Damage Index; eGFR = estimated glomerular filtration rate; MDRD = Modified Diet in Renal Disease.

In response to CHMP's request, the applicant provided baseline characteristics per stratum, see table below. The following differences of subjects' baseline characteristics in the CYC/AZA stratum compared with the RTX stratum were identified:

- Higher mean age
- More males than females
- Predominantly newly diagnosed versus relapsed subjects

- Consistent with a higher proportion of newly diagnosed subjects, a substantially shorter disease duration
- Higher BVAS
- Worse renal function based on eGFR

In summary, the patients in the CYC stratum exhibited characteristics associated with a more severe disease and worse outcomes compared with the patients in the RTX stratum at the time of randomisation to avacopan or prednisone.

Baseline characteristics per background treatment

	Cyclophosphamide/Azathioprine			Rituximab		
	Prednisone N=57	Avacopan N=59	Total N=116	Prednisone N=107	Avacopan N=107	Total N=214
Age (year) mean (SD)	61.7 (11.10)	63.8 (12.59)	62.7 (11.88)	59.9 (16.03)	59.7 (15.40)	59.8 (15.68)
Sex n (%)						
Male	36 (63.2)	37 (62.7)	73 (62.9)	52 (48.6)	61 (57.0)	113 (52.8)
Female	21 (36.8)	22 (37.3)	43 (37.1)	55 (51.4)	46 (43.0)	101 (47.2)
BMI kg/m^2 mean (SD)	27.1 (5.490)	27.02 (5.919)	27.06 (5.688)	26.6 (5.074)	26.55 (6.061)	26.58 (5.576)
GPA n (%)	26 (45.6)	26 (44.1)	52 (44.8)	64 (59.8)	65 (60.7)	129 (60.3)
MPA n (%)	31 (54.4)	33 (55.9)	64 (55.2)	43 (40.2)	42 (39.3)	85 (39.7)
Relapsed n (%)	5 (8.8)	7 (11.9)	12 (10.3)	(45 (42.1)	44 (41.1)	89 (41.6)
Newly diagnosed n (%)	52 (91.2)	52 (88.1)	104 (89.7)	62 (57.9)	63 (58.9)	125 (58.4)
Duration of AAV (months) mean (SD)	2.32 (9.553)	5.11 (15.304)	3.74 (12.827)	29.62 (47.003)	32.76 (62.308)	31.19 (55.081)
Duration of AAV (months) median	0.17	0.20	0.17	0.80	0.53	0.62
Baseline BVAS mean (SD)	17.2 (4.67)	17.9 (5.88)	17.6 (5.31)	15.6 (6.11)	15.5 (5.71)	15.5 (5.90)
Renal disease n (%)	52 (91.2)	53 (89.8)	105 (90.5)	82 (76.6)	81 (75.7)	163 (76.2)
Baseline eGFR (ml/min/1.73 m^2) mean (SD)	47.3 (30.86)	38.4 (24.22)	42.9 (28.01)	56.0 (33.35)	57.1 (32.22)	56.6 (32.72)

Notes: AAV=ANCA-associated vasculitis; BMI=Body mass index; BVAS=Birmingham Vasculitis Activity Score; eGFR=Estimated glomerular filtration rate; GC=Glucocorticoids; GPA=Granulomatosis with polyangiitis; ITT=Intent=to=treat; MPA=Microscopic polyangiitis; SD=Standard deviation.

Numbers analysed

Analysis populations in Study CL010_168

Category	Prednisone n (%)	Avacopan n (%)	Total n (%)
Randomised	165 (100)	166 (100)	331 (100)
Safety Population	164 (99.4)	166 (100)	330 (99.7)
ITT Population	164 (99.4)	166 (100)	330 (99.7)
PP Population	161 (97.6)	162 (97.6)	323 (97.6)

Outcomes and estimation

Primary endpoints

The results for the two primary endpoints are shown below.

Phase 3 Study CL010_168: Summary of Primary Efficacy Results – Primary Endpoints (Intent-to-Treat Population)

	Comparator group (N=164)	Avacopan Group (N=166)	P-value for Difference Between Groups[a]
Primary Endpoints			
Remission[b] at Week 26, n (%)	115 (70.1)	120 (72.3)	<0.0001 (non-inferiority) 0.2387 (superiority)
Estimate of common difference in percentages	--	3.4	
Two-sided 95% confidence interval for common difference	--	-6.0, 12.8	
Sustained remission[c] at Week 52, n (%)	90 (54.9)	109 (65.7)	<0.0001 (non-inferiority) 0.0066 (superiority)
Estimate of common difference in percentages	--	12.5	
Two-sided 95% confidence interval for common difference	--	2.6, 22.3	

[a] *One-sided P-values*
[b] *Remission was defined as having a BVAS of zero at week 26 and not having received any glucocorticoids for ANCA-associated vasculitis within the 4 weeks prior to the week 26 visit.*
[c] *Sustained remission was defined as remission at week 26 and remission at week 52 (BVAS of 0 and not taking glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to Week 52) and without relapse between week 26 and 52.*
n=number of subjects with evaluable data; N=number of subjects in the treatment groups (Intent-to-Treat Population).

The results of the two primary endpoints in Study CL010_168, remission at Week 26 and sustained remission at Week 52, in various subgroups are summarised in the following tables.

Proportion of Subjects with Disease Remission at Week 26 by Stratification Factor and Subgroup in Study CL010_168 (ITT Population)

Stratification Factor/Subgroup Treatment	N	n (%)	95% CI	Difference in percentages	Two-sided 95% CI for the difference
Subjects receiving IV rituximab					
Prednisone	107	81 (75.7)	(66.5, 83.5)		
Avacopan	107	83 (77.6)	(68.5, 85.1)	1.9	(-9.5, 13.2)
Subjects receiving IV or oral cyclophosphamide					
Prednisone	57	34 (59.6)	(45.8, 72.4)		
Avacopan	59	37 (62.7)	(49.1, 75.0)	3.1	(-14.7, 20.8)
Subjects with PR3 ANCA positivity					
Prednisone	70	50 (71.4)	(59.4, 81.6)		
Avacopan	72	51 (70.8)	(58.9, 81.0)	-0.6	(-15.5, 14.3)
Subjects with MPO ANCA positivity					
Prednisone	94	65 (69.1)	(58.8, 78.3)		
Avacopan	94	69 (73.4)	(63.3, 82.0)	4.3	(-8.7, 17.2)
Subjects with newly diagnosed ANCA-associated vasculitis					
Prednisone	114	76 (66.7)	(57.2, 75.2)		
Avacopan	115	76 (66.1)	(56.7, 74.7)	-0.6	(-12.8, 11.7)
Subjects with relapsed ANCA-associated vasculitis					
Prednisone	50	39 (78.0)	(64.0, 88.5)		
Avacopan	51	44 (86.3)	(73.7, 94.3)	8.3	(-6.6, 23.1)
Subjects with granulomatosis with polyangiitis					
Prednisone	90	65 (72.2)	(61.8, 81.1)		
Avacopan	91	65 (71.4)	(61.0, 80.4)	-0.8	(-13.9, 12.3)
Subjects with microscopic polyangiitis					
Prednisone	74	50 (67.6)	(55.7, 78.0)		
Avacopan	75	55 (73.3)	(61.9, 82.9)	5.8	(-8.9, 20.4)

95% CIs for treatment proportions were calculated using the Clopper and Pearson Method. Two-sided 95% CIs were calculated for the difference in proportions (avacopan minus prednisone) using the Wald Method.
ANCA = anti-neutrophil cytoplasmic autoantibody; MPO = myeloperoxidase; PR3 = proteinase 3; IV = intravenous; ITT = intent-to-treat; CI = confidence interval.

Proportion of Subjects with Sustained Disease Remission at Week 52 by Stratification Factor and Subgroup in Study CL010_168 (ITT Population)

Stratification Factor/Subgroup Treatment	N	n (%)	95% CI	Difference in percentages	Two-sided 95% CI for Difference
Subjects receiving IV rituximab background therapy					
Prednisone	107	60 (56.1)	(46.1, 65.7)		
Avacopan	107	76 (71.0)	(61.5, 79.4)	15.0	(2.2, 27.7)
Subjects receiving IV or oral cyclophosphamide					
Prednisone	57	30 (52.6)	(39.0, 66.0)		
Avacopan	59	33 (55.9)	(42.4, 68.8)	3.3	(-14.8, 21.4)
Subjects with PR3 ANCA positivity					
Prednisone	70	40 (57.1)	(44.7, 68.9)		
Avacopan	72	43 (59.7)	(47.5, 71.1)	2.6	(-13.6, 18.8)
Subjects with MPO ANCA positivity					
Prednisone	94	50 (53.2)	(42.6, 63.6)		
Avacopan	94	66 (70.2)	(59.9, 79.2)	17.0	(3.3, 30.7)
Subjects with newly diagnosed ANCA-associated vasculitis					
Prednisone	114	66 (57.9)	(48.3, 67.1)		
Avacopan	115	70 (60.9)	(51.3, 69.8)	3.0	(-9.7, 15.7)
Subjects with relapsed ANCA-associated vasculitis					
Prednisone	50	24 (48.0)	(33.7, 62.6)		
Avacopan	51	39 (76.5)	(62.5, 87.2)	28.5	(10.4, 46.6)
Subjects with granulomatosis with polyangiitis					
Prednisone	90	52 (57.8)	(46.9, 68.1)		
Avacopan	91	56 (61.5)	(50.8, 71.6)	3.8	(-10.5, 18.0)
Subjects with microscopic polyangiitis					
Prednisone	74	38 (51.4)	(39.4, 63.1)		
Avacopan	75	53 (70.7)	(59.0, 80.6)	19.3	(4.0, 34.7)

95% CIs for treatment proportions were calculated using the Clopper and Pearson Method. Two-sided 95% CIs were calculated for the difference in proportions (avacopan minus prednisone) using the Wald Method.
ANCA = anti-neutrophil cytoplasmic autoantibody; MPO = myeloperoxidase; PR3 = proteinase 3; IV = intravenous; ITT = intent-to-treat; CI = confidence interval.

The applicant also provided additional results for the proportion of patients with BVAS=0 by study visit, irrespective of relapses and irrespective of GC use within the 4-week period prior to Weeks 26 and 52. These sensitivity analyses were requested by the CHMP to be provided for confirmation of the efficacy results, especially since the results at Week 52 differed between the RTX and CYC strata. Due to the high impact of intercurrent events on the response rates and the fact that sustained response at Week 52 is defined from a single time point (Week 26) onwards, it was considered relevant to see the results on BVAS without these restrictions. Overall, a great majority (>80%) of patients had BVAS = 0 from Week 16 onwards in both study arms.

Proportion of patients with BVAS=0 by study visit, overall population

Visit	Prednisone + Standard of Care (N=164)	Avacopan + Standard of Care (N=166)
Week 4	112 (68.3)	102 (61.4)
Week 10	127 (77.4)	127 (76.5)
Week 16	135 (82.3)	139 (83.7)
Week 26	135 (82.3)	144 (86.7)
Week 39	140 (85.4)	141 (84.9)
Week 52	138 (84.1)	144 (86.7)

In the rituximab stratum (Table below), the proportion of subjects with BVAS = 0 fluctuated over time, being alternately higher in the comparator and the avacopan arms. From Week 26 onwards, there appears to be no clear difference between the arms despite the fact that the comparator group was using placebo after end of induction treatment.

Proportion of patients with BVAS=0 by study visit, overall population, rituximab stratum

Visit	Prednisone + Standard of Care (N=107)	Avacopan + Standard of Care (N=107)
Week 4	73 (68.2)	63 (58.9)
Week 10	87 (81.3)	81 (75.7)
Week 16	93 (86.9)	89 (83.2)
Week 26	92 (86.0)	95 (88.8)
Week 39	91 (85.0)	94 (87.9)
Week 52	90 (84.1)	95 (88.8)

In the cyclophosphamide stratum, fluctuation in the proportion of subjects with BVAS = 0 is also seen. (Table below). At Week 52, the proportions are similar: 48/75 subjects (84.2%) in the prednisone arm and 49/59 subjects (83.1%) in the avacopan arm.

Proportion of patients with BVAS=0 by study visit, overall population, cyclophosphamide stratum

Visit	Prednisone + Standard of Care (N=57)	Avacopan + Standard of Care (N=59)
Week 4	39 (68.4)	39 (66.1)
Week 10	40 (70.2)	46 (78.0)
Week 16	42 (73.7)	50 (84.7)
Week 26	43 (75.4)	49 (83.1)
Week 39	49 (86.0)	47 (79.7)
Week 52	48 (84.2)	49 (83.1)

Hence, at Week 52, in the rituximab stratum, 84.1% of subjects in the comparator arm had BVAS = 0 vs. 88.8% in the avacopan arm.

The applicant also included tables regarding remitters and non-remitters by reason causing non-remission as is shown below.

Summary of Patient Remission at Week 26 and Sustained Remission at Week 52 Status Subjects Receiving IV Rituximab Background Therapy (ITT)

ad hoc D150 Table Q29-2-9
Summary of Patient Remission at Week 26 and Sustained Remission at Week 52 Status
Subjects receiving IV Rituximab background therapy (Intent-to-Treat Population)

	Prednisone + Standard of Care (N=107)	Avacopan + Standard of Care (N=107)
Week 26		
Remitters	81 (75.7)	83 (77.6)
Non-remitters	26 (24.3)	24 (22.4)
Non-remitters due to study discontinuation	3 (2.8)	4 (3.7)
Non-remitters due to missing data	2 (1.9)	0 (0.0)
Observed non-remitters	21 (19.6)	20 (18.7)
Due to BVAS not equal to 0 at Wk 26	7 (6.5)	6 (5.6)
Due to GC Use with 4 weeks prior to Wk 26	11 (10.3)	12 (11.2)
Due to both BVAS not equal to 0 and GC Use with 4 weeks prior to Wk 26	3 (2.8)	2 (1.9)
Week 52		
Sustained remitters	60 (56.1)	76 (71.0)
Non-sustained remitters	47 (43.9)	31 (29.0)
Non-sustained remitters due to study discontinuation	6 (5.6)	7 (6.5)
Non-sustained remitters due to missing data	0 (0.0)	0 (0.0)
Observed non-sustained remitters	41 (38.3)	24 (22.4)
Due to remission not achieved at Wk 26	23 (21.5)	18 (16.8)
Due to relapse between Wk 26 and Wk 52	12 (11.2)	6 (5.6)
Due to BVAS not equal to 0 at Wk 52	3 (2.8)	0 (0.0)
Due to GC Use with 4 weeks prior to Wk 52	3 (2.8)	0 (0.0)
Due to both BVAS not equal to 0 and GC Use with 4 weeks prior to Wk 52	0 (0.0)	0 (0.0)

GC=Glucocorticoid, Wk 26=Week 26, Wk 52=Week 52

Summary of Patient Remission at Week 26 and Sustained Remission at Week 52 Status Subjects Receiving IV or Oral Cyclophosphamide Background Therapy (ITT

ad hoc D150 Table Q29-2-10
Summary of Patient Remission at Week 26 and Sustained Remission at Week 52 Status
Subjects receiving IV or Oral Cyclophosphamide background therapy (Intent-to-Treat Population)

	Prednisone + Standard of Care (N=57)	Avacopan + Standard of Care (N=59)
Week 26		
Remitters	34 (59.6)	37 (62.7)
Non-remitters	23 (40.4)	22 (37.3)
Non-remitters due to study discontinuation	4 (7.0)	6 (10.2)
Non-remitters due to missing data	1 (1.8)	0 (0.0)
Observed non-remitters	18 (31.6)	16 (27.1)
Due to BVAS not equal to 0 at Wk 26	3 (5.3)	3 (5.1)
Due to GC Use with 4 weeks prior to Wk 26	9 (15.8)	12 (20.3)
Due to both BVAS not equal to 0 and GC Use with 4 weeks prior to Wk 26	6 (10.5)	1 (1.7)
Week 52		
Sustained remitters	30 (52.6)	33 (55.9)
Non-sustained remitters	27 (47.4)	26 (44.1)
Non-sustained remitters due to study discontinuation	6 (10.5)	8 (13.6)
Non-sustained remitters due to missing data	0 (0.0)	0 (0.0)
Observed non-sustained remitters	21 (36.8)	18 (30.5)
Due to remission not achieved at Wk 26	17 (29.8)	15 (25.4)
Due to relapse between Wk 26 and Wk 52	3 (5.3)	3 (5.1)
Due to BVAS not equal to 0 at Wk 52	0 (0.0)	0 (0.0)
Due to GC Use with 4 weeks prior to Wk 52	1 (1.8)	0 (0.0)
Due to both BVAS not equal to 0 and GC Use with 4 weeks prior to Wk 52	0 (0.0)	0 (0.0)

GC=Glucocorticoid, Wk 26=Week 26, Wk 52=Week 52

Secondary endpoints (not controlled for multiplicity)

Glucocorticoid toxicity index

The glucocorticoid toxicity index (GTI) was comprised of individual measurements including body mass index (BMI), glucose tolerance, blood pressure, lipids, steroid myopathy, skin toxicity, neuropsychiatric toxicity, and infection. Both a cumulative worsening score (CWS) and aggregate improvement score (AIS) were determined at both Week 13 and 26, see below.

Phase 3 Study CL010_168: Summary of Efficacy Results – Glucocorticoid Toxicity Index (Intent-to-Treat Population)

	Comparator group (N=164)	Avacopan Group (N=166)		P-value for Difference Between Groups[a]
Glucocorticoid Toxicity Index Cumulative Worsening Score (GTI-CWS)				
Week 13 (LSM ± SEM)	36.6 ± 3.41 (n=161)	25.7 ± 3.40 (n=160)		0.014
Week 26 (LSM ± SEM)	56.6 ± 3.45 (n=153)	39.7 ± 3.43 (n=154)		0.0002
Glucocorticoid Toxicity Index Aggregate Improvement Score (GTI-AIS)				
Week 13 (LSM ± SEM)	23.2 ± 3.46 (n=161)	9.9 ± 3.45 (n=160)		0.003
Week 26 (LSM ± SEM)	23.4 ± 3.50 (n=153)	11.2 ± 3.48 (n=154)		0.008

[a] Two-sided P-values
LSM=least squares mean; n=number of subjects with evaluable data; N=number of subjects in the treatment groups (Intent-to-Treat Population); SEM=standard error of the mean.

Quality of life assessments

Short Form-36 Version 2 (SF-36):

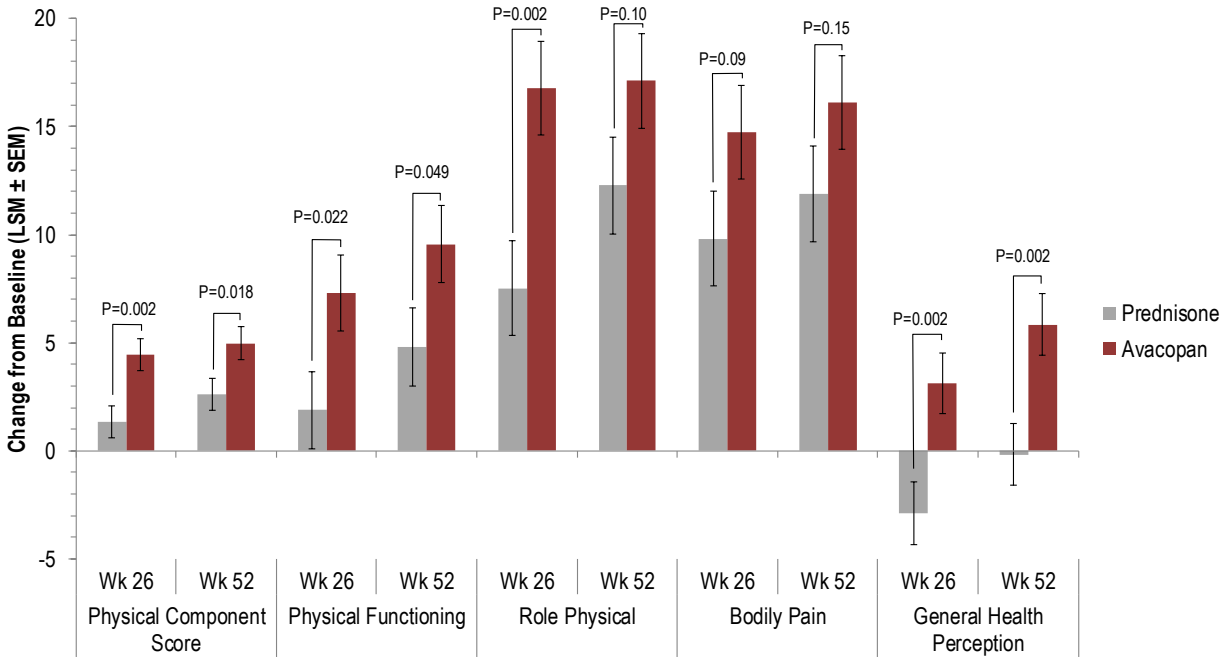
Health-Related Quality of Life Short Form-36 Version 2 Analyses in Study CL010_168 (ITT Population)

	Prednisone (N=164)	Avacopan (N=166)	Difference Between Groups[a]
Physical Component Score			
Baseline, mean±SEM (n)	40.1±0.83 (n=160)	39.2±0.80 (n=165)	
Change from baseline to Week 26, LSM±SEM (n)	1.34±0.74 (n=147)	4.45±0.73 (n=153)	P=0.002
Change from baseline to Week 52, LSM±SEM (n)	2.63±0.75 (n=144)	4.98±0.74 (n=147)	P=0.018
Mental Component Score			
Baseline, mean±SEM (n)	42.1±1.05 (n=160)	44.2±0.98 (n=166)	
Change from baseline to Week 26, LSM±SEM (n)	3.27±0.84 (n=147)	4.85±0.83 (n=154)	P=0.16
Change from baseline to Week 52, LSM±SEM (n)	4.69±0.85 (n=144)	6.39±0.84 (n=148)	P=0.13

[a] Two-sided P-values.
ITT = intent-to-treat; LSM = least squares mean; SEM = standard error of mean.

The SF-36 Physical Component Score (PCS) and Other Physical Aspects are shown in figure below.

SF-36 Change from Baseline for Physical Component Score and Other Physical Aspects in Study CL010_168 (ITT Population)



ITT = intent-to-treat; LSM = least squares mean; SEM = standard error of mean.

The EuroQuality of Life-5 Domains-5 Levels (EQ-5D-5L) is a generic health-related quality of life instrument designed to capture overall quality of life. Two scores are calculated, the first based on a visual analogue scale (VAS) ranging from 0 to 100 and the second based on a population norm-based index.

The findings of the EQ-5D-5L analyses are summarised here:

Health-Related Quality of Life EQ-5D-5L Index Analyses in Study CL010_168 (ITT Population)

	Prednisone (N=164)	Avacopan (N=166)	Difference Between Groups[a]
Visual Analogue Scale			
Baseline, mean±SEM (n)	63.4±1.78 (n=162)	65.8±1.51 (n=166)	
Change from baseline to Week 26, LSM±SEM (n)	5.5±1.39 (n=150)	9.1±1.38 (n=153)	P=0.053
Change from baseline to Week 52, LSM±SEM (n)	7.1±1.41 (n=146)	13.0±1.39 (n=149)	P=0.002
Index			
Baseline, mean±SEM (n)	0.774±0.018 (n=160)	0.752±0.018 (n=166)	
Change from baseline to Week 26, LSM±SEM (n)	-0.0010±0.0146 (n=146)	0.0229±0.0144 (n=152)	P=0.217
Change from baseline to Week 52, LSM±SEM (n)	-0.0038±0.0147 (n=145)	0.0474±0.0145 (n=149)	P=0.009

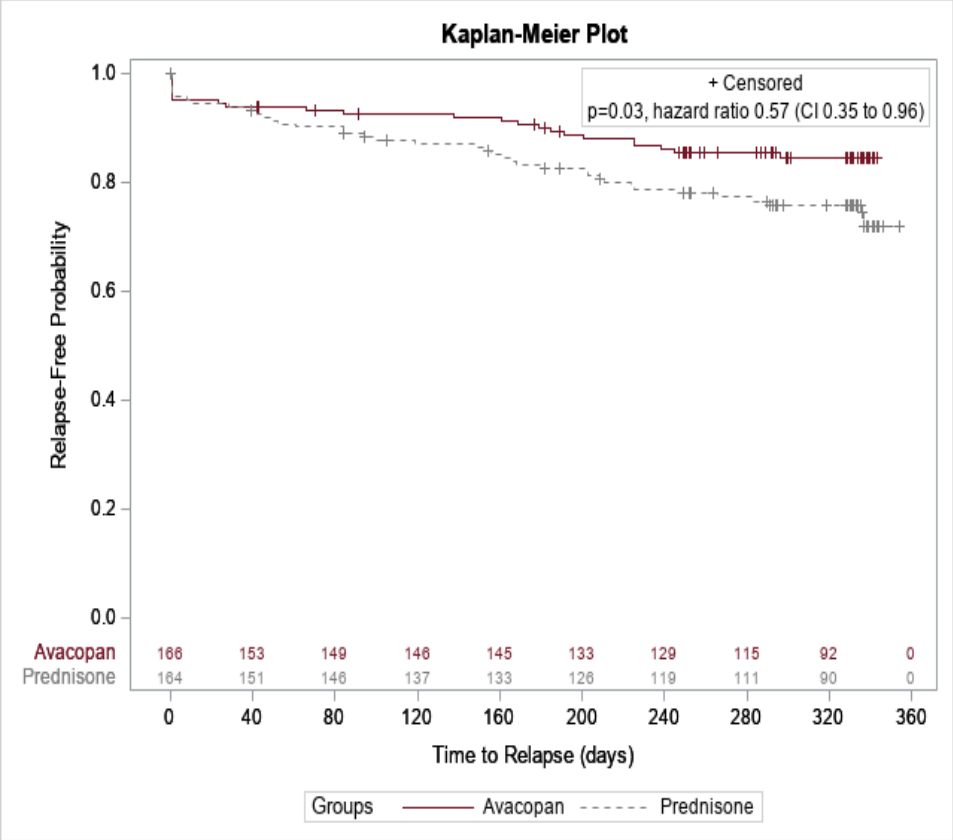
[a] *Two-sided P-values*
EQ-5D-5L = EuroQuality of Life-5 Domains-5 Levels; ITT = intent-to-treat; LSM = least squares mean; SEM = standard error of mean.

Time to relapse

Relapse in ANCA-associated vasculitis was defined as the occurrence of at least one major BVAS item, at least 3 non-major items, or 1 or 2 non-major items on at least 2 consecutive visits after remission had been achieved. Two analyses were performed, the first in subjects who achieved remission at Week 26 and the second in subjects who achieved BVAS=0 at any time during the treatment period.

The incidence of adjudicated relapse after remission had been achieved at Week 26 was 14 of 115 subjects (12.2%) in the comparator group and 9 of 120 subjects (7.5%) in the avacopan group (P=0.081). The applicant also performed a post-hoc analysis on relapses over the entire duration of the study starting from the baseline. A Kaplan-Meier plot of time to relapse from this post-hoc analysis is shown below.

Kaplan-Meier Plot of Time to Relapse in Study CL010_168



Mean Change from Baseline in Estimated Glomerular Filtration Rate in Subjects with Renal Disease at Baseline

Change from baseline in kidney function, as measured by eGFR (based on the MDRD equation), was measured in subjects with renal disease based on the BVAS renal component. A summary of the results is provided below.

Change in Estimated Glomerular Filtration Rate in Study CL010_168 (ITT Population)

	Prednisone (N=164)	**Avacopan (N=166)**	**Difference Between Groups[a]**
eGFR (ml/min/1.73 m²) in subjects with renal disease at baseline based on BVAS			
Baseline, mean±SEM (n)	45.6±2.36 (n=134)	44.6±2.42 (n=131)	
Change from baseline to Week 26, LSM±SEM (n)	2.9±1.03 (n=127)	5.8±1.04 (n=121)	P=0.046
Change from baseline to Week 52, LSM±SEM (n)	4.1±1.03 (n=125)	7.3±1.05 (n=119)	P=0.029

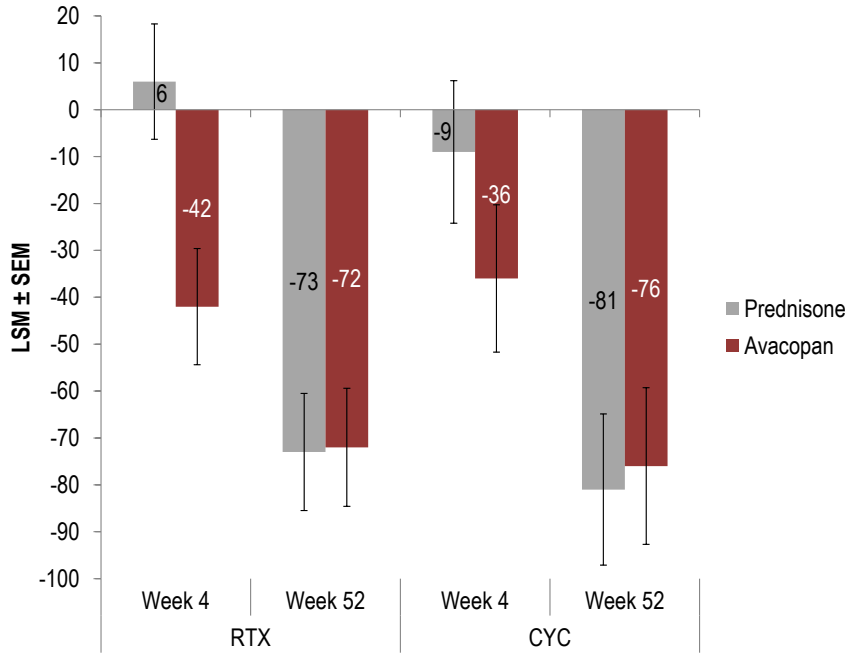
[a] *Two-sided P-values*

ITT = intent-to-treat; LSM = least squares mean; SEM = standard error of mean; eGFR = estimated glomerular filtration rate; BVAS = Birmingham Vasculitis Activity Score.

Albuminuria

Results from measurements of albuminuria based on the urinary albumin:creatinine ratio (UACR) are presented by stratum below.

Percent Change from Baseline in UACR at Weeks 4 and 52 in the RTX and CYC strata in Phase 3 Study CL010_168 (Subjects with Renal Disease Based on BVAS)



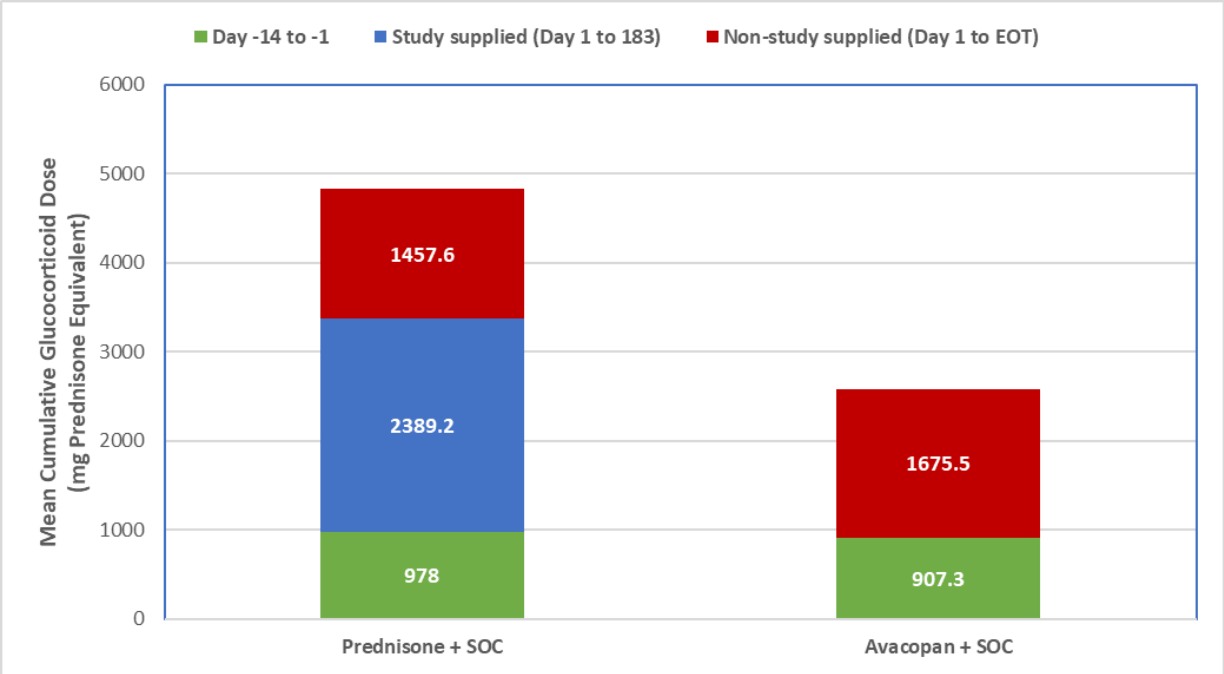
Notes:BVAS=Birmingham Vasculitis Activity Score; CYC=Cyclophosphamide; LSM=Least squares mean; RTX=Rituximab; UACR=Urinary albumin:creatinine ratio.

Urinary albumin:creatinine ratio (UACR) was followed in the subgroup with renal disease and albuminuria at baseline. In the comparator and active groups, respectively, baseline UACR was 648.7 and 723.6 mg/g creatinine in the RTX stratum and 663.6 and 1008.4 mg/g creatinine in the CYC stratum.

Other endpoints

Cumulative steroid dose

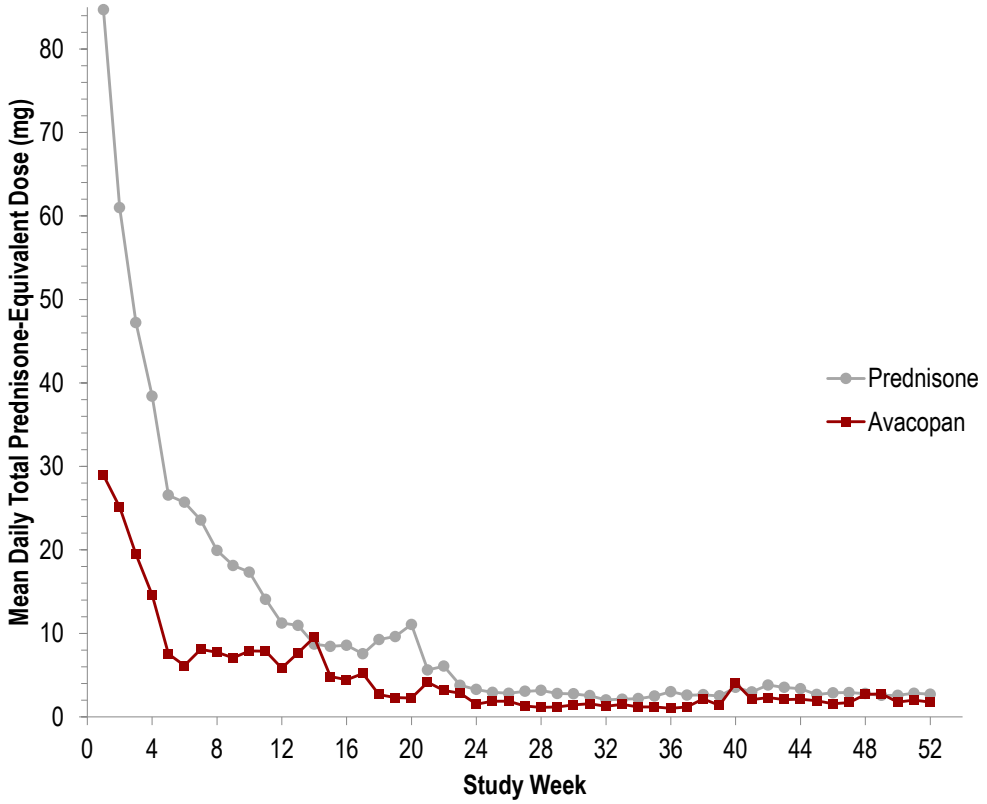
Overall Glucocorticoid Use During the Treatment Period in Study CL010_168 (ITT Population)



ITT = intent-to-treat.

Glucocorticoid use over the course of the study is shown below. There was a marked difference in GC use between study arms from baseline to Week 26; mainly due to the protocol-defined 20-week course of prednisone tapered down from an initial dose of 60 mg/d in the comparator group. The use of GCs was closely similar between study arms from end of Week 26 to Week 52.

Line graph of total mean daily prednisone-equivalent glucocorticoid dose per patient by study week (study CL010_168, ITT population)



Persistence of efficacy

Phase 3 Study CL010_168 included an 8-week follow-up period. The number of subjects experiencing relapses during the follow-up period was similar between the two groups (7 in the comparator group compared to 6 in the avacopan group).

Ancillary analyses

Relevant ancillary analyses are described above.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Summary of efficacy for trial CL010_168

Title: A RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROLLED, PHASE 3 STUDY TO EVALUATE THE SAFETY AND EFFICACY OF CCX168 (AVACOPAN) IN PATIENTS WITH ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODY (ANCA)-ASSOCIATED VASCULITIS TREATED CONCOMITANTLY WITH RITUXIMAB OR CYCLOPHOSPHAMIDE/AZATHIOPRINE	
Study identifier	Protocol CL010_168; EudraCT number 2016-001121-14

Design	Randomised, Double-Blind, Double-dummy, Active-Controlled	
	Duration of main phase:	52 weeks
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	8 weeks (follow-up)
Hypothesis	For the two primary efficacy endpoints, the proportion of subjects achieving disease remission at Week 26 and sustained disease remission at Week 52 were tested sequentially using a gatekeeping procedure; the two-sided 95% confidence intervals for the difference in proportions (Avacopan minus control) will be greater than -0.20 for the non-inferiority and greater than 0.0 for the superiority.	
Treatment groups	Avacopan group:	- Avacopan 30 mg twice daily orally for 52 weeks - Oral prednisone-matching placebo tapering regimen over 20 weeks
	Comparator group (comparator group):	- Avacopan-matching placebo twice daily orally for 52 weeks - Oral prednisone tapering regimen over 20 weeks
Endpoints and definitions	First primary endpoint	Proportion of patients achieving disease remission at Week 26 defined as a BVAS of 0 and not taking glucocorticoids for treatment of AAV within 4 weeks prior to Week 26.
	Secondary primary endpoint	Proportion of patients achieving sustained disease remission defined as remission at Week 26 without relapse to Week 52 (BVAS of 0 and not taking glucocorticoids for treatment of AAV within 4 weeks prior to Week 52).
	Key secondary endpoint	Glucocorticoid-induced toxicity measured by change from baseline over the first 26 weeks in the glucocorticoid toxicity index (GTI).
	Key secondary endpoint	Change from baseline over 52 weeks in health-related quality-of-life as measured by the domains and component scores of the SF-36 v2 and EQ-5D-5L Health Scale VAS and Health Scale Index.
	Key secondary endpoint	Proportion of patients and time to experiencing a relapse after previously achieving remission at Week 26 in the study.
	Key secondary endpoint	In patients with renal disease at baseline (based in the BVAS renal component), the change in estimated glomerular filtration rate (eGFR) from baseline over 52 weeks.
Database lock	20 November 2019	
<u>Results and Analysis</u>		
Analysis description	**Pre-specified first Primary Analysis: Disease remission at Week 26**	

Analysis population and time point description	Analysis population: ITT (subjects who were randomised and had received at least one dose of study drug) Time point: Week 26		
Descriptive statistics and estimate variability	Treatment group	Avacopan group	Comparator group
	Number of subjects	166	164
	Remission at Week 26 n (%)	120 (72.3)	115 (70.1)
	95% CI in %	64.8, 78.9	62.5, 77.0
Effect estimate per comparison	Primary endpoint Disease remission at Week 26	Comparison groups	Avacopan group vs Comparator group
		Estimate of Treatment Difference in %	3.4
		95% CI in %	-6.0, 12.8
		Non-inferiority p-value	<0.0001
		Superiority p-value	0.2387
Analysis description	**Pre-specified Secondary Primary Analysis: Sustained remission at Week 52**		
Analysis population and time point description	Analysis population: ITT (subjects who were randomised and had received at least one dose of study drug) Time point: Week 52		
Descriptive statistics and estimate variability	Treatment group	Avacopan group	Comparator group
	Number of subjects	166	164
	Remission at Week 52 n (%)	109 (65.7)	90 (54.9)
	95% CI in %	57.9, 72.8	46.9, 62.6
Effect estimate per comparison	Primary endpoint Sustained remission at Week 52	Comparison groups	Avacopan group vs Comparator group
		Estimate of Treatment Difference in %	12.5
		95% CI in %	2.6, 22.3
		Non-inferiority p-value	<0.0001
		Superiority p-value	0.0066
Analysis description	**Pre-specified secondary analysis - Glucocorticoid Toxicity Index - Cumulative Worsening Score (GTI-CWS) – Week 26**		
Analysis population and time point description	Analysis population: ITT (subjects who were randomised and had received at least one dose of study drug). Time point: Week 26		

Descriptive statistics and estimate variability	Treatment group	Avacopan group	Comparator group
	Number of subjects	154	153
	Mean	39.8	56.7
	LS Mean 95% CI	33.0, 46.5	49.8, 63.3
Effect estimate per comparison	Key Secondary Endpoint GTI-CWS at Week 26	Comparison groups	Avacopan group vs Comparator group
		LSM Difference (SEM)	-16.8 (4.48)
		95% CI	-25.6, -8.0
		p-value	0.0002
Analysis description	**Pre-specified secondary analysis - Change from baseline over 52 weeks in health-related quality-of-life as measured by the General Health Perception domain of the SF-36 v2**		
Analysis population and time point description	Analysis population: ITT (subjects who were randomised and had received at least one dose of study drug). Time point: Week 52		
Descriptive-Statistics and estimate variability	Treatment group	Avacopan group	Comparator group
	Number of subjects	150	145
	Mean Change from baseline	6.35	0.89
	LS Mean 95% CI	3.05, 8.63	-3.01, 2.66
Effect estimate per comparison	Key Secondary Endpoint SF-36 v2: General Health Perception at Week 52	Comparison groups	Avacopan group vs Comparator group
		LSM Difference (SEM)	6.02 (1.906)
		95% CI	2.27, 9.76
		p-value	0.0017
Analysis description	**Pre-specified secondary analysis - Change from baseline over 52 weeks in health-related quality-of-life as measured by the domains of the EQ-5D-5L Heath Scale VAS Score**		
Analysis population and time point description	Analysis population: ITT (subjects who were randomised and had received at least one dose of study drug). Time point: week 52		
Descriptive Statistics and estimate variability	Treatment group	Avacopan group	Comparator group
	Number of subjects	149	146
	Mean Change from Baseline	13.1	9.0

	LS Mean 95% CI	10.3, 15.7	4.3, 9.8
Effect estimate per comparison	Key Secondary Endpoint EQ-5D-5L Health Scale VAS at Week 52	Comparison groups	Avacopan group vs Comparator group
		LSM Difference (SEM)	5.9 (1.86)
		95% CI	2.3, 9.6
		p-value	0.0015
Analysis description	**Pre-specified secondary analysis - Change from baseline over 52 weeks in health-related quality-of-life as measured by the domains of the EQ-5D-5L Health Scale Index Score**		
Analysis population and time point description	Analysis population: ITT (subjects who were randomised and had received at least one dose of study drug). Time point: Week 52		
Descriptive Statistics and estimate variability	Treatment group	Avacopan group	Comparator group
	Number of subjects	149	145
	Mean Change from Baseline	0.0682	0.0045
	LS Mean 95% CI	0.0189, 0.0759	0.0327, 0.0251
Effect estimate per comparison	Key Secondary Endpoint EQ-5D-5L Health Scale Index Score at Week 52	Comparison groups	Avacopan group vs Comparator group
		LSM Difference (SEM)	0.0512 (0.01950)
		95% CI	0.0130, 0.0895
		p-value	0.0088
Analysis description	**Pre-specified secondary analysis - Proportion of Subjects Experiencing a Relapse After Previously Achieving Disease Remission at Week 26**		
Analysis population and time point description	Analysis population: ITT (subjects who were randomised and had received at least one dose of study drug). Time point: between Week 26 and Week 52		
Descriptive statistics and estimate variability	Treatment group	Avacopan group	Comparator group
	Number of subjects	120	115
	n (%)	9 (7.5)	14 (12.2)
	95% CI	3.5, 13.8	6.8, 19.6
Effect estimate per comparison	Key Secondary Endpoint	Comparison groups	Avacopan group vs Comparator group

	Relapse between Week 26 and Week 52	Estimate of Common Difference in %	-6.0
		95% CI in %	-14.4, 2.4
		Superiority p-value	0.0810
Analysis description	**Pre-specified secondary analysis - Mean Change from Baseline in Estimated Glomerular Filtration Rate in Subjects with Renal Disease at Baseline**		
Analysis population and time point	Analysis population: ITT (subjects who were randomised and had received at least one dose of study drug). Time point: Week 52		
Descriptive statistics and estimate variability	Treatment group	Avacopan group	Comparator group
	Number of subjects	166	164
	Mean Change from Baseline	7.7	4.3
	LS Mean 95% CI	5.2, 9.4	2.1, 6.1
Effect estimate per comparison	Key Secondary Endpoint eGFR (mL/min/1.73 m²) at Week 52	Comparison groups	Avacopan group vs Comparator group
		LSM Difference (SEM)	3.2 (1.48)
		95% CI	0.3, 6.1
		p-value	0.0294

Analysis performed across trials (pooled analyses and meta-analysis)

The efficacy data from CL002_168, CL003_168 and CL010_168 have not been integrated, given the substantial differences in the primary efficacy endpoints, treatment regimens, and the treatment duration among these 3 studies.

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	76 (31.8%)	32 (13.4%)	0 (0%)
Non Controlled trials (Phase 1 Hepatic Impairment Study CL013_168)	11 (2.17%)	0 (0%)	0 (0%)

Supportive studies

Two supportive Phase 2 clinical trials (CL002_168 and CL003_168) in 109 patients with ANCA-associated vasculitis (AAV) were conducted evaluating the efficacy and safety of avacopan for AAV.

Phase 2 study CL002_168: Clinical trial CL002_168 was a randomised, double-blind, placebo-controlled clinical study to assess the efficacy, safety, and tolerability of avacopan in subjects with newly-diagnosed or relapsing active ANCA-associated vasculitis when administered in combination with guideline recommended immunosuppressants, cyclophosphamide or rituximab (Yates et al., 2016). The primary efficacy objective was improvement from baseline in the BVAS of at least 50% with no worsening in any organ system. The primary safety objective was to evaluate the safety and tolerability of avacopan in subjects with ANCA-associated vasculitis receiving cyclophosphamide or rituximab treatment.

Subjects were randomised to one of three treatment groups:

- The full-dose comparator group: subjects received avacopan-matched placebo plus cyclophosphamide or rituximab and the full starting dose (60 mg per day) of prednisone
- The avacopan + low-dose comparator group: subjects received avacopan 30 mg twice daily plus cyclophosphamide or rituximab plus a one-third starting dose (20 mg per day) of prednisone
- The avacopan + no comparator group: subjects received avacopan 30 mg twice daily plus cyclophosphamide or rituximab plus prednisone-matching placebo

Cyclophosphamide was administered at 15 mg/kg (up to 1.2 g) IV every 2 to 4 weeks and rituximab at 375 mg/m^2 IV weekly for 4 weeks. Treatment duration was 12 weeks, with a subsequent 12-week follow-up period. Results for the primary efficacy endpoint, BVAS response, is shown in table below.

Analysis of Clinical Response Based on Birmingham Vasculitis Activity Score at Day 85 – ITT Population

Treatment	N'	n (%)	Difference in Percentages vs Placebo	Two-Sided 90% CI for Difference	Non-Inferior P-Value
Placebo + Full Dose Prednisone (N = 20)	20	14 (70.0)			
CCX168 + Low-Dose Prednisone (N = 22)	22	19 (86.4)	16.4	(-4.3, 37.1)	0.0019
CCX168 + No Prednisone (N = 21)	21	17 (81.0)	11.0	(-11.0, 32.9)	0.0102
All CCX168 (N = 43)	43	36 (83.7)	13.7	(-5.5, 33.0)	0.0020

BVAS response was defined as achieving a 50% reduction from baseline in the BVAS plus no worsening in any body system component.
n = number of subjects who responded.
N' = number of subjects with evaluation.
BVAS = Birmingham Vasculitis Activity Score; CI = confidence interval; ITT = Intent-to-Treat; vs = versus.
Source: Post-text Table 14.2.1.1

The results for the clinically relevant secondary endpoint of BVAS remission is shown below.

Analysis of Clinical Remission Based on Birmingham Vasculitis Activity Score at Day 85 – ITT Population in study CL002_168

Clinical Remission Definition	Treatment	N'	n (%)	Difference in Percentages vs Placebo	Two-Sided 90% CI for Difference	Non-Inferior P-Value
BVAS of 0 or 1, plus no worsening in eGFR, and urinary RBC count <10/hpf at Day 85 [1]	Placebo + Full Dose Prednisone (N = 20)	20	7 (35.0)			
	CCX168 + Low-Dose Prednisone (N = 22)	22	6 (27.3)	-7.7	(-31.2, 15.8)	0.1950
	CCX168 + No Prednisone (N = 21)	21	4 (19.0)	-16.0	(-38.5, 6.6)	0.3837
	All CCX168 (N = 43)	43	10 (23.3)	-11.7	(-32.2, 8.8)	0.2538
BVAS of 0 at Day 85	Placebo + Full Dose Prednisone (N = 20)	20	8 (40.0)			
	CCX168 + Low-Dose Prednisone (N = 22)	22	10 (45.5)	5.5	(-19.6, 30.5)	0.0476
	CCX168 + No Prednisone (N = 21)	21	7 (33.3)	-6.7	(-31.4, 18.1)	0.1875
	All CCX168 (N = 43)	43	17 (39.5)	-0.5	(-22.3, 21.3)	0.0702
BVAS of 0 at Days 29 and 85	Placebo + Full Dose Prednisone (N = 20)	20	1 (5.0)			
	CCX168 + Low-Dose Prednisone (N = 22)	22	3 (13.6)	8.6	(-5.8, 23.1)	ND
	CCX168 + No Prednisone (N = 21)	21	6 (28.6)	23.6	(5.5, 41.7)	ND
	All CCX168 (N = 43)	43	9 (20.9)	15.9	(3.0, 28.9)	ND

n = number of subjects who responded.
N' = number of subjects with evaluation.
ND = not done.
1. Definition in protocol (Appendix 16.1.1). Disease remission was defined as achieving a BVAS score of 0 or 1 plus no worsening in eGFR and urinary RBC <10/hpf.
BVAS = Birmingham Vasculitis Activity Score; CI = confidence interval; eGFR = estimated glomerular filtration rate; hpf = high power field; ITT = intent-to-treat; RBC = red blood cell; vs = versus.
Sources: Post-text Tables 14.2.3.1.1, 14.2.3.1.2, and 14.2.3.1.3

Phase 2 study CL003_168: The Phase 2 study CL003_168 enrolled 42 patients with active ANCA-associated vasculitis to evaluate the safety of avacopan when given on top standard of care treatment, consisting of glucocorticoids plus cyclophosphamide or rituximab. Study CL003_168 was a prospective, randomised, double-blind, double-dummy, placebo-controlled study designed to evaluate safety in the target population. Treatment duration was 12 weeks, with a subsequent 12-week follow-up period. All patients received high dose steroids, and the study does not provide any supportive efficacy data for the proposed dose regimen.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Avacopan is intended in combination with a cyclophosphamide or rituximab regimen for the treatment of adult patients with active, severe granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA). Three clinical studies have been included in support of this claim; two phase 2 studies (CL002_168 and CL003_168) including a total of 109 patients, and one pivotal phase 3 study (CL010_168) including 331 patients. The first study, CL002_168, met its primary endpoint as avacopan, with or without reduced dose of prednisone, was non-inferior to the comparator (full dose prednisone) regarding BVAS response at day 85. There were, however, uncertainties regarding the statistical analyses affecting the reliability of these results. After 12 weeks of follow-up, the response rate for both avacopan groups was inferior to the comparator, questioning the efficacy of avacopan over time. There was also a concern on the clinical relevance of the primary endpoint, as there is a general consensus that the aim of vasculitis induction therapy is not the induction of response, but rather the induction of remission. For the secondary endpoint of BVAS remission, avacopan with or without low-dose prednisone appeared inferior to the comparator. The second phase 2 study, CL003_168, was primarily a safety study and did not provide additional supportive efficacy data for the proposed avacopan dose regimen.

Phase 3 study, CL010_168

CL010_168 was a randomised, double-blind, active-controlled clinical study assessing the efficacy and safety of avacopan in subjects with newly diagnosed or relapsing active ANCA-associated vasculitis when administered against a standard background cyclophosphamide or rituximab regimen. The study

treatment period was 52 weeks with an 8-week follow-up period. Eligible patients had a clinical diagnosis of GPA or MPA consistent with the well-established Chapel-Hill Consensus Conference definitions, were 12 years and above and had positive anti-PR3 or anti-MPO antibodies. Patients needed to have active disease defined by at least one major item, or at least 3 minor items, or at least the 2 renal items of proteinuria and haematuria in the Birmingham Vasculitis Activity Score (BVAS) and a clinical need for treatment with cyclophosphamide or rituximab. Hence, mild cases were excluded. In addition, subjects with very severe AAV requiring invasive pulmonary ventilation support due to alveolar haemorrhage or with dialysis or plasma exchange with 12 weeks prior to screening were excluded. Therefore, the study participants did not represent the entire spectrum of AAV, as subjects with mild disease and, on the other hand, subjects with severe progressive disease were excluded.

Acknowledged are the limitations in the study design which hinder the non-inferiority assessment. One issue is that the primary endpoint was assessed at Week 26, even though the other medications in the induction treatment combinations had ended prior to Week 26 whereas avacopan was continued. Rituximab ended after 4 weekly injections, prednisone taper in the comparator arm continued up to Week 20, and cyclophosphamide ended after Week 15 (IV until week 13, oral until week 15), when it was substituted by azathioprine or mycophenolate. Especially in the comparator arms, treatment response may have started to decrease after cessation of induction therapies, which might favour the avacopan group. Efficacy and safety results are affected also by use of non-study defined glucocorticoids and immunosuppressants in this setting. Consequently, the magnitude of the contribution of avacopan to the observed efficacy is difficult to quantify.

The originally proposed indication was: *"Tavneos is indicated for the treatment of adult patients with granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA)."*

In the clinical studies, avacopan was administered in combination with rituximab or cyclophosphamide (followed by azathioprine or mycophenolate mofetil). This was raised as a major issue by the CHMP. In response, the applicant revised the indication to include information on the combination with rituximab or cyclophosphamide, and to include that only patients with severe, active disease are eligible for therapy. The treatment duration was 12 months and there are no data available for long-term treatment:

"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 section 4.2)."

Patients with severe life- or organ-threatening disease such as alveolar haemorrhage requiring invasive pulmonary ventilation support, and patients with GFR <15 mL/minute/1.73 m^2 or in need of dialysis or plasma exchange were excluded from the study. Consequently, section 4.2 of the SmPC was updated on request of the CHMP to adequately reflect that there are no data in patients with GFR <15 mL/minute/1.73 m^2 or in need of dialysis.

The Chapel-Hill Consensus Conference definitions include histopathological signs of necrotising vasculitis. The applicant was asked to confirm that the diagnosis was confirmed by biopsy in all patients and summarise from which organs these biopsies were taken. The applicant clarified that the diagnosis of AAV in the pivotal study was based on a positive test for antibodies against either PR3 or MPO, and that a biopsy was not mandatory for patients to be included in the pivotal study. Renal biopsy results at baseline were available for a total of 80 subjects (48.8%) and 79 subjects (47.6%) in the prednisone and avacopan groups, respectively.

According to the "EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis", "*Histopathological evidence of vasculitis, such as pauci-immune glomerulonephritis or necrotising vasculitis in any organ, remains the gold standard for diagnostic purposes"*. Although the

lack of diagnostic biopsy is considered to be a limitation of the study, the issue is not considered meaningful to be further pursued at this stage.

Patients were randomised to one of two treatment groups:

- Comparator group: full starting dose of prednisone (60 mg/day (if ≥ 55 kg) or 45 mg/day (if <55 kg)), followed by prednisone tapered according to a pre-specified protocol to reach 10 mg at day 71, 5 mg at day 99 and 0 mg at day 141.
- Avacopan group: avacopan 30 mg twice daily

It should be noted that, according to the protocol, steroids were allowed also in the avacopan group. All patients received background treatment with standard of care with either rituximab 375 mg/m^2 IV once weekly over 4 weeks or cyclophosphamide (oral or IV) for ~14 weeks followed by azathioprine or mycophenolate mofetil. The induction and maintenance doses of cyclophosphamide and azathioprine are in line with the EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Regarding rituximab, however, the applicant states that the dose of 375 mg/m^2 IV once weekly over 4 weeks was based on the approved rituximab label at the time of initiating of the trial. However, in 2018, rituximab was approved also for maintenance treatment and hence, the applicant was asked to comment on this, and whether patients in the rituximab stratum can be considered sub-optimally treated beyond 6 months. In their response, the applicant clarified that RTX was dosed according to the Mabthera SmPC at time of study start, when Mabthera was only approved for induction treatment, and that one of the goals of the ADVOCATE study was to evaluate whether avacopan (as monotherapy) could sustain remission at Week 52. The applicant's comment that there is no general consensus about RTX use in the maintenance setting is not completely agreed on. The SmPC for Mabthera includes a clear recommendation on 500 mg IV infusions every 6 months up to at least 24 months, which is also reflected in the EULAR/ERA-EDTA recommendations.

Thus, for maintenance of remission after induction treatment, the comparison in the rituximab stratum was between avacopan and placebo. Nonetheless, it is agreed that the results for avacopan in the RTX stratum, where RTX treatment was limited to 4 weekly infusions, are compelling and that remission achieved with induction with RTX seems to be sufficiently maintained by avacopan in monotherapy. Maintenance of remission was achieved by a higher proportion of patients treated with avacopan/rituximab, than in all other treatment groups.

In the cyclophosphamide stratum, however, avacopan combined with azathioprine (or mycophenolate) was compared with azathioprine (or mycophenolate) alone. Therefore, in the cyclophosphamide stratum, also the comparator arm received maintenance treatment (with azathioprine or mycophenolate). Nevertheless, also in this stratum, the comparison of sustained remission was in practice between avacopan and placebo, since these were the treatments combined with azathioprine or mycophenolate.

In the protocol assistance, the CHMP considered there was a risk that the steroid dose in the control arm was suboptimal. Following this, the applicant suggested to add criteria to the protocol allowing more corticosteroids to patients in need of more, which has been implemented. Although the steroid dosing in the comparator arm is largely in line with the EULAR recommendation and patients were given extra steroids as rescue if needed, the applicant was asked to further justify that subjects in the prednisolone arm were not sub-optimally treated. A clear summary of the glucocorticoid regimens used in other clinical trials in AAV was presented, and it was noted that the steroid tapering regimen in the ADVOCATE study is very similar to the tapering regimens used in the other trials. It is agreed with the applicant that patients in the control group in the ADVOCATE study were adequately treated with glucocorticoids.

Prior to randomisation, subjects were stratified according to three standard treatments: IV rituximab, IV cyclophosphamide, or oral cyclophosphamide, selection of treatment at the discretion of the investigator. After stratification, subjects were randomised in a ratio of 1:1 to receive prednisone according to a tapering plan + avacopan-matching placebo or avacopan + prednisone-matching placebo. Randomisation was performed centrally via an IRT system and minimisation algorithm, using the stratification factors: 1) IV rituximab, IV cyclophosphamide, or oral cyclophosphamide use; 2) anti-PR3 or anti-MPO ANCA-associated vasculitis, and 3) newly diagnosed or relapsed disease.

The study included two primary endpoints: 1) disease remission at week 26, and 2) sustained disease remission at week 52. Disease remission was defined as BVAS of 0, no glucocorticoids within 4 weeks prior to the timing of the endpoint, and no BVAS >0 during the 4 weeks prior to Week 26 (if collected for an unscheduled assessment). Additionally, to fulfil sustained remission, no relapse was allowed between week 26 and 52. BVAS remission and off steroids is a clinically relevant endpoint and has been widely used in previous clinical trials. The two primary endpoints were tested sequentially using a gatekeeping procedure to preserve the overall Type 1 error rate at the 5% level, according to the following sequence: (1) non-inferiority at Week 26, (2) non-inferiority at Week 52, (3) superiority at Week 52, and (4) superiority at Week 26. The non-inferiority margin was -20%.

The primary endpoint definition at week 26 was endorsed by the CHMP; however, the CHMP requested that patients were treated and followed for 52 weeks to evaluate also the duration of remission, and that the primary efficacy endpoint was only considered to be achieved if patients have both been off steroids and had a BVAS score of 0 for the past 4 weeks.

The definition of the second primary endpoint (sustained remission at week 52) is very close to what was requested from the CHMP and is considered highly clinically relevant. Hence, the deviation from the CHMP advice is not considered to have relevantly affected the obtained results.

The NI margin is considered wide, and a 20% difference in response rates would unlikely be considered not clinically meaningful. The NI margin has been discussed at a previous Scientific Advice and the CHMP recognised the limitations related to a narrower margin, in particular related to a study with ~900 patients. Hence, the study was planned with a NI margin of 20% and the assessment is based on the totality of data.

Important secondary endpoints were glucocorticoid toxicity index, BVAS remission at week 4, quality of life assessments, proportion of subjects with and time to relapse, change in eGFR, reduction of proteinuria, and change in vasculitis damage index.

None of the secondary endpoints in study CL010_168 were multiplicity controlled.

Efficacy data and additional analyses

A total of 331 patients were enrolled and randomised in the study, whereof 330 were included in the ITT population (prednisone n=164, avacopan n=166). The proportion of patients discontinuing study drug due to AEs was relatively high: 17.6 % in the comparator group and 15.7 % in the avacopan group. It is unclear how patients discontinuing study medication were handled in the primary analysis due to the differences of the definition of non-responder given in the SAP, CSR and SCE. Missing data was imputed as non-remission in the ITT analysis, and protocol deviations were imputed as non-remission in the PP analysis. The applicant provided tipping point analyses for missing data and study discontinuation; these results were robust. The applicant also provided more detailed information on imputation of data in the PP populations for intercurrent events such as immunosuppressant use OR non-compliance. In the PP analysis 109/161 in the comparator group and 110/162 in the avacopan group had disease remission at for week 26. Immunosuppressant use and non-compliance were coded

as non-remission in this non-inferiority analysis. The applicant has provided a comprehensive description of coding of these intercurrent events. There was some numerical difference in between the treatment and control group at week 26, primarily driven by non-compliance imputation, 8 in the avacopan group and 4 in the control (Prednisone) group. This difference was however to a disadvantage for the avacopan group. Remission Status changed from Yes to No due to IS use OR non-compliance imputation in 9 for the Avacopan group and 6 for the control group. Since the discrepancy between these numbers is larger than the discrepancy in the total numbers for the PP analysis, and to the disadvantage of the avacopan group, it should not have masked differences between groups. The applicant claims that patients who discontinued treatment or study did not do well clinically. However, according to the CSR, adverse events seem to be a common reason as well.

The mean age of the patients was ~60 years, and the majority were of Caucasian ethnicity. A total of 70% were newly diagnosed. Around 55% had a diagnosis of GPA and 45% had a diagnosis of MPA, which was balanced across the groups. The proportion of male subjects was slightly higher in the avacopan group (59%) than in the comparator group (53.7%), but the difference is not considered to be clinically meaningful. The most frequent induction treatment agent was rituximab (65% in both groups). The remaining patients received either oral or IV cyclophosphamide. At baseline, the proportion of subjects with prior glucocorticoid use was higher in the comparator group compared with avacopan (82.3% versus 75.3%). This is somewhat unexpected in a randomised trial. The applicant was asked to clarify and explain in detail the root cause for the difference and whether there is a systemic error in the reporting and analysis of concomitant medications or whether there is an issue related to randomisation. Furthermore, the applicant was asked to discuss the potential implication of the root cause on reporting of concomitant medications also during the treatment period and provide updated results as appropriate. Following the response evaluation, it was agreed that the noted numerical difference in prior GC use was a chance finding. However, 7% difference is not negligible and the difference may have affected the use of GC in the study arms during the study. At week 26, the difference in achieving remission at week 26 was 14% in the group not using GCs during screening in favour of the avacopan group. On the contrary, in subjects who used GCs during screening, the difference in achieving remission at Week 26 was 1.6% in favour of the control group. At week 52, sustained remission was also achieved by a slightly larger proportion of subjects not having used GCs during screening and belonging to the avacopan group vs. control group (13.5% vs. 9.1%) than in the majority having used GCs during screening. Hence, GC use during screening may have partly masked the effect by avacopan during the first part of the trial. However, the issue was not pursued further.

The first primary endpoint, BVAS remission at week 26, was achieved by 115 of 164 subjects (70.1%) in the comparator group compared to 120 of 166 subjects (72.3%) in the avacopan group. Non-inferiority was met (estimate of common difference in percentages 3.4%, $p<0.0001$, 95% CI: -6; 12.8). Avacopan was not statistically superior to prednisone ($p=0.2387$).

The second primary endpoint, sustained BVAS remission at week 52, was achieved by 90 of 164 subjects (54.9%) in the comparator group compared to 109 of 166 subjects (65.7%) in the avacopan group (estimate of common difference in percentages 12.5%, non-inferiority $p<0.0001$, 95% CI: 2.6; 22.3). Both non-inferiority and superiority ($p=0.0066$) was met.

The two primary endpoints were tested sequentially using a gatekeeping procedure according to the following sequence: (1) non-inferiority at Week 26, (2) non-inferiority at Week 52, (3) superiority at Week 52, and (4) superiority at Week 26, and the difference for the first three analyses was thus statistically significant. The results were similar in the per protocol analyses. The results are considered clinically relevant.

In the pre-defined subgroups of ANCA subtype (PR3 or MPO), newly diagnosed or relapsed disease, and disease subtype (GPA or MPA), the results were similar as in the primary analysis. For the second

primary endpoint of sustained remission, the results in all subgroups were numerically in favour of avacopan. The efficacy of the treatment regimen including avacopan combined with rituximab was higher than the efficacy of the treatment regimen including avacopan combined with cyclophosphamide, both at week 26 and week 52. Furthermore, the safety profile seems more favourable in the rituximab stratum. This could partially be explained by the fact that choice of background therapy was made at the discretion of the investigator. This led to an imbalance in baseline characteristics, with patients with more severe vasculitis receiving treatment with CYC.

Mixing of active and placebo and placebo only comparators after the induction treatment regimens in the rituximab and cyclophosphamide strata compromise interpretation of the joint treatment effect estimate; especially since the obtained results in the two strata were different: the observed superiority in the joint analysis was driven by the rituximab stratum.

The efficacy of avacopan in combination with AZA in terms of promoting maintenance of achieved vasculitis remission does not seem impressive when compared to the efficacy of AZA alone in the later parts of the study, i.e. adding avacopan to azathioprine or mycophenolate did not seem to increase the proportion of patients who manage to remain in remission until Week 52. Hence, the decisions regarding efficacy in the cyclophosphamide stratum were based on results on secondary endpoints. Most importantly, the reduction in cumulative steroid dose between the active and control arms is considered clinically meaningful. Also, considering the limited treatment options in patients with AAV, it might be beneficial to have an alternative to prednisone with a different safety profile.

The efficacy was overall consistent across subgroups of race, age and sex.

Secondary endpoints were not controlled for multiplicity.

The glucocorticoid toxicity index (GTI) was comprised of individual measurements including body mass index (BMI), glucose tolerance, blood pressure, lipids, steroid myopathy, skin toxicity, neuropsychiatric toxicity, and infection. The applicant provided a literature review considered adequate for verification of clinical usefulness of the GTI. The measure is relatively new, with only 3 published trials to date using the score. It is however agreed that the cited literature and the results of the study CL010_168 overall support the potential of GTI to reflect GC related toxicity. Even though the MCID of GTI in AAV is not known, the results are deemed clinically relevant. The GTI was only followed up to Week 26. However, the GC use after Week 26 was similar in the avacopan and comparator arms in the RTX stratum, and the slightly higher CG use in the comparator arm of the CYC stratum is small. Hence, the GTI would not be likely to differ from Week 26 to 52. For the secondary endpoint of BVAS 0 at week 4, avacopan was numerically inferior to prednisone. This could be due to a more rapid effect of prednisone.

Health-related quality-of-life (HRQoL) changes were assessed based on the Medical Outcomes Survey Short Form-36 version 2 (SF-36v2) and EuroQuality of Life-5 Domains-5 Levels (EQ-5D-5L) in the avacopan group compared to the comparator group. The HRQoL increased markedly in both treatment arms during the study, and the differences in improvement between arms were small. Based on SF-36v2, the avacopan arm of the study had statistically significantly better results on the SF-36-PCS score at 52 weeks and already at 26 weeks; but not in the SF-36 MCS. However, there were in both PSC and MCS individual domains with better result in the avacopan arm compared with the prednisone arm of the study. The results on the total SF-36v2 score were submitted by the applicant upon request. An improvement of 11.4 at Week 26 and 13.7 at Week 52 was observed in the avacopan arm from a baseline of 56.7. In the comparator arm, the increase was slightly lower: 7.2 at Week 26 and 9.5 from a baseline of 55.8. The results were overall similar in the RTX and CYC/AZA strata.

At the predefined primary analysis time point (change from baseline to 52 weeks), the improvement in HRQoL as measured by the EQ-5D-5L was larger in the avacopan group than in the comparator group.

At 26 weeks, the difference was not yet significant between the study arms. The applicant was in day 120 LoQ requested to discuss the clinical relevance of the results and provide the MCID for EQ-5D-5L and VAS. Based on the response, EQ-5D-5L increased markedly during the study in both study arms, however, the differences between avacopan and comparator arms were minor even though in favour of avacopan, and similar in both RTX and CYC strata of the study. The differences between study arms in the change from baseline to Week 52 in the EQ-5D-5L VAS were 4.7 in the RTX stratum and 7.9 in the CYC stratum from the baseline values of 63.2 and 64.6 in the RTX stratum and 63.7 and 67.9 in the CYC stratum.

The incidence of relapse after remission had been achieved at Week 26 was numerically higher in the comparator group (14 of 115 subjects, 12.2%) than in the avacopan group (9 of 120 subjects, 7.5%). Furthermore, the applicant's post-hoc analysis on time to relapse over the entire study duration favours avacopan-containing regimens compared to the comparator regimens. The difference in time to relapse is mostly achieved prior to Week 26 but maintained thereafter.

In patients with renal disease, the mean increase from baseline to week 52 was 4.1 mL/min/1.73 m^2 in the comparator group and 7.3 mL/min/1.73 m^2 in the avacopan group. This difference in eGFR of around 3 mL/min/1.73 m^2 between the study arms is small taking in account baseline of 56.6 ml/min/1.73 m^2 in the RTX stratum and 42.9 ml/min/1.73 m^2 in the CYC/AZA stratum. Mean reduction of proteinuria was numerically slightly larger for prednisone (-77) than for avacopan (-74), however, also this difference is small. It should be noted that the secondary endpoints on relapse and on change in eGFR were not conducted between randomised groups, since relapses were only compared between subjects with initial remission and change in eGFR only between subjects who had renal disease at baseline.

Regarding vasculitis damage index, both treatment groups showed a similar mean increase in LSM change in VDI from baseline to Week 52 (1.17 in the avacopan group and 1.15 in the comparator group).

As expected, the cumulative steroid dose was by far higher in the comparator group than in the avacopan group (3846.9 mg versus 1675.5 mg, respectively). However, it needs to be highlighted that a significant amount of steroids was actually needed also in the avacopan group. During the procedure, concern was raised on a potential interaction between avacopan and prednisone. Following the applicant's response, it was concluded that there is no clinically significant interaction and that the difference in cumulative steroid dose corresponds to a "true" steroid-sparing effect of avacopan.

2.5.4. Conclusions on the clinical efficacy

Overall, the 52-week results demonstrate overall statistical superiority of the avacopan regimens compared with the so-called "prednisone arm". The results are driven by the numerical superiority in the rituximab stratum. Although a cautious approach is warranted when interpreting the outcome of efficacy data from subgroup analyses, the benefit of avacopan in combination with CYC/AZA/MMF, in terms of promoting sustained disease remission, seems more limited as compared to the benefit of combining avacopan with RTX. Rather, clinical value dependent on other benefits than remission must be shown. It is agreed with the applicant that some of the secondary endpoints provides some further support for the efficacy of avacopan, however the lack of control for type 1 error hampers full reliability of these results. The most important support for the efficacy of avacopan in this stratum is its steroid-sparing effect.

Taken together, the efficacy of avacopan in combination with rituximab is considered established. Although the efficacy of avacopan in combination with AZA is not fully impressive when compared to the efficacy of AZA alone in the later parts of the study in terms of sustained remission, the reduction

in cumulative steroid dose is still considered clinically meaningful supporting efficacy of avacopan in both strata.

2.6. Clinical safety

Patient exposure

Subject Enrolment by Study in the Avacopan Clinical Study Programme

Study Number	All Subjects	Subjects Receiving Avacopan
Clinical Pharmacology		
CL001_168	48	35
CL004_168	6	6
CL007_168	16	16
CL008_168	32	32
CL013_168	24	24
CL014_168	58	29
CCX1101	80	64
Subtotal	**264**	**206**
Adequate and Well-Controlled Studies		
CL002_168 (Phase 2)	67	44
CL003_168 (Phase 2)	42	29
CL010_168 (Phase 3)	331	166
Subtotal	**440**	**239**
Uncontrolled Studies		
Compassionate-use programme in ANCA-associated vasculitis (worldwide)	4	4
Compassionate-use programme in C3G (worldwide)	3	3
Compassionate-use in pemphigoid	1	1
Compassionate-use in aHUS	2	2
Early-access programme in ANCA-associated vasculitis (Europe and Australia)	12	12
Managed-access programme in C3G (Italy)	1	1
Subtotal	**23**	**23**
Uncontrolled Studies in Other Indications		
CL005_168 (IgAN)	7	7
CL006_168 (aHUS)	6	6
CL009_168 (C3G)	1	1
Subtotal	**14**	**14**
Other Studies (ongoing)		
CL011_168 (C3G)	52*	
CL016_168 (hidradenitis suppurativa)	409*	
Subtotal	**461**	
TOTAL	**1202**	**482****

* Blinded ongoing studies, with numbers as of 24 March 2020.
** Not including subjects receiving avacopan in blinded ongoing studies CL011_168 and CL016_168.

In the seven Phase I clinical trials, all subjects were healthy volunteers, except for study CL013_168, in which mild or moderate impairment of liver function was studied. Avacopan doses up to 100 mg twice daily have been tested in Phase 1 studies, with the longest duration of dosing being 17 days. Overall, in the avacopan clinical study programme (as of 24 March 2020), 482 subjects received at least one dose of avacopan. Of the 239 subjects received avacopan in the phase II and phase III vasculitis studies, 226 were exposed to the proposed dose of 30 mg BID.

The main focus of the safety assessment is placed on the relatively large 52-week phase III study. In this study, subjects were randomised to either avacopan 30 mg x 2 (n=166) or full starting dose of

prednisone (n=165 randomised, 164 in the Safety population). Both treatments were given on top of cyclophosphamide→ azathioprine or rituximab.

Supportive clinical safety data for this application comes from the two phase II studies. Treatment duration was 12 weeks+12-week follow-up. In these studies, different background therapy and avacopan doses were explored. Patients in the control groups of both the phase II studies (n=23 in study CL002_168 and n=13 in study CL003_168) received full SOC treatment (i.e. placebo plus a full starting dose of 60 mg prednisone + either cyclophosphamide→ azathioprine or rituximab). In the phase II study CL003_168, patients in the active group received either 10 mg x 2 (n=13) or 30 mg x2 (n=16) avacopan on top of full SOC (including full starting dose of steroids). In contrast, in study CL002_168, patients in the active group received 30 mgx2 avacopan on top of reduced SOC; either with reduced starting dose of 20 mg prednisone per day (n = 22 subjects) or no prednisone (n = 22).

Pooling of data: The safety data sets from the Phase 2 clinical studies in ANCA-associated vasculitis were pooled and summarised separately to support the Phase 3 data to complement the safety data set for the target patient population. In addition, descriptive analysis of the Phase 1 studies and Phase 2 studies in other indications is available. Pooling of the two Phase 2 studies and the Phase 3 study was performed to evaluate the exposure-adjusted rate of all deaths, serious adverse events, withdrawal of study medication due to adverse events, and events of interest (infections, hepatic enzyme abnormalities, WBC count decreases (neutropenia and lymphopenia), and hypersensitivity events. The Safety Population in the Phase 3 study CL010_168 included all subjects who were randomised and received at least one dose of study medication in the study. Safety Population in Phase 2 studies in AAV includes all subjects who were randomised and received at least one dose of study medication in either study CL002_168 or CL003_168.

Adverse events

An overview of AEs reported in the Phase III study CL010_168 is presented in the table below. A total of 1779 TEAEs were reported by 164 subjects (98.8%) in the avacopan group while a total of 2139 TEAEs were reported by 161 subjects (98.2%) in the comparator group. There were in total 166 SAEs in the comparator group reported in 74 subjects (45.1%) and 116 SAES in the avacopan group reported in 70 subjects (42.2%) in the phase III study.

Overview of Treatment-Emergent Adverse Events in the phase III Study CL010_168 (Safety Population)

Category	Prednisone (N=164) n (%)	Avacopan (N=166) n (%)
TEAE	161 (98.2)	164 (98.8)
Maximum severity of TEAE		
Mild	34 (20.7)	33 (19.9)
Moderate	68 (41.5)	82 (49.4)
Severe	41 (25.0)	39 (23.5)
Life-threatening	14 (8.5)	8 (4.8)
Death	4 (2.4)	2 (1.2)
SAE	74 (45.1)	70 (42.2)
TEAEs leading to study medication discontinuation	28 (17.1)	27 (16.3)

Source: CSR CL010_168 Table 14.3.1

An overview of AEs in the Phase II study pool (based on CL002_168 and CL003_168) is presented in the table below. In the phase II data, 311 TEAEs were reported in the comparator group and 556 TEAEs in the avacopan group. There were 13 SAEs in the comparator group and 34 SAEs in the avacopan group.

Overview Treatment-Emergent Adverse Events in Phase II Studies in ANCA-Associated Vasculitis (Pooled Safety Population)

Category	Prednisone (N=36) n (%)	Avacopan (N=73) n (%)
TEAE	34 (94.4)	69 (94.5)
Maximum severity of TEAE		
Mild	15 (41.7)	21 (28.8)
Moderate	15 (41.7)	34 (46.6)
Severe	4 (11.1)	12 (16.4)
Life-threatening	0 (0)	2 (2.7)
Death	0 (0)	0 (0)
SAE	8 (22.2)	24 (32.9)
TEAEs leading to discontinuation of study medication	4 (11.1)	8 (11.0)

Source: ISS Table 4

Only one of the clinical studies (CL003_168) investigated multiple doses and this study investigated only two doses. Numerically more SAEs were observed in the higher dose group vs the low dose group and for events belonging to the following SOCs: general disorders and administration site conditions, musculoskeletal and connective tissue, skin and subcutaneous tissue, cardiac and endocrine. Both in phase II and phase III, the SOC with the highest subject incidence in the avacopan treated subjects were Infections and Infestations and Gastrointestinal Disorder. See below table for phase III that summarizes TEAEs by SOC reported in ≥5% of subjects in either treatment group.

Treatment-Emergent Adverse Events by System Organ Class in the Phase III Study CL010_168 (Safety Population)

System Organ Class	Prednisone (N=164) n (%)	Avacopan (N=166) n (%)
Infections and Infestations	124 (75.6)	113 (68.1)
Gastrointestinal Disorders	83 (50.6)	101 (60.8)
Musculoskeletal and Connective Tissue disorders	93 (56.7)	92 (55.4)
General Disorders and Administrative Site Conditions	87 (53.0)	76 (45.8)
Skin and Subcutaneous Tissue Disorders	85 (51.8)	73 (44.0)
Nervous System Disorders	73 (44.5)	71 (42.8)
Investigations	67 (40.9)	69 (41.6)
Respiratory, Thoracic and Mediastinal Disorders	80 (48.8)	68 (41.0)
Metabolism and Nutrition Disorders	62 (37.8)	55 (33.1)
Vascular Disorders	48 (29.3)	48 (28.9)
Blood and Lymphatic System Disorders	54 (32.9)	45 (27.1)
Injury, Poisoning and Procedural Complications	48 (29.3)	37 (22.3)
Psychiatric Disorders	44 (26.8)	32 (19.3)
Immune System Disorders	41 (25.0)	30 (18.1)
Renal and Urinary disorders	28 (17.1)	27 (16.3)
Cardiac Disorders	21 (12.8)	26 (15.7)
Eye Disorders	43 (26.2)	25 (15.1)
Ear and Labyrinth Disorders	16 (9.8)	20 (12.0)
Hepatobiliary Disorders	3 (1.8)	10 (6.0)
Reproductive System and Breast Disorders	6 (3.7)	8 (4.8)
Neoplasm Benign Malignant and Unspecified	16 (9.8)	6 (3.6)
Endocrine Disorders	22 (13.4)	5 (3.0)
Surgical and Medical Procedures	0 (0.0)	1 (0.6)
Product Issues	1 (0.6)	0 (0.0)

Source: CSR CL010_168 Table 14.3.1.1.1.

In the Phase III study, nausea was the most frequently reported TEAE in the avacopan group. Peripheral oedema was the most frequently reported TEAE in the comparator group. Those TEAEs with a subject incidence ≥2% higher in the avacopan group compared with the comparator group for TEAEs ≥5% in either treatment group were nausea, headache, vomiting, and rash. Nausea and vomiting were reported predominantly in subjects in the cyclophosphamide stratum.

Incidences of TEAEs possibly related to avacopan/matching placebo were 103 subjects (62.8%) in the comparator group compared with 100 subjects (60.2%) in the avacopan group. In addition, prior to unblinding, all TEAEs were reviewed to identify those considered possibly related to glucocorticoid use based on European League Against Rheumatism-recommended search terms. The incidence of TEAEs considered possibly related to glucocorticoid use was 80.5% in the comparator group compared with 66.3% in the avacopan group. A higher subject incidence in the comparator group compared with the avacopan group was observed for AEs of weight increased, insomnia, hyperlipidaemia, adrenal insufficiency, increased blood glucose, and irritability.

Potential Adverse Drug Reactions (ADRs): The following methodology was applied to identify potential ADRs based on: the incidence or rate of events compared with the control group; biologic plausibility; clinical impressions of individual cases; statistical assessment of the strength and magnitude of the

observed effect; dose relationship (limited because most subjects received 30 mg avacopan twice daily); event severity; consistency of findings across studies; consistency of findings from similar events; consistency of findings from similar compounds (limited because avacopan is the only member of its class); and clinical relevance. In addition, all TEAEs were reviewed in a stepwise manner to identify potential ADRs based on their incidence and the relative incidence in the comparator group and whether it was a pre-specified event of interest i.e. infection, increase in liver function tests, decrease in WBC count [neutropenia and lymphopenia], and hypersensitivity/angioedema.

The ADRs, as classified by the applicant, are summarised under the following headings as well as data for Infections, Low WBC and Cardiac manifestations that were viewed as items that could also be considered for inclusion as ADRs.

Liver function test increased (proposed ADR): There were exclusion criteria and suspension of medication-criteria with regards to deranged liver tests in the clinical studies. Both AEs of hepatic function test and SAEs of hepatic function test were more frequent in the avacopan group vs the steroid group in the pooled phase II/phase III data and in the phase III data, please refer to table below.

Incidence of Treatment-Emergent Adverse Events Associated with Elevated Hepatic Function Tests by System Organ Class and Preferred Term in the phase III Study CL010_168 (Safety Population)

System Organ Class Preferred Term	Prednisone (N=164) n (%)	Avacopan (N=166) n (%)
Any TEAE associated with hepatic function test abnormalities	19 (11.6)	22 (13.3)
Investigations	18 (11.0)	16 (9.6)
Hepatic enzyme increased	7 (4.3)	5 (3.0)
ALT increased	6 (3.7)	3 (1.8)
Blood bilirubin increased	0 (0.0)	3 (1.8)
Liver function test increased	1 (0.6)	3 (1.8)
AST increased	4 (2.4)	2 (1.2)
Transaminases increased	3 (1.8)	2 (1.2)
Liver function test abnormal	2 (1.2)	0 (0.0)
Hepatobiliary disorders	1 (0.6)	6 (3.6)
Hepatic function abnormal	0 (0.0)	3 (1.8)
Drug-induced liver injury[a]	0 (0.0)	1 (0.6)
Hepatitis cholestatic	0 (0.0)	1 (0.6)
Hepatocellular injury	1 (0.6)	1 (0.6)

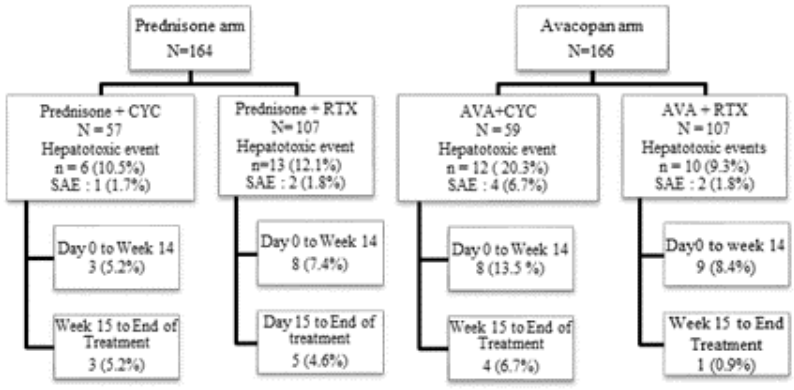
[a] Reported term: azathioprine induced liver toxicity
Source: CSR CL010_168 Table 14.3.1.10.1

Of the 22 subjects in the avacopan group with any liver function test AE, 7 discontinued study medication (1 had an interruption and then discontinuation) and 2 subjects interrupted their study medication as a result of the liver function test AE. The time to onset of liver function test AEs was within 4 days of treatment onset in 1 subject, within 5 to 90 days of treatment onset in 15 subjects, and more than 90 days after start of treatment in 6 subjects. The AEs resolved in all cases; the event was "ongoing" in 1 subject who subsequently died due to worsening of GPA. In 7 of the 22 cases, the event was considered as severe. Confounding factors were present in many of the cases.

In response the CHMP's request, it was clarified that AEs potentially representing signs or symptoms of hepatotoxicity are spread across multiple SOCs. In order to specifically investigate hepatotoxicity, the AEs of particular interest were assessed together as "hepatic events" irrespective of which SOC they coded to. The PTs reported in the study were pre-specified in the Statistical Analysis Plan prior to unblinding and included drug-induced liver injury, hepatic function abnormal, hepatocellular injury, alanine aminotransferase (ALT) increased, aspartate aminotransferase increased, blood bilirubin

increased, blood bilirubin unconjugated increased, hepatic enzyme increased, liver function test abnormal, liver function test increased, transaminases increased, and hepatitis cholestatic. Using this definition, a total of 19 (11.6%) subjects in the comparator group and 22 (13.3%) subjects in the avacopan group experienced a hepatic event, see below figure which also displays the frequency in each background treatment stratum.

Number of Subjects Experiencing Hepatic Disorder in different stratum



Notes: Ava=Avacopan; AZA=Azathioprine; CYC=Cyclophosphamide; RTX=Rituximab; N=Number of subjects per treatment group; n=Number of subjects with observation; SAE=Serious adverse event.

Study medication was interrupted or discontinued in 3 of 6 cases of hepatic function test SAEs in the comparator group and 6 of 9 cases in the avacopan group in the phase III study. All events resolved. According to the CSR, none of the cases of liver enzyme elevations in the avacopan group met Hy's law criteria. In both treatment groups, several of the subjects with SAEs of hepatic function tests had a documented increased bilirubin around the time of the event. In addition, in both treatment groups, several (but not all) of the subjects with SAEs of hepatic function tests had a documented increased ALP in relation to the event. One subject in each treatment group had elevated liver function tests at baseline. In the prednisolone group 2/6 subjects belonged to the cyclophosphamide stratum while 4/6 belonged to the rituximab stratum. In the avacopan group, 6/9 belonged to the cyclophosphamide stratum (at least one of those received MMF) while 3/9 belonged to the rituximab stratum. The Hepatobiliary disorders SOC included 6 events in the avacopan group and 1 in the comparator group. In the avacopan group the PTs were: Hepatic function abnormal, Cholelithiasis, Drug-induced liver injury, Hepatitis, Hepatitis cholestatic and Hepatocellular injury. It is also reported that, in the phase III study, the incidence of hepatobiliary disorders leading to study medication discontinuation was 5 of 166 subjects (i.e. 3.0%) in the avacopan group compared with none (0.0%) in the comparator group. Study medication was, according to the CSR, paused or discontinued permanently due to hepatic enzyme abnormalities in 5 subjects (3.0%) in the comparator group and 9 subjects (5.4%) in the avacopan group in the phase III study.

Angioedema (proposed ADR): Two events of angioedema occurred in the phase III study in the avacopan group (2/166=1.2%) vs none in the comparator group (0/164=0.0%). In the first case, study medication was discontinued, anti-allergic treatment was given, and the event resolved without sequelae. In the second case, study medication was interrupted, and the event resolved. Study medication was then re-started, the angioedema did not recur, and the event was not considered related to study medication.

Overall, in this study, 70 subjects (42.7%) in the comparator group and 68 subjects in the avacopan group (41.0%) had any TEAEs of hypersensitivity. The majority of the hypersensitivity events were mild in severity.

Blood creatine phosphokinase increased (proposed ADR): The incidence in the phase III study was 1 of 164 subjects (0.6%) in the comparator group and 6 of 166 subjects (3.6%) in the avacopan group, please see table below. No blood creatine phosphokinase increases were reported as SAEs in this study. No events of rhabdomyolysis or myositis were observed. There appeared to be no association between creatine phosphokinase increase and cardiac TEAEs, with no cardiac AEs observed at the time of creatine phosphokinase elevation in these subjects.

Treatment-Emergent Adverse Events of Increased Blood Creatine Phosphokinase in Study CL010_168 (Safety Population)

Start date	Severity	CTCAE grade	AEs occurring with the elevation	Outcome	Action with study drug	Relatedness
Prednisone Group						
Day 28	Moderate	1	Muscle spasm, blepharitis, elevated blood lactate dehydrogenase	Resolved Day 92	None	Possibly related
Avacopan Group						
Day 225	Mild	2	Bone pain, anxiety, rash, ear discomfort	Ongoing	None	Possibly related
Days 92 and 246	Mild, mild	3	Viral upper respiratory tract infection, myalgia, fatigue	Resolved on Days 99 and 261	Study drug interrupted for both events	Probably not related, possibly related
Day 49	Moderate	2	Painful dry nose, joint pain, worsening dry cough, painful dry eyes	Resolved Day 141	None	Possibly related
Day 30	Severe	3	Increased amylase and lipase	Ongoing	Study drug discontinued	Probably not related
Day 93 and 276	Mild, mild	1	Back pain	Resolved Day 225, ongoing	None for both events	Probably not related, probably not related
Day 113	Mild	1	Increased blood lactate dehydrogenase, diarrhoea	Ongoing	None	Probably not related

In the Phase II studies, 3 subjects in the avacopan group had TEAEs of increased blood creatine phosphokinase; none of the events were serious.

Headache, Nausea, Vomiting (proposed ADR): These events were reported more often in the avacopan group vs the comparator group in the phase III study. The frequency for nausea among avacopan-treated was 23.5%, for headache 20.5% and for vomiting 15.1%.

Cardiac manifestations; cardiac failure: In the phase III study, there were 4 subjects in the avacopan group and no subjects in the comparator group in the phase III study with cardiac failure. The applicant states that the 4 subjects all had a medical history of cardiovascular disease and the incidence of serious major cardiovascular events was higher in the comparator group. Two SAEs each of angina pectoris and cardiac failure were observed in the avacopan group, see further below. The events related to the SOC cardiac disorders were overall somewhat more frequent in the avacopan

group vs the comparator group across the phase II and phase III studies. In addition, there were several cardiac SAEs in studies in other studied indications (unstable angina, cardiac asystole that resulted in deaths, atrial fibrillation).

Infections: The incidence of infections in the phase III study is presented in the table below.

Incidence of Treatment-Emergent Infection in the phase III Study CL010_168 (Safety Population)

Category	Prednisone (N=164) n (%)	Avacopan (N=166) n (%)
Any treatment-emergent infection	124 (75.6) 291 events	113 (68.1) 233 events
Any serious treatment-emergent infection	25 (15.2) 31 events	22 (13.3) 25 events
Any severe treatment-emergent infection	10 (6.1)	12 (7.2)
Any treatment-emergent infection leading to study withdrawal	5 (3.0)	4 (2.4)
Any life-threatening treatment-emergent infection	2 (1.2)	1 (0.6)
Any treatment-emergent infection leading to death	2 (1.2)	1 (0.6)
Most common infection TEAEs (≥3% in any treatment group)		
Nasopharyngitis	30 (18.3)	25 (15.1)
Upper respiratory tract infection	24 (14.6)	24 (14.5)
Urinary tract infection	23 (14.0)	12 (7.2)
Pneumonia	11 (6.7)	11 (6.6)
Sinusitis	12 (7.3)	10 (6.0)
Bronchitis	10 (6.1)	5 (3.0)
Gastroenteritis	1 (0.6)	5 (3.0)
Lower respiratory tract infection	8 (4.9)	5 (3.0)
Rhinitis	2 (1.2)	5 (3.0)
Herpes zoster	6 (3.7)	4 (2.4)
Influenza	8 (4.9)	4 (2.4)
Oral candidiasis	7 (4.3)	4 (2.4)
Oral herpes	6 (3.7)	4 (2.4)
Viral upper respiratory tract infection	5 (3.0)	4 (2.4)
Viral infection	5 (3.0)	2 (1.2)
Most common serious infection TEAEs (≥1% in any treatment group)		
Pneumonia	6 (3.7)	8 (4.8)
Urinary tract infection	2 (1.2)	3 (1.8)
Device-related infection	0 (0)	2 (1.2)
Influenza	1 (0.6)	2 (1.2)
Herpes zoster	2 (1.2)	0 (0)
Infectious pleural effusion	2 (1.2)	0 (0)
Pneumonia bacterial	2 (1.2)	0 (0)
Respiratory syncytial virus infection	2 (1.2)	0 (0)

Eleven subjects (6.7%) had serious opportunistic infections in the comparator group compared with 6 subjects (3.6%) in the avacopan group. PTs of opportunistic infections in the avacopan arm included pneumonia (n=3) infective exacerbation of chronic obstructive airways disease, Campylobacter gastroenteritis and hepatitis B. In the phase III study, Otitis Media was reported with a frequency of 0.6% in the comparator group and 2.4% in the avacopan group while Cellulitis was reported in 0.0% in the comparator group and 2.4% in the avacopan group. In the pooled phase II studies, the overall incidence of infection was 41.7% in the comparator group and 52.1% in the avacopan group. No Neisseria meningitidis infections were reported.

Low White Blood Cell Count: Overall, the incidences of this event across the phase III and the phase II studies were generally not higher than in the comparator group i.e. the steroid group.

In the phase III study, 39 subjects (23.8%) in the comparator group and 31 subjects (18.7%) in the avacopan group had TEAEs associated with low WBC count. A total of 8 subjects (4.9%) in the comparator group had serious TEAEs of neutropenia or lymphopenia compared with 4 subjects (2.4%) in the avacopan group; in all of these cases the event resolved, in 3 of the cases (2 comparator group and 1 in the avacopan group) treatment was interrupted or discontinued.

However, in the phase II study, the incidence of Grade 3 lymphopenia was 23.3% in the avacopan group compared with 5.9% in the comparator group, but no Grade 4 lymphopenia events were observed in the Phase II studies. The higher incidence of Grade 3 lymphopenia seen in the avacopan treatment group in the Phase II studies is inconsistent with results from the Phase III study, where the incidence was similar for both groups (30.1% in the comparator group and 28.3% in the avacopan group). Moreover, the incidence of Grade 4 lymphopenia was higher in the comparator group in the Phase 3 study (8.0% vs. 2.4% in the avacopan group).

Serious adverse event/deaths/other significant events

Deaths: During the phase III study, 2 subjects (1.2%) in the avacopan group and 4 subjects (2.4%) in the comparator group died. In the avacopan group, the causes of death were GPA for 1 subject and pneumonia for the other. These 2 subjects were not receiving avacopan at the time of death. The two discontinuations occurred on Day 236 in one subject who died on Day 315 and on Day 50 in one subject who died on Day 160. In the comparator group the causes of death in the phase III study were diarrhoea, vomiting, and fungal infection; infectious pleural effusion; death of unknown cause; and acute myocardial infarction.

Serious adverse events: The most common SAEs by SOC in the phase III study were Infections and Infestations, which occurred in 25 subjects (15.2%) in the comparator group and 22 subjects (13.3%) in the avacopan group. The only SOC with an SAE incidence of ≥2% in the avacopan group compared with the comparator group was Hepatobiliary Disorders (see above). Serious adverse events reported by ≥1% of subjects both treatment groups are presented in the table below.

Serious Treatment-Emergent Adverse Events by Preferred Term Occurring in ≥1% of Subjects in Either Treatment Group in Study CL010_168 (Safety Population)

Preferred Term	Prednisone (N=164)		Avacopan (N=166)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
Any SAE	74 (45.1)	166	70 (42.2)	116
ANCA-positive vasculitis	20 (12.2)	25	12 (7.2)	12
Pneumonia	6 (3.7)	6	8 (4.8)	9
GPA	1 (0.6)	1	5 (3.0)	5
Acute kidney injury	1 (0.6)	2	3 (1.8)	3
Urinary tract infection	2 (1.2)	2	3 (1.8)	3
Angina pectoris	0 (0.0)	0	2 (1.2)	2
Cardiac failure	0 (0.0)	0	2 (1.2)	2
Device-related infection	0 (0.0)	0	2 (1.2)	2
Drug hypersensitivity	2 (1.2)	3	2 (1.2)	2
Hepatic enzyme increased	3 (1.8)	3	2 (1.2)	2
Hepatic function abnormal	0 (0.0)	0	2 (1.2)	2
Hyperglycaemia	1 (0.6)	1	2 (1.2)	2
Influenza	1 (0.6)	1	2 (1.2)	2
Pyrexia	3 (1.8)	3	2 (1.2)	3
Acute myocardial infarction	2 (1.2)	2	1 (0.6)	1
Agranulocytosis	2 (1.2)	2	1 (0.6)	1
Blood creatinine increased	2 (1.2)	2	1 (0.6)	1
Lymphopenia	3 (1.8)	3	1 (0.6)	1
Pulmonary alveolar haemorrhage	2 (1.2)	2	1 (0.6)	1
Anaemia	2 (1.2)	2	0 (0.0)	0
Dehydration	2 (1.2)	2	0 (0.0)	0
Diarrhoea	3 (1.8)	3	0 (0.0)	0
Epistaxis	2 (1.2)	2	0 (0.0)	0
Glomerulonephritis	2 (1.2)	2	0 (0.0)	0
Herpes zoster	2 (1.2)	2	0 (0.0)	0
Infectious pleural effusion	2 (1.2)	2	0 (0.0)	0
Large intestine polyp	2 (1.2)	2	0 (0.0)	0
MPA	2 (1.2)	2	0 (0.0)	0
Mononeuropathy multiplex	2 (1.2)	2	0 (0.0)	0
Neutropenia	2 (1.2)	2	0 (0.0)	0
Pneumonia bacterial	2 (1.2)	2	0 (0.0)	0
Prostate cancer	2 (1.2)	2	0 (0.0)	0
Pulmonary embolism	3 (1.8)	3	0 (0.0)	0
Respiratory syncytial virus infection	2 (1.2)	2	0 (0.0)	0
Thrombocytopenia	2 (1.2)	2	0 (0.0)	0
Vomiting	2 (1.2)	2	0 (0.0)	0

In the phase III study, the most common SAE was anti-neutrophil cytoplasmic antibody positive vasculitis (worsening), with 25 events reported in 20 subjects (12.2%) in the comparator group and 12 events in 12 subjects (7.2%) in the avacopan group. When all preferred terms referring to vasculitis worsening were combined, i.e., anti-neutrophil cytoplasmic antibody positive vasculitis/granulomatosis with polyangiitis/microscopic polyangiitis, the incidence was higher in the comparator group, 23 of 164 subjects (14.0%), compared to the avacopan group, 17 of 166 subjects (10.2%). The other most

common SAEs in the avacopan group were pneumonia, acute kidney injury, and urinary tract infection. Regarding the cases of acute kidney injury or serum creatinine increase (3 in the comparator group and 4 in the avacopan group), all 7 cases resolved, none were considered related to study medication, and in all four cases in the avacopan group, the eGFR was similar or higher at the end of treatment compared to baseline.

In the phase III study, 2 SAEs each of angina pectoris and cardiac failure were observed in the avacopan group, with none in the comparator group. With respect to the major cardiac AEs (defined as nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death) there were 3 in the comparator group compared with 1 in the avacopan group. There were two non-fatal myocardial infarction and one fatal myocardial infarction in the comparator group and one non-fatal myocardial infarction in the avacopan group.

In an integrated analysis of subject incidence of all SAEs by SOC and PT in Phase II and III studies, the exposure-adjusted overall subject SAE incidence was 82 of 200 subjects (39.4%) in the comparator group and 94 of 239 subjects (39.9%) in the avacopan group. The overall SAE first incidence rate was 60.1 per 100 subject-years in the comparator group and 61.6 per 100 subject-years in the avacopan group. The overall SAE event rate was 91.5 per 100 subject-years in the comparator group and 70.7 per 100 subject-years in the avacopan group; the difference in event rate was -20.8 (95% CI -38.3, -3.3).

In the combined phase II study pool, SAEs were most commonly reported in the Infections and Infestations, Renal and Urinary Disorders, and Vascular Disorders SOCs. Serious adverse events reported in ≥2 subjects and with a >1% higher incidence in the avacopan group were respiratory tract infection, renal impairment, vasculitis, and increased C-reactive protein.

No serious adverse events were observed among avacopan-treated subjects in the Phase I studies.

Laboratory findings

Decreases in mean leukocytes, neutrophil, lymphocyte and thrombocyte counts were noted both in phase III and phase II. Also, grade 3-4 severity shifts in lymphocyte counts occurred both in the avacopan group and the comparator group. Mean change from baseline in Liver Function Test Parameters in the avacopan group was, according to the applicant, overall consistent with the changes in the comparator group in the phase III study. Increases in creatine phosphokinase were noted in both treatment groups in the phase III study; however, the magnitude of these increases was greater in the avacopan group at several visits.

In the phase III study, at baseline, both creatinine and blood urea nitrogen levels (mean and median) were above the ULN for both treatment groups. For both parameters, decreases in mean and median values were observed over time and maintained for the duration of the study.

Vital Signs, Physical Findings and Other Observations in the phase II and phase III studies: Changes from baseline in vital sign parameters were generally similar for avacopan and control groups in the clinical studies. However, body mass index (BMI) appeared to increase more in the comparator group compared with the avacopan group in the phase III study and the phase II study CL002_168. In the phase III study, a total of 20 subjects had an abnormal ECG finding that were considered clinically significant during the study, comprising 8 subjects in the comparator group and 12 subjects in the avacopan group.

Cardiovascular Safety: A thorough QT/QTc study, CL014_168, was conducted to evaluate the effects of therapeutic (30 mg twice daily) and supratherapeutic (100 mg twice daily) doses of avacopan on cardiac electrophysiology, including the QTc interval. This was a double-blind, randomised, placebo-

and positive-controlled (moxifloxacin), double-dummy, parallel-group, multiple-dose study in 58 healthy subjects with a nested crossover comparison between avacopan, moxifloxacin, and placebo. Subjects in the avacopan cohort received 30 mg avacopan twice daily for 7 days, followed by 100 mg twice daily for another 7 days. Avacopan showed no clinically meaningful effects on cardiac repolarisation, i.e., QT/QTc intervals, or cardiac conduction.

The primary ECG endpoint was change-from-baseline QTcF (ΔQTcF). Mean change-from-baseline QTcF (ΔQTcF) on avacopan was according to the applicant similar to ΔQTcF on placebo on Days 1, 7, and 14, ranging across all 3 days from −5.5 to 3.5 ms on avacopan and from −6.9 to 1.4 ms on placebo. Mean placebo-corrected ΔQTcF (ΔΔQTcF) across all 3 days ranged from −1.0 to 4.9 ms. The upper bound of the 90% CI of ΔΔQTcF was below 10 ms at all postdose time points on all days. After dosing with 400 mg moxifloxacin, a clear increase of mean ΔΔQTcF was observed with a peak value of 15.8 ms (90% CI: 10.84 to 20.77) at 3 hours post-dose.

There were no deaths or subject discontinuations due to AEs reported in the study. One subject in receiving avacopan placebo and moxifloxacin experienced a serious adverse event (SAE) of transverse myelitis. The percentage of subjects reporting AEs was 38% following multiple supratherapeutic doses of avacopan and 21% following multiple therapeutic doses. No treatment- or dose-related trends were observed with respect to clinical laboratory, vital sign, ECG, or physical examination safety assessments.

The potential effect of avacopan and its main metabolite CCX168-M1 on cardiac safety was also evaluated in 16 healthy volunteers in study CL007_168. The CSR concluded that there was no exposure-response relationship between CCX168, CCX168-M1, or CCX168 plus CCX168-M1 and QTcI observed in this study across a broad concentration range. Overall, there were no remarkable observations in the categorical analysis and cardiodynamic ECG abnormalities were overall minimally reported.

Safety in special populations

Intrinsic Factors

The AE data from adult subjects by gender, age, race, renal function (eGFR), ANCA status, vasculitis stage (newly diagnosed vs. relapsing), vasculitis type (GPA vs. MPA), and hepatic function, in both the phase 2 and 3 studies were analysed and summarised. Avacopan is not recommended for subjects with severe hepatic impairment (SmPC sec. 4.2), but no dose-adjustment is proposed with regards to renal function. The recommendations are based on PK-data from patients with mild to moderate hepatic impairment and population PK analysis examining exposures in mild to severe renal impairment, please refer to PK-assessment. In the phase III study, there was an increasing trend with increasing age in the incidence of infections and infestations both in the avacopan and comparator groups. An increasing trend with increasing age was also noted for hepatobiliary disorders in the avacopan group (2.5% in those aged <65 years, 6.7% in those aged 65 to 74 years, and 15.4% in those aged ≥75 years) but not in the comparator group (2.2%, 0.0%, and 4.0% respectively). A comprehensive presentation of the safety data in the elderly, summarised as per the standard table was not provided with the initial submission. Data is almost exclusively derived from adults.

Regarding the race, in the phase III study, comparison of TEAE incidence by race was limited by the disparity in sample size between White and non-White subjects (>80% of all subjects enrolled in the Phase 3 study were White). Hepatic enzyme increase occurred in 0.0% (0/138) of White subjects vs. 17.9% (5/28) of non-White subjects in the avacopan group compared with 2.9% (4/140) and 12.5% (3/24) respectively in the comparator group.

Extrinsic Factors

With regards to Background Immunosuppressive Therapy, in the phase III study, the TEAE incidence across many SOCs was higher in the cyclophosphamide compared with the rituximab stratum for both treatment groups including Infections and infestations, Gastrointestinal disorders, Blood and lymphatic system disorders.

For Infections and infestations, 76.3% of the subjects that received avacopan + cyclophosphamide had such event compared to 63.6% of subjects that received avacopan +rituximab. In the comparator group, 82.5% that received the combination with cyclophosphamide had such event compared to 72.0% that received the combination with rituximab.

The SOCs that had a ≥5% difference in subject TEAE incidence between the two strata in the avacopan group but did not show the same trend in the comparator group, included Cardiac disorders, and Hepatobiliary disorders.

For cardiac disorders, the incidence was 25.4% in the cyclophosphamide vs. 10.3% in the rituximab strata in the avacopan group and 12.3% vs. 13.1% in the comparator group. Angina pectoris, cardiac failure, and palpitations appeared to be more common in the cyclophosphamide compared with the rituximab stratum in the avacopan group.

Regarding Hepatobiliary disorders, the incidence was 10.2% in the cyclophosphamide vs. 3.7% in the rituximab strata in the avacopan group and 0.0% vs. 2.8% in the comparator group.

The AEs potentially representing signs or symptoms of hepatotoxicity are spread across multiple SOCs. In order to specifically investigate hepatotoxicity, the AEs of particular interest were assessed together as "hepatic events" irrespective of which SOC they coded to. Using this definition, a total of 19 (11.6%) subjects in the comparator group and 22 (13.3%) subjects in the avacopan group experienced a hepatic event. Focusing on the CYC/AZA stratum, a total of 6 (10.5%) subjects in the comparator group and 12 (20.3%) subjects in the avacopan group experienced a hepatic event. In the Pred/RTX-stratum, 13 (12.1%) had such an event and in the avacopan/RTX stratum, 10 (9.3%) subjects had such event.

Furthermore, in the phase II study studies, the TEAE incidence for many SOCs was higher in the cyclophosphamide compared with the rituximab stratum in both treatment groups.

Analysis for SAE, AESI and discontinuations occurring during the first 20 Weeks (the period during which prednisone was administered to the prednisone control group) and during the weeks from week 21 to the end of the phase IIII study was also performed. During the first 20 Weeks, the overall subject SAE incidence was 54 of 164 subjects (32.9%) in the comparator group and 49 of 166 subjects (29.5%) in the avacopan group. From week 21 to the End of Study, the overall subject incidence of SAEs was 44 of 164 subjects (26.8%) in the comparator group and 32 of 166 subjects (19.3%) in the avacopan group. During the First 20 Weeks, the overall subject incidence of discontinuation of study medication due to a TEAE was 19 of 164 subjects (11.6%) in the comparator group and 22 of 166 subjects (13.3%) in the avacopan group. From Week 21 to the End of Study, the overall subject incidence of discontinuation of study medication due to a TEAE was 9 of 164 subjects (5.5%) in the comparator group and 5 of 166 subjects (3.0%) in the avacopan group. During the First 20 Weeks, the overall subject incidence of infection was 90 of 164 subjects (54.9%) in the comparator group and 82 of 166 subjects (49.4%) in the avacopan group. From Week 21 to the End of Study, the overall subject incidence of infection was 86 of 164 subjects (52.4%) in the comparator group and 73 of 166 subjects (44.0%) in the avacopan group. During the First 20 Weeks, the overall subject incidence of hepatic test AEs was 13 of 164 subjects (7.9%) in the comparator group and 19 of 166 subjects (11.4%) in the avacopan group. From Week 21 to the End of Study, the overall subject incidence of hepatic test

AEs was 7 of 164 subjects (4.3%) in the comparator group and 4 of 166 subjects (2.4%) in the avacopan group.

Avacopan is not recommended during pregnancy and in women of childbearing potential not using contraception, as adequately reflected in the SmPC.

Immunological events

Immunological events have not been reported by the applicant. This is acceptable as avacopan is not a biological medical product and issues with anti-drug antibodies are not foreseen.

Safety related to drug-drug interactions and other interactions

Pharmacokinetic safety related interactions have been discussed above.

Discontinuation due to adverse events

In the phase III study, the incidence of hepatobiliary disorders leading to study medication discontinuation was higher in the avacopan group (5 of 166 subjects i.e. 3.0%) compared with none (0.0%) in the comparator group. Integrated analysis of the subject incidence of TEAEs leading to study medication discontinuation in Phase II and III studies showed that the overall subject incidence of TEAEs leading to discontinuation of study medication was 32 of 200 subjects (15.6%) in the comparator group and 35 of 239 subjects (14.9%) in the avacopan group. The overall incidence rate of TEAEs leading to discontinuation of study medication (first incidence rate) was 18.0 per 100 subject-years for the comparator group and 18.2 per 100 subject-years for the avacopan group, with a difference in rate of 0.2 (95% CI -8.4, 8.9). The overall rate of TEAEs leading to discontinuation of study medication was 21.5 per 100 subject-years in the comparator group and 21.7 per 100 subject-years in the avacopan group, with a difference in rate of 0.2 (95% CI -8.8, 9.2).

Post marketing experience

Not applicable as avacopan was not authorised in any region at the time of this assessment.

2.6.1. Discussion on clinical safety

General features of the submitted safety data and exposure

This application concerns a first-in-class, small molecule, C5aR inhibitor with the following currently intended indication: "*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 section 4.2).*"

The proposed posology is 30 mg twice daily taken as capsules.

Inhibitors of C5 have been associated with an increased risk of infections with encapsulated bacteria, such as Neisseria meningitidis. However, avacopan does not significantly affect membrane attack complex formation, as claimed by the applicant.

Regarding non-clinical data, no dose-limiting effects or target organ of toxicity were noted in the chronic studies and, therefore, the toxicology/safety of avacopan is not considered fully explored and will be further characterised in the post-marketing phase (PASS).

The human safety data to support the application derives from 7 Phase I studies, 2 Phase II studies (CL002_168 and CL003_168) and 1 Phase III study (CL010_168). The main focus of the safety assessment is placed on the relatively large 52-week phase III study. In this study, subjects were randomised to either avacopan 30 mg x 2 (n=166) or full starting dose of prednisone (n=165 randomised, 164 in the Safety population). Both treatments were given on top of cyclophosphamide→ azathioprine or rituximab. Thus, this study compared SOC (full dose steroids) vs avacopan in the currently applied for posology.

Supportive clinical safety data for this application comes from the two phase II studies. Treatment duration was 12 weeks+ 12-week follow-up. In these studies, different background therapy and avacopan-doses were explored. Patients in the control groups of both the phase II studies (n=23 in study CL002_168 and n=13 in study CL003_168) received full SOC treatment (i.e. placebo plus a full starting dose of 60 mg prednisone + either cyclophosphamide→ azathioprine or rituximab). In the phase II study CL003_168, patients in the active group received either 10 mg x 2 (n=13) or 30 mg x2 (n=16) avacopan on top of full SOC (including full starting dose of steroids). In contrast, in study CL002_168, patients in the active group received 30 mgx2 avacopan on top of reduced SOC; either with reduced starting dose of 20 mg prednisone per day (n = 22 subjects) or no prednisone (n = 22). The interpretation of the safety data from the phase II studies is thus limited by the fact that in: 1) some subjects in the active group received a lower avacopan dose that this application concerns and 2) many of the subjects in the avacopan groups of these studies also received scheduled doses of steroids.

For the safety assessment it is important to note that all subjects in the phase II and phase III studies received either a background treatment with cyclophosphamide/azathioprine or rituximab. Cyclophosphamide is associated with myelosuppression, infections, urinary tract and renal toxicity as well as cardiotoxicity. Hepatoxicity is also among reported adverse reactions. Azathioprine is associated with bone marrow suppression, infections and hepatoxicity. Rituximab is associated with infections, neutropenia, thrombocytopenia, infusion related reactions and some cardiac disorders. It is further noted that in the phase III study, if azathioprine was not tolerated, mycophenolate mofetil or mycophenolate sodium may have been given instead. Similarly, in the phase II studies, after the initial cyclophosphamide treatment, mycophenolate mofetil or potentially also methotrexate or could have been used by subjects in case azathioprine was not tolerated. These medicinal products are also known to potentially affect the liver, cause cytopenias and an increased risk for infections. In the phase III study 44 patients used AZA in combination with avacopan, 15 subjects used mycophenolate mofetil and 2 subjects used mycophenolate sodium in combination with avacopan. Only very few subjects were treated with methotrexate and with mycophenolate as non-protocol specified medications.

Overall, in the avacopan clinical study programme, 482 subjects received at least one dose of avacopan. Of the 239 subjects received avacopan in the phase II and phase III vasculitis studies, 226 who were exposed to the proposed dose of 30 mg BID. Regarding 1-year exposure, the phase III trial was the only study with that length of exposure and in this study 166 patients were randomised to 30 mg avacopan twice daily. Of those 166 subjects 37 subjects had early discontinuation of study medication and therefore, a total of 129 subjects completed the 52-week treatment period of the Phase 3 study.

Exposure is limited and will affect the ability to capture less frequently occurring events but can be accepted given the rarity of this condition. Two further caveats should be noted:

- Patients with very severe disease were largely excluded from the clinical trials as well as patients with severe hepatic impairment. This is reflected in the SmPC.
- The studies conducted to date are far too limited with regards to follow-up time and total exposure to provide any reassurance vid regards to the risk for malignancy. As this is not an

unreasonable concern considering the mechanism of action (and so far also without complete preclinical data addressing the issue), this is included as a safety concern (with expected latency) and addressed post-marketing and also reflected in the SmPC. There is a planned PASS, which will be conducted after the approval.

Overview of Adverse Events and proposed ADRs

In the phase III study, the subject incidence of TEAEs, SAEs and TAES leading to study medication discontinuation was similar in the avacopan group as compared to the comparator group. Also, in the phase II data, these incidences were similar, but the incidence of SAEs was numerically higher in the avacopan group as compared to the steroid group. The total number of TEAEs in the phase III study was higher in the comparator group as compared to the avacopan group: 2139 TEAEs vs 1779 TEAEs, as claimed by the applicant. However, in the phase II data, the opposite was noted; 311 TEAEs were reported in the comparator group and 556 events in the avacopan group. A similar pattern was seen for SAEs. There were in total 166 SAEs in the comparator group and 116 SAEs in the avacopan group in the phase III study. In the phase II data, there were 13 SAEs in the comparator group and 34 SAEs in the avacopan group. Because of the limitations of the safety data derived from the phase II studies (as highlighted above) the data from the relatively large phase III study with longer duration will be given more weight.

With the data provided, it is not straightforward to assess if the risks associated with avacopan are generally dose dependent. Only one of the clinical studies investigated two doses. It is noted that numerically more SAEs were observed in the higher dose group vs the low dose group and for events belonging to the following SOCs: general disorders and administration site conditions, musculoskeletal and connective tissue, skin and subcutaneous tissue, cardiac and endocrine. However, conclusions are hampered by the low number of subjects in the study and the heavy background treatment.

It should be noted that there is no requirement to demonstrate fulfilment of an unmet need, such as a steroid-sparing effect leading to overall safety benefits (as compared to SOC). Nonetheless, the potential safety benefits of any steroid-sparing effect, is still a major area of interest. Steroids may, according to the phase III study protocol, be given also in the avacopan arm (subjects who experienced a relapse of their ANCA-associated vasculitis may have been treated with IV glucocorticoids and/or oral glucocorticoids, these subjects may have continued study drug treatment and were to continue in the study). In the clinical data, there were indeed indications of a decreased frequency of AEs typically attributed to steroids such as weight increase, insomnia, increased blood glucose in the avacopan group vs the steroid group.

Both in phase II and phase III, the SOC with the highest subject incidence in the avacopan treated subjects were Infections and Infestations and Gastrointestinal Disorder. Based on these data, the applicant initially proposed that the following items should be listed as ADRs in the summary table in section 4.8 of the SmPC: Headache, Nausea, Vomiting, Liver function test increased and Blood creatine phosphokinase increased and Angioedema (see further discussion below).

Overall, since the numbers of subjects with TEAEs are overlapping between avacopan and comparator groups and as the comparator group is not a placebo group, omission of any ADRs from section 4.8 based on lower frequency in the avacopan group as opposed to comparator group was not deemed acceptable by the CHMP. In response to the CHMP, the applicant reanalysed and provided a discussion of TEAEs occurring at >2%, and evaluated the possible causal relationship, between avacopan and the adverse events. The current presentation of the ADRs includes: all infections occurring in >2% of patients in the avacopan group, neutropenia, headache, nausea, diarrhoea, vomiting, abdominal pain upper, liver function test abnormal, angioedema, blood creatine phosphokinase increased, leukopenia, and white blood cell count decreased, and is reflected in the SmPC.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety profile of avacopan in this rare target indication, is considered acceptably characterised by the submitted safety data, in particular by the data from the relatively large 52-week phase III study. However, some concerns need to be followed post-marketing such as malignancy and infections. Thus, a robust post marketing follow-up is critical. There is a planned PASS, which the applicant agreed to conduct.

From the currently available data it is apparent that: 1) a CYC/AZA/MMF-regimen in itself has a hepatotoxic potential (based on previous knowledge, which is reflected in current PIs of these drugs and to some extent confirmed by the data in the limited avacopan clinical dataset) and 2) that avacopan in itself has a hepatotoxic potential (based on data from the overall avacopan programme). Based on this, there seems to be a risk (which is also to some extent supported by data from the limited avacopan clinical dataset) that the additive effect of these drugs on the liver may further increase the risks as compared to when the drugs are given as monotherapy. In addition, knowing that avacopan is intended for a population that may also have additional factors that contribute to their risk for a hepatic injury, this will be monitored in the post-marketing setting (PASS, PSUR).

However, the view of the CHMP is that the risks associated with avacopan-treatment, also in combination with a CYC/AZA/MMF-regimen, will be mitigated to an acceptable level by the currently proposed comprehensive SmPC wordings, see separate SmPC document. Further, the risks will be followed post-marketing.

The CHMP considers the following measures necessary to address issues related to safety:

- *"Avacopan Real World Evidence in ANCA Associated Vasculitis":* Characterisation of the safety concerns of avacopan (i.e. liver injury, serious infections, malignancies and cardiovascular events) beyond the known safety profile based on clinical trial data limited to 52 weeks of exposure.

2.7. Risk Management Plan

Safety concerns

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

Pharmacovigilance plan

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)					
PASS study Planned	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	Planned	Protocol submission Interim reports Final report	3 months post EC decision Every 12 months (after FPFV estimated Q2 2022) Estimated Q2 2029

Prior to the protocol submission for the PASS based on existing disease registries, the MAH should conduct and submit a complete feasibility assessment including an assessment of the potential data sources from national vasculitis registries.

Risk minimisation measures

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 Section 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: PASS study
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: PASS study
Serious infection	Routine risk minimisation measures: SmPC Section 4.2, 4.4 and Section 4.8 PIL Section 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: PASS study
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: PASS study
Missing Information		
None	NA	NA

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of avacopan with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them. The CHMP, based on the available data, considers avacopan to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Quick Response (QR) code

A request to include a QR code in the labelling (i.e. outer carton) for the purpose of providing statutory and additional information has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code: link to a website (URL: www.tavneos-patient.eu) providing the package leaflet (statutory information) and a dose reminder card (additional information).

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tavneos (avacopan) is included in the additional monitoring list as it contains a new active substance which was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Tavneos is proposed "*in combination with a rituximab or cyclophosphamide regimen, for the treatment of adult patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)"*.

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a multisystem autoimmune condition that occurs due to production of anti-neutrophil cytoplasmic antibodies. The disease is characterised by generalised inflammation of small to medium sized blood vessels that can affect many different organ systems but commonly involves the kidneys. The two main forms of the disease are granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).

GPA can affect any organ or tissue but has a predilection for the upper and lower respiratory tracts and the kidneys, with >75% of patients having renal involvement that is associated with progressive glomerular nephritis. GPA is most commonly associated with ANCA positivity by immunofluorescence and positive testing for the proteinase 3 (PR3)-antigen. MPA can be distinguished from other forms of small vessel vasculitides by the absence of granuloma formation, and by the predominance of perinuclear ANCA staining by immunofluorescence and positive testing for the myeloperoxidase (MPO) antigen. If left untreated, 80% of patients with GPA or MPA die within 2 years of disease onset and mortality is higher for patients with renal involvement.

3.1.2. Available therapies and unmet medical need

The basic principles of AAV treatment is:

1. Remission induction with potent immunosuppressive drugs

followed by

2. Remission maintenance with less potent immunosuppressive drugs

Cyclophosphamide plus glucocorticoids or rituximab plus glucocorticoids are considered the standard of care induction therapy for organ or life-threatening AAV. Maintenance treatment includes immunosuppressive drugs such as azathioprine, mycophenolate mofetil, or methotrexate. Glucocorticoid treatment is also often used during maintenance. Adjuvant treatment includes plasmapheresis in patients with severe progressive renal failure. Due to the serious side effects associated with current therapies, including glucocorticoids, there is a need for new therapeutic agents in AAV.

3.1.3. Main clinical studies

Key design features of the single pivotal trial (CL010_168) and the two supportive phase-II trials (CL003_168 and CL002_168) are described below:

Study Phase	Study Sites/ Location	Study Start/End Enrolment	Design Type	Study Drug Regimen	Subjects Entered /Completed (by Study Arm)	Duration	Gender Median Age (range)	Diagnostic Inclusion Criteria	Primary Objectives/ Endpoints
CL010_168 Phase 3	239 sites; 143 sites enrolled subjects in North America, Europe, Australia, New Zealand, and Japan	15-Mar-2017 to 01-Nov-2019 331 subjects enrolled	Randomised, double-blind, double-dummy, active-controlled	Avacopan and matching placebo: 30 mg avacopan twice daily, orally Prednisone and prednisone-matching placebo: 60 mg prednisone once daily, tapered to 0 by Week 21	Entered Control:165 Avacopan:166 Completed Control: 150 Avacopan: 151	52 weeks of treatment; 8 weeks of follow-up	187 males/ 144 females aged 64.0 (13 to 88) years	GPA, MPA	Safety and tolerability: AE incidence Efficacy: BVAS remission at Week 26; sustained remission to Week 52
CL003_168 Phase 2	47 sites in the USA and Canada	04-Feb-2015 to 19-Jul-2016 42 subjects enrolled	Randomised, double-blind, placebo-controlled	Avacopan and matching placebo: 10 mg or 30 mg avacopan twice daily, orally Prednisone and matching placebo: all groups: 60 mg prednisone once daily, tapered to 0 by Week 21	Entered Control: 13 10 mg avacopan: 13 30 mg avacopan: 16 Completed Control: 13 10 mg avacopan: 12 30 mg avacopan: 15	12 weeks of treatment 12 weeks of follow-up	19 males/ 23 females aged 58.5 (26 to 83) years	GPA, MPA, or renal limited vasculitis	Safety and tolerability: AE incidence Efficacy: BVAS response at Week 12
CL002_168 Phase 2	60 sites in Austria, Belgium, the Czech Republic, Hungary, France, Germany, Ireland, the Netherlands, Poland, Sweden, and the United Kingdom	27-Sep-2011 to 18-Jan-2016 67 subjects enrolled	Randomised, double-blind, double-dummy, placebo-controlled	Avacopan and matching placebo: 30 mg avacopan twice daily, orally Prednisone and matching placebo: 60 mg prednisone once daily, tapered to 0 by Week 21	Entered Control: 23 Avacopan+low-dose prednisone: 22 Avacopan alone: 22 Completed Control: 18 Avacopan+low-dose prednisone: 19 Avacopan alone: 18	12 weeks of treatment 12 weeks of follow-up	47 males/ 20 females aged 59.3 (20 to 82) years	GPA, MPA, or renal limited vasculitis	Efficacy: BVAS response at Week 12 Safety and tolerability: AE incidence

ANCA = anti-neutrophil cytoplasmic autoantibody; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; AE = adverse event; BVAS = Birmingham Vasculitis Activity Score.

The pivotal study was a phase III, randomised, active-controlled study comparing avacopan (n=166) vs. prednisone (n=164) in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis treated concomitantly with rituximab or cyclophosphamide/azathioprine.

3.2. Favourable effects

Pivotal study CL010_168

In the main clinical trial CL010_168, avacopan combined with IV rituximab or IV or oral cyclophosphamide was compared to standard treatment with a an oral 20-week regimen of prednisone starting from 60 mg daily and tapered to zero by Day 141 combined with IV rituximab or IV or oral cyclophosphamide.

Primary endpoints: The study had two primary endpoints, both tested for non-inferiority and superiority. The first primary endpoint, non-inferiority in BVAS remission at week 26, was achieved by 115/164 patients (70.1%) in the comparator group and 120/166 (72.3%) in the avacopan group (95% CI: -6.0, 12.8, p<0.0001 (non-inferiority) and 0.2387 (superiority)). The second primary endpoint, sustained remission at week 52, was achieved by 90/164 patients (54.9%) in the comparator group and 109/166 patients (65.7%) in the avacopan group (95% CI: 2.6, 22.3, p=<0.0001 (non-inferiority), 0.0066 (superiority)).

Secondary endpoints: None of the secondary endpoints were controlled for multiplicity. The incidence of relapse after remission had been achieved at Week 26 was numerically higher in the comparator group (14 of 115 subjects, 12.2%) than in the avacopan group (9 of 120 subjects, 7.5%).

The proportion of patients using glucocorticoids beyond week 26 was 27.1% in the avacopan group vs 39% in the comparator group.

The glucocorticoid toxicity index (GTI) includes individual measurements including body mass index (BMI), glucose tolerance, blood pressure, lipids, steroid myopathy, skin toxicity, neuropsychiatric toxicity, and infection. Both a cumulative worsening score (CWS) and aggregate improvement score (AIS) were determined at both Week 13 and 26. At week 13, the Cumulative Worsening Score (GTI-CWS) was 25.7 ± 3.40 (LSM ± SEM) in the avacopan group and 36.6 ± 3.41 in the comparator group. At week 26, the cumulative worsening score was 39.7 ± 3.43 in the avacopan group and 56.6 ± 3.45 in the comparator group.

The aggregate improvement score (GTI-AIS) was at week 13 9.9 ± 3.45 in the avacopan group and 23.2 ± 3.46 in the comparator group. At week 26, the aggregate improvement score was 11.2 ± 3.48 in the avacopan group and 23.4 ± 3.50 in the comparator group.

Additional endpoints: The cumulative steroid dose was 3846.9 mg in the comparator group and 1675.5 mg in the avacopan group.

Relevant subgroups: In the pre-defined subgroups of background therapy (RTX or CYC), ANCA subtype (PR3 or MPO), newly diagnosed or relapsed disease, and disease subtype (GPA or MPA), the results for the first primary endpoint were similar as in the overall analysis. The response rate was higher in the rituximab stratum than in the cyclophosphamide stratum, in both treatment arms (RTX/predn: 75.7%, RTX/avacopan: 77.6%, CYC/predn: 59.6%, CYC/avacopan: 62.7%). For the second primary endpoint of sustained remission, the response rate in all subgroups were numerically higher for avacopan. The difference was most prominent in the rituximab stratum (RTX/predn: 56.1%, RTX/avacopan: 71.0%, CYC/predn: 52.6%, CYC/avacopan: 55.9%).

The majority of subjects had renal disease at baseline: 95/135 and 99/134 subjects in the prednisone and avacopan groups, respectively. Of those with renal disease at baseline, subjects receiving avacopan showed a greater improvement in eGFR over the course of the 52-week treatment period. In the comparator group, change from baseline eGFR (mean 45.6 ml/min/1.73 m2) to Week 52 was 4.1±1.03 (n=125); and in the avacopan group, change from baseline (mean 44.6 ml/min/1.73 m2) to Week 52 was 7.3±1.05 (n=119).

Supportive studies

The phase 2 studies included only a 12-week treatment period. This is too short for a reliable assessment of the remission-inducing efficacy. The remission rate was higher in the pivotal study (72% in BVAS remission at week 26) than in phase II study CL002_168 (19% in BVAS remission at week 12).

3.3. Uncertainties and limitations about favourable effects

The exact effect size of avacopan is difficult to quantify because of the study design with background induction treatment and concomitant use of steroids in both treatment arms. The interpretation is further complicated by the different treatment regimens in the active and comparator arms and, in particular, the fact that the responses at week 26 were induced through different combination therapies.

It is not evident that remission at week 26 is the optimal, sensitive time point to demonstrate non-inferiority between the active and control arms in response rates. Avacopan treatment was continued until week 26 whereas the other components of induction therapy were discontinued at weeks 4, 13 (15) and 20 for RTX, CYC IV (oral) and prednisone, respectively. RTX and CYC where included in both arms; prednisone in the comparator arm. Furthermore, AZA maintenance therapy was started already at week 15 in the CYC stratum in both groups. For these reasons, interpretation of results at week 26 is not straightforward as it is not evident which components of the treatment regimen have induced the observed responses.

The week 52 endpoint measures sustained remission, that is, whether patients who were in response at week 26 are still in response at week 52. In the CYC stratum, patients received AZA in both arms and in the active arm avacopan in addition. In the RTX stratum, the comparator arm received placebo and the active arm avacopan. Superiority was demonstrated, mainly driven by the efficacy in the RTX stratum.

The efficacy of the combination of avacopan with azathioprine was similar compared to azathioprine alone in maintaining remission after induction treatment with cyclophosphamide combined with avacopan or high-dose prednisone. Hence, the conclusion of efficacy of the avacopan regimen used in the cyclophosphamide stratum of the study at week 26 was based on non-inferiority, but the efficacy for sustained remission at week 52 had to be made based on other findings including secondary endpoints. The main basis for acceptance of the treatment regimen in the CYC stratum was the steroid-sparing effect by avacopan, which was mostly confined to first 26 weeks of the trial.

Prior to Week 26, the difference is partly due to protocol-mandated prednisone course in the comparator arm, which is standard therapy. However, as glucocorticoids were allowed to be used according to need in both active and comparator arms, it is expected that GCs were used when needed in the avacopan group; therefore, the observed difference in glucocorticoid use is partly due to efficacy of avacopan. Additionally, some of the non-multiplicity-controlled secondary endpoints support efficacy of avacopan also in this regimen, even if the noted benefit in, e.g., renal endpoints and PROs is small.

It is noteworthy that the actual number of patients who relapsed between weeks 26 and 52 is very small across the strata and treatment arms, which brings some uncertainty to the sensitivity of the endpoints and duration of follow up and complicates the interpretation of results. In the CYC stratum, the number of relapses after Week 26 was even similar between active and comparator arms (3 in both arms). However, the applicant's post-hoc analysis on relapses over the entire duration of the study shows a difference in relapses prior to Week 26 in favour of avacopan. Furthermore, there is no obvious reason to believe that the pharmacological effect of avacopan would depend on the combinations used, since the mode of action is new and different from other immunosuppressive treatments.

3.4. Unfavourable effects

In the pivotal phase III study, a total of 1779 TEAEs were reported by 164 subjects (98.8%) in the avacopan group while a total of 2139 TEAEs were reported by 161 subjects (98.2%) in the comparator group. There were in total 166 SAEs in the Comparator group reported in 74 subjects (45.1%) and 116 SAES in the avacopan group reported in 70 subjects (42.2%) in the phase III study.

In phase III, six subjects died during the study, comprising 2 subjects (1.2%) in the avacopan group and 4 subjects (2.4%) in the comparator group; one additional death occurred during the screening period. In the avacopan group, the causes of death in the phase III study were GPA for 1 subject and pneumonia for the other; these subjects were not receiving avacopan at the time of death. No deaths occurred in Phase I or Phase II studies.

Both in phase II and phase III, the SOCs with the highest subject incidence in the avacopan treated subjects were infections and infestations and gastrointestinal disorder. Headache, nausea and vomiting were reported more often in the avacopan group vs the comparator group in the phase III study. The incidence of infections in the phase III study was 75.6% in the comparator group vs 68.1% in the avacopan group. For serious infections the incidences in the phase III study were 15.2% in the comparator group vs 13.3% in the avacopan group. Eleven subjects (6.7%) had serious opportunistic infections in the comparator group compared with 6 subjects (3.6%) in the avacopan group. PTs of opportunistic infections in the avacopan arm included pneumonia (n=3) infective exacerbation of chronic obstructive airways disease, Campylobacter gastroenteritis and hepatitis B. No Neisseria meningitidis infections were reported.

In the Phase III study, the incidence of TEAEs considered possibly related to glucocorticoid use was 80.5% in the comparator group compared with 66.3% in the avacopan group. A higher subject incidence in the comparator group compared with the avacopan group was observed for AEs of weight increased, insomnia, hyperlipidaemia, adrenal insufficiency, increased blood glucose, and irritability.

Both AEs of hepatic function test and SAEs of hepatic function test were more frequent in the avacopan group vs the steroid group in the pooled phase II/phase III data and in the phase III data.

In the phase III study, there were 22/166 subjects in the avacopan group (13.3%, n=16 for SOC Investigations and n=6 for SOC Hepatobiliary disorders) compared to 19/164 subjects in the comparator group (11.6%, n=18 for SOC Investigations and n=1 for SOC Hepatobiliary disorders) with Any liver function test AE in the pivotal phase III study. The AEs resolved in all cases; the event was "ongoing" in 1 subject (who subsequently died due to worsening of GPA).

In the CYC/AZA stratum, a total of 6 (10.5%) subjects in the comparator group and 12 (20.3%) subjects in the avacopan group experienced a hepatic event. In the prednisone/RTX-stratum, 13 (12.1%) had such an event and in the avacopan/RTX stratum, 10 (9.3%) subjects had such event.

Liver function test increased occurred with an SAE incidence of 6 of 164 subjects (3.7%) in the comparator group and 9 of 166 subjects (5.4%) in the avacopan group in Phase III study. Study medication was interrupted or discontinued in 3 of 6 cases of hepatic function test SAEs in the comparator group and 6 of 9 cases in the avacopan group in the phase III study. All events resolved. According to the CSR, no liver enzyme elevations in the avacopan group met Hy's law criteria. However, in both treatment groups, several of the subjects with SAEs of hepatic function tests had a documented increased bilirubin around the time of the event. In the prednisolone group 2/6 subjects belonged to the cyclophosphamide stratum while 4/6 belonged to the rituximab stratum. In the avacopan group, 6/9 belonged to the cyclophosphamide stratum while 3/9 belonged to the rituximab stratum.

It is also reported that, in the phase III study, the incidence of hepatobiliary disorders leading to study medication discontinuation was 5 of 166 subjects (i.e. 3.0%) in the avacopan group compared with none (0.0%) in the comparator group. Study medication was, according to the CSR, paused or discontinued permanently due to hepatic enzyme abnormalities in 5 subjects (3.0%) in the comparator group and 9 subjects (5.4%) in the avacopan group in the phase III study.

Two events of angioedema occurred in the phase III study in the avacopan group (2/166=1.2%) vs none in the comparator group (0/164=0.0%). In the first case, study medication was discontinued, anti-allergic treatment was given, and the event resolved without sequelae. In the second case, study medication was interrupted, and the event resolved, study medication was then re-started on Day 83 and the angioedema did not recur.

Creatine phosphokinase increases occurred more often among avacopan treated subjects than among subjects in the steroid control group both in phase II and phase III. The incidence in the phase III

study was 1 of 164 subjects i.e. 0.6% in the comparator group and 6 of 166 subjects i.e. 3.6% in the avacopan group. Associated milder symptoms from muscles or joints/back were reported in many of the cases but no serious events, such as rhabdomyolysis, were reported and treatment could often be continued. The majority of the events resolved.

In the phase III study, there were 4 subjects in the avacopan group and no subjects in the comparator group in the phase III study with cardiac failure. The applicant states that the 4 subjects all had a medical history of cardiovascular disease and the incidence of serious major cardiovascular events was higher in the comparator group. Two SAEs each of angina pectoris and cardiac failure were observed in the avacopan group, with none in the comparator group. For 3 of the 4 events it was reported that study medication was interrupted but restarted and the subject completed the study, for 1 subject it was reported that the study medication was discontinued, and the event resolved.

Events related to the SOC cardiac disorders was overall somewhat more frequent in the avacopan group vs the comparator group across the phase II and phase III studies.

The incidences of low white blood cell count were generally not higher than in the comparator group i.e. the steroid group. In the phase III study, 39 subjects (23.8%) in the comparator group and 31 subjects (18.7%) in the avacopan group had TEAEs associated with low WBC count. A total of 8 subjects (4.9%) in the comparator group had serious TEAEs of neutropenia or lymphopenia compared with 4 subjects (2.4%) in the avacopan group; in of all these cases the event resolved, in 3 of the cases (2 comparator group and 1 in the avacopan group) treatment was interrupted or discontinued.

In the phase I study CL001_168, a slight decrease in mean WBC and neutrophil count was, according to the CSR, observed more frequently in the healthy subjects receiving CCX168 compared to those receiving placebo.

With regards to background immunosuppressive therapy, in the phase III study, the TEAE incidence across many SOCs were higher in the cyclophosphamide compared with the rituximab stratum for both treatment groups including infections and infestations, gastrointestinal disorders, blood and lymphatic system disorders. SOCs that had a ≥5% difference in subject TEAE incidence between the two strata in the avacopan group, but did not show the same trend in the comparator group included cardiac disorders, and hepatobiliary disorders. Also, in the phase II study studies, the TEAE incidence for many SOCs was higher in the cyclophosphamide compared with the rituximab stratum in both treatment groups.

Further, the applicant provided analyses, comparing those occurring in the whole study and those during the first 20 weeks of the pivotal study (the period during which prednisone was administered to the prednisone control group); and similarly comparing those occurring in the whole study to those occurring in the time period from Week 21 to the end of the study. The safety results of the entire pivotal study, as a whole, and safety results of the 'on-treatment' period of the study, showed comparable results. Also, when analyses were conducted according to different descriptive comparative subgroup analyses, including analyses of safety data (TEAE by SOC, PT, and SAEs) in time periods before the cut off time points 26- and 15-weeks, analyses in all subjects, by treatment group and by treatment groups strata (RTX and CYC strata), no new significant safety issues that could be interpreted as distinct safety signals, in any of the comparisons performed were revealed.

3.5. Uncertainties and limitations about unfavourable effects

- In the non-clinical data, no dose-limiting effects or target organ of toxicity were noted in the chronic studies and therefore, the toxicology of avacopan is not considered fully explored;

however, the repeat-dose toxicity profile is considered to have been explored to the extent feasible and completes the non-clinical profile of avacopan.

- With the data provided it is difficult to assess if the risks associated with avacopan are generally dose dependent. Just one of the clinical studies investigated multiple doses and this study investigated only two doses. The conclusions that can be drawn is hampered by the low number of subjects in the study. The fact that this cannot be fully assessed influences the assessments of some of the risks associated with avacopan such as hepatotoxicity. Appropriate measures have been reflected in the product information and the RMP.
- Considering the heavy background treatment given in both the avacopan groups and the comparator groups in the clinical studies, the attribution of avacopan itself to the observed unfavourable effects are not always possible to delineate. The safety profile of avacopan as monotherapy is somewhat uncertain, but the regular PSUR reports in the post-authorisation phase will be monitored by the PRAC.
- Patients with very severe disease (manifested as alveolar haemorrhage requiring invasive pulmonary ventilation support and patients with GFR <15 mL/minute/1.73 m^2 or requirement for dialysis or plasma exchange) were largely excluded from the clinical trials as well as patients with severe hepatic impairment, as reflected in the PI.
- Immunomodulatory medicinal products may increase the risk of malignancies. However, the clinical studies conducted to date are far too limited with regards to follow-up time and total exposure to provide any substantial reassurance with regards to this risk. Currently, long-term safety data up to 52 weeks derives only from the single pivotal study and data beyond this time point is so far missing. There is a post-authorisation safety study planned and agreed.
- The significance of the observed imbalance in the events related to cardiac disorders in the avacopan group vs the comparator group across the phase II and phase III studies is still not fully known. The applicant agreed to conduct a post-authorisation PASS.
- There are several limitations of the data that precludes a definitive evaluation of the assessment of the risk for severe drug-induced liver injury. These include an overall limited clinical safety data base, very limited data from any other dose than 30 mg (which precludes an evaluation of dose-dependence), numerous potentially confounding factors and the uncertainty of the magnitude of risk increase when avacopan is combined with CYC/AZA (MMF).

3.6. Effects Table

Effects Table for Tavneos for the treatment of vasculitis based on data from the pivotal phase III study, database lock date: 20 November 2019

Effect	Short Description	Unit	Avacopan	Comparator	Uncertainties/ Strength of evidence	References
Favourable Effects						
Remission at week 26	BVAS 0 and no BVAS>0 or steroids within 4 weeks prior to week 26.	N (%)	120 (72.3)	115 (70.1)	Non-inferiority but not superiority was met. Lower effect (in both treatment groups) observed in the CYC stratum than in the RTX stratum.	CL010_168 CSR

Effect	Short Description	Unit	Avacopan	Comparator	Uncertainties/ Strength of evidence	References
Remission at week 52	Remission at week 26 as defined above + BVAS 0 week 52 and no steroids within 4 weeks prior to week 52 + no relapse week 26-52.	N (%)	109 (65.7)	90 (54.9)	Non-inferiority and superiority met. Largest difference between avacopan and prednisone in the RTX stratum which might be due to lack of re-treatment (=sub-optimal treatment, which applies to both arms).	CL010_168 CSR
Cumulative steroid dose	Study-supplied and non-study supplied Day 1 to end of treatment	mg	1675.5	3846.9		CL010_168 CSR
GTI-CWS week 26	Glucocorticoid Toxicity Index Cumulative Worsening Score	LSM± SEM	39.7 ± 3.43	56.6 ± 3.45		CL010_168 CSR
GTI-AIS week 26	Glucocorticoid Toxicity Index Aggregate Improvement Score	LSM± SEM	11.2 ± 3.48	23.4 ± 3.50		CL010_168 CSR
Unfavourable Effects						
TEAEs	Subject incidence	N (%)	164 (98.8)	161 (98.2)		CL010_168 CSR
SAEs	Subject incidence	N (%)	70 (42.2)	74 (45.1)		CL010_168 CSR
Deaths	Subject incidence	N (%)	2 (1.2)	4 (2.4)		CL010_168 CSR
Infections	Subject incidence	N (%)	113 (68.1)	124 (75.6)		CL010_168 CSR
Serious Infections	Subject incidence	N (%)	22 (13.3)	25 (15.2)		CL010_168 CSR
Liver AEs	Subject incidence, Liver function test increased	N (%)	22 (13.3)	19 (11.6)		CL010_168 CSR
Serious liver AEs	Subject incidence, Liver function test increased	N (%)	9 (5.4%)	6 (3.7%)		CL010_168 CSR

Abbreviations: CYC=cyclophosphamide, RTX=rituximab

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

ANCA-associated vasculitis is a serious and potentially organ- and life-threatening disease. Standard remission induction treatment includes cyclophosphamide or rituximab in combination with high doses of steroids, the latter associated with severe side effects of for example infections, osteoporosis, hypertension and diabetes. There is a high unmet need for steroid-sparing agents.

In the pivotal clinical trial CL010_168, avacopan combined with IV rituximab or IV or oral cyclophosphamide followed by azathioprine (or mycophenolate, if azathioprine was not tolerated) was compared to standard treatment with a an oral 20-week regimen of prednisone starting from 60 mg daily and tapered to zero by Day 141 combined with IV rituximab or IV or oral cyclophosphamide. The primary objective was to evaluate the efficacy of avacopan to induce and sustain remission in subjects with active ANCA-associated vasculitis, when used with cyclophosphamide followed by azathioprine, or with rituximab. The study included the two primary endpoints, disease remission at week 26 and sustained remission at week 52. The two primary endpoints were first tested for noninferiority and then for superiority according to a prespecified multiplicity procedure.

Non-inferiority, but not superiority, compared to the comparator arm was achieved at week 26 with respect to induction of remission. Superiority was reached at week 52 for sustained remission. Thus, the objectives of the studies were met. The non-inferiority margin of 20% may seem large, but it should be noted that the lower 95% CI was -6%. Non-inferiority at week 26 was reached despite a lower GC-dose in the avacopan arm. The clinical relevance of this observation is supported by the outcome of the secondary endpoint "glucocorticoid toxicity scale".

The absolute difference between treatment arms for sustained remission was not large (12.5%), but was of clear statistical significance. This superiority analysis at week 52 was the third level in a hierarchical testing where the first two levels (non-inferiority at week 26 and non-inferiority at week 52), was met. The definition of the primary endpoints included the requirement "no glucocorticoid use during the last 4 weeks"; a criteria of high clinical relevance (supported by previous CHMP SA). However, remission irrespective of glucocorticoid use was included as a pre-specified sensitivity analysis. In the sensitivity analysis of remission (BVAS=0) irrespective of glucocorticoid use, avacopan was non-inferior to high dose prednisone. In conclusion, this superiority of avacopan vs high dose prednisone at week 52 is considered to be statistically robust and to be the most reliable analysis for the efficacy assessment.

Analyses of the primary endpoints in strata divided by background treatment (RTX or CYC/AZA) demonstrated that the results obtained with avacopan on sustained disease remission at Week 52 were consistent with the results in the total study population in the rituximab stratum (which comprised approximately 2/3 of total study population). In the cyclophosphamide/AZA stratum, the efficacy of avacopan added to azathioprine or mycophenolate seemed less pronounced compared to the total study population for sustained remission. However, this stratum was small, and the CI was wide. In addition, the proportion of patients needing steroids during the maintenance phase of the study was lower in the avacopan arm compared to the comparator arm, indicating that also these patients benefitted from continued treatment after w 26. However, this analysis was not included in the type I error control.

Patients were treated with avacopan for 12 months and there are no data available for long-term treatment.

Importance of the unfavourable effects

An important observation is that in the pivotal phase III study, the subject incidence of TEAEs, SAEs and TEAEs leading to study medication discontinuation was similar in the avacopan group as compared to the comparator group i.e. to current standard of care for ANCA-associated vasculitis. The incidence of infections was numerically lower in the avacopan group vs the comparator group (68.1% vs 75.6%). Also, not unexpected, TEAEs considered possibly related to glucocorticoid use was lower in the avacopan group vs the prednisolone group (66.3% vs 80.5%). Given these data, avacopan may provide a useful alternative to steroid treatment in the remission induction and maintenance treatment of ANCA-associated vasculitis. However, a requirement for this is that the observed and potential risks if avacopan are adequately reflected in the product information and followed post-marketing.

As the safety database is considered reasonable for an initial MA risk assessment in this rare indication but still too limited to for a complete characterisation of many important concerns, the post-marketing follow-up beyond 52 weeks is important. Further, it should be noted that patients with very severe disease (manifested as alveolar haemorrhage requiring invasive pulmonary ventilation support and patients with GFR <15 mL/minute/1.73 m^2 or requirement for dialysis or plasma exchange) were largely excluded from the clinical trials. This is, however, adequately addressed in the SmPC.

Infection is an important concern. As infections have the potential to be fatal, it is of outmost importance that appropriate risk-mitigating recommendations are included in the SmPC. Such wording includes a recommendation for pneumocystis prophylaxis and also address the risk for reactivation of hepatitis. In addition, the risks of TB, HIV and the risks associated with having received a recent live vaccination has been reflected. Further, recommendations for monitoring of WBC has been included. In addition, based on the mechanism of action, the potentially increased risk of infections with Neisseria meningitidis was also addressed in the product information.

Cardiac safety and hepatotoxicity are also important concerns, they are appropriately reflected in the SmPC.

In addition, to further characterise the safety profile of avacopan a PASS "Avacopan Real World Evidence in ANCA Associated Vasculitis" will be conducted, The PASS is included as a Category 3 study within the risk management plan together with agreed milestones, including protocol submission 3 months post European Commission Decision. In addition, as a first step of planned PASS based on existing disease registries, the MAA should conduct a complete feasibility assessment (to be submitted post EC decision), including an assessment of the potential data sources from national vasculitis registries to ensure feasibility of the requested analyses.

With regards to background immunosuppressive therapy, in the phase III study, the TEAE incidence across many SOCs were higher in the cyclophosphamide/AZA (MMF) stratum compared with the rituximab stratum for both treatment groups including infections and infestations, gastrointestinal disorders, blood and lymphatic system disorders. Adequate information and precautions have been included in the SmPC.

For the theoretical risk for malignancies, the studies conducted to date have a too short follow-up time and limited total exposure to provide any substantial reassurance. This concern is thus included in the RMP for post-marketing follow-up and is also addressed in the SmPC.

3.7.2. Balance of benefits and risks

The pivotal phase III study met its primary objective. Avacopan+background therapy was non-inferior to prednisone+background therapy at week 26 (despite a lower dose of glucocorticoids in the avacopan arm) with respect to induction of remission and reached superiority at week 52 for sustained remission. The absolute difference at week 52 is modest, but statistically robust and of clinical relevance.

Hepatoxicity is an identified risk, in particular in combination with CYC/AZA (MMF). Precautions are included in the product information and a PASS will be performed to further characterise avacopan safety profile. The B/R of avacopan for the claimed indication is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Tavneos is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tavneos is favourable in the following indication:

> 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 section 4.2).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that avacopan is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0103/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Tavneos as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/tavneos