EMA/CHMP/570808/2019
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Vynpenta (previously AvacopanChemoCentryx)

International non-proprietary name: avacopan

Procedure No. EMEA/H/C/004487

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

AAV	ANCA-associated vasculitis
AE	adverse event
aHUS	atypical haemolytic uremic syndrome
ALT	alanine aminotransferase
ANCA	anti-neutrophil cytoplasmic autoantibody
AST	aspartate aminotransferase
AUC	area under concentration-time curve
BMI	body mass index
bpm	beats per minute
BVAS	Birmingham Vasculitis Activity Score
C3G	complement 3 glomerulopathy
C5a	complement 5a
C5aR	complement 5a receptor, also called CD88
CCR2	C-C chemokine receptor 2
CCX168	avacopan
CMA	Conditional Marketing Authorisation
C_{max}	maximum concentration
CK	creatine phosphokinase
CSR	clinical study report
CYP	cytochrome P450
DoE	design of experiment
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EQ-5D-5L	EuroQuality of Life-5 Domains-5 Levels
EUVAS	European Vasculitis group
GPA	granulomatosis with polyangiitis
hERG	human ether-a-go-go-related gene
hpf	high power field
hsCRP	high-sensitivity C-reactive protein
IC_{50}	concentration to provide 50% inhibition
IgAN	immunoglobulin A nephropathy
ITT	intent-to-treat
IV	intravenous(ly)
MAC	membrane attack complex

MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCP-1	monocyte chemoattractant protein-1
MCV	mean corpuscular volume
MDRD	modification of diet in renal disease
MPA	microscopic polyangiitis
MPO	myeloperoxidase
NOR	normal operating ranges
PAR	process acceptable ranges
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PR3	proteinase 3
PT	prothrombin time
PTT	partial thromboplastin time
QOL	quality of life
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SEM	standard error of mean
SF-36	Medical Outcomes Survey Short Form-36
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TCC	terminal complement complex
TEAE	treatment-emergent adverse event
UACR	urinary albumin:creatinine ratio
ULN	upper limit of normal
VAS	visual analogue scale
VDI	vasculitis damage index
WBC	white blood cell

1. Recommendations

Based on the CHMP review of the Conditional Marketing Authorisation (CMA) data on quality, safety, efficacy and risk management plan, the CHMP considers that the application for Vynpenta, in combination with cyclophosphamide or rituximab, is indicated for the induction of response in adult patients with granulomatosis with polyangiitis (Wegener's) (GPA) or microscopic polyangiitis (MPA) (see Section 5.1)

is not approvable since major objections remain, which preclude a recommendation for the conditional marketing authorisation. The details of these major objections can be summarised as follows:

The available data from the phase II studies as submitted by the applicant does not support a positive benefit/risk (MO B/R and CMA).

The drug substance manufacturing process controlled under GMP is insufficient to support a positive benefit/risk.

Questions to be posed to additional experts

Not applicable.

Inspection issues

GMP inspection(s)

No pre-approval inspections to verify GMP compliance are deemed necessary at this stage.

GCP inspection(s)

None. (See section 2.4 of this AR.)

New active Substance status

Based on the review of the data the CHMP considers that the active substance avacopan contained in the medicinal product Vynpenta could be qualified as a new active substance in itself.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The Applicant proposes for this Contiditional Marketing Authorisation the following indication:

Vynpenta is indicated for induction treatment of adult patients with organ or life-threatening granulomatosis with polyangiitis (Wegener's) (GPA) or microscopic polyangiitis (MPA) in combination with cyclophosphamide (CYC) or rituximab (RTX).

Granulomatosis with polyangiitis (GPA) (previously named Wegener's granulomatosis) and microscopic polyangiitis (MPA) are forms of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) that affect small to medium vessels and share a number of clinical, pathologic, and laboratory features. GPA can affect any organ or tissue but has a predilection for the upper and lower respiratory

tracts and the kidneys. 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. The similarities in disease course, treatment, and association with ANCA, have led to GPA and MPA being referred to as ANCA-associated vasculitides (AAV), or ANCA disease (Falk and Jennette, 2010).

2.1.2. Epidemiology

GPA and MPA have respective annual incidence rates of 2.1–14.4 and 2.4–10.1 per million in Europe, and the prevalence of AAV is estimated at to be 46–184 per million. The 5-year survival rates for GPA and MPA are estimated to be 74–91% and 45–76%, respectively (Yates et al, Ann Rheum Dis 2016).

The relapse rates of AAV are high with approximately 50% of the patients relapsing within 5 years after onset of the disease.

These conditions are considered orphan diseases, with a combined prevalence estimated to be of <5 per 10,000 people in Europe. According to the conclusion of the COMP (Opinion dated 09/10/2014) the prevalences of MPA and GPA are 1.0 and 1.6 per 10000 individuals, respectively, in the European Union (EU).

2.1.3. Aetiology and pathogenesis

According to the many studies, GPA and MPA are less common in non-European populations suggesting that genetics may have a vital role in the aetiology of AAV. It has also been suggested that some environmental factors (infections, ultraviolet radiation, silica, heavy metal exposure and tobacco smoke) could have a role in the development of AAV.

AAV are characterized by the production of circulating autoantibodies against the neutrophil-expressed antigens myeloperoxidase (MPO) and proteinase 3 (PR3) and involve complement activation and C5a production.

A central role for C5a and its receptor C5aR in the pathogenesis of AAV has been proposed (Halbwachs and Lesavre, 2012; Furuta and Jayne, 2013; Kettritz, 2014). C5a can prime neutrophils and enhance ANCA-induced neutrophil activation (Schreiber et al, 2009). Neutrophils activate the alternative complement pathway through endogenous properdin secretion and neutrophils also release C5a when stimulated by inflammatory cytokines such as TNFα (Camous et al, 2011). C5a, acting on C5aR, is a potent neutrophil chemoattractant and agonist, which triggers homotypic neutrophil aggregation via interactions of the TNF-activated αMβ2 (Mac-1)-integrins with ICAM-3 or iC3b on bystander neutrophils (Hammerschmidt et al, 1981). Deformability is important for non-activated neutrophils for unperturbed movement through small blood vessels such as in the glomeruli. C5a decreases neutrophil deformability, particularly in the presence of ANCA (Tse et al, 2005). ANCA bound to endothelial-adherent neutrophils activate the classical complement pathway (Huugen et al, 2007). Lastly, C5a activates endothelial cells, promoting retraction and increased permeability (Foreman et al, 1994; Schraufstatter et al, 2002). Avacopan is a selective C5aR inhibitor and is hoped to block these effects of C5a in AAV.

2.1.4. Clinical presentation, diagnosis

According to the International Chapel Hill Consensus Conference, AAV is necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (capillaries, venules, arterioles and small

arteries). The absolute majority of the patients are ANCA-positive but ANCA-negative AAV is not an unknown entity (10-20% of the AAV patients).

AAV can in principle affect any organ system. In MPA necrotizing glomerulonephritis is a very common manifestation. Also, pulmonary capillaritis occurs often. In GPA necrotizing granulomatous inflammation involving most commonly the respiratory tract and necrotizing glomerulonephritis are the most common manifestations. In both diseases, generalized nonspecific manifestations of systemic inflammation (fever, weight loss, arthralgia, myalgia) and cutaneous involvement (purpura, nodular lesions) are often present.

The common signs of glomerulonephritis in GPA and MPA patients are hematuria, proteinuria and renal failure. The renal failure is often characterized with rapid progression, although a subacute or chronic glomerulonephritis has also been reported. Both MPA and GPA can induce pulmonary hemorrage.

The diagnosis of AAV is based on clinical characteristics of the patients, serologic testing for ANCA and biopsy of the affected organ. ANCA diagnostics should include both indirect immunofluorescence (IIF) assay and enzyme-linked immunosorbent assay (ELISA). IIF differentiates the ANCA to cytoplasmic ANCA (c-ANCA) with diffuse staining of the cytoplasm of neutrophils and to perinuclear ANCA (p-ANCA). Respectively, by ELISA testing, most c-ANCA has specificity for PR3 and most p-ANCA for MPO. In GPA, 70% of the patients are c-ANCA/PR 3 positive, 25% p-ANCA/MPO positive and 5% are ANCA-negative. In MPA, the respective proportions are 40%, 50% and 10%.

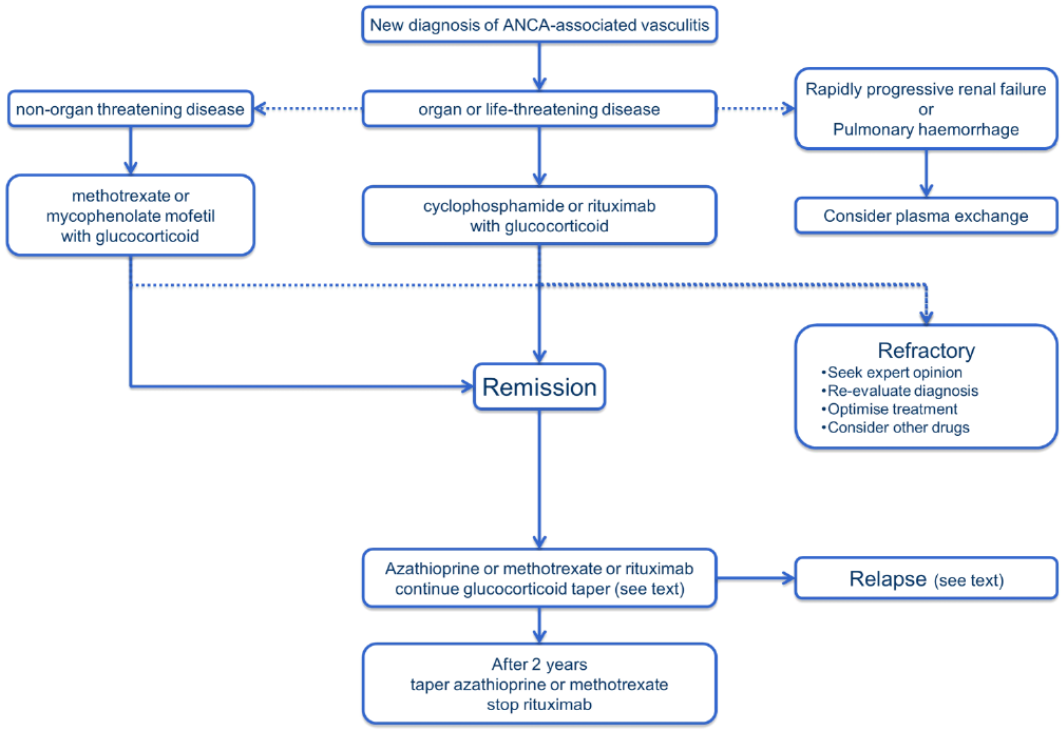
Histopathological evidence derived from organ biopsy remains the golden standard for diagnosis of AAV. The diagnostic benefit is highest in renal biopsies where definite diagnosis can be made in up to 91% of the patients.

Older age, pulmonary hemorrhage and severe renal insufficiency are significant markers for poor prognosis. GPA and MPA account for 80% of the rapidly progressing glomerulonephritis and with prompt diagnosis and initiation of therapy the progression to end-stage renal disease can be prevented. It has also been proposed that becoming ANCA-negative after induction treatment is associated with reduced risk of disease relapse.

2.1.5. Management

EULAR recommendations for the treatment of ANCA-associated vasculitis are presented in **Error! Reference source not found.**. The standard treatment for remission-induction of new-onset organ-threatening or life-threatening AAV consists of either cyclophosphamide or rituximab combined with glucocorticoids.

Figure 1. Algorithm to describe the management of new antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis



Source: EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis, Yates M, et al. Ann Rheum Dis 2016

Before the advent of cyclophosphamide glucocorticoids were the only beneficial treatment option for AAV. Cyclophosphamide has been an established treatment for AAV already since 1970s and it is nationally authorised for treatment of vasculitides in many EU countries. Cyclophosphamide can be administered orally or intravenously, but currently intravenous administration is favoured due to reduced total cyclophosphamide dose and due to reduced bladder-related complications. Importantly, it has been shown that there are no significant differences in overall survival or renal function associated with the method of administration. In remission-induction treatment, intravenous cyclophosphamide dose is 12-15 mg/kg given 2-3 times in two weeks intervals and thereafter in 3-week intervals. Usually a total of 6-10 pulses are given. Administration of oral or intravenous 2-mercaptoethanesulfonate sodium (MESNA) and trimethoprim/sulfamethozazole is also recommended to prevent bladder complications and pneumocystis infection related to cyclophosphamide use. After induction of remission, maintenance treatment with azathioprine or alternatively with rituximab, methotrexate or mycophenolate mofetil is usually initiated.

Rituximab was authorized in 2013 in EU for the induction of remission in adult patients with severe, active AAV. It was shown in the authorization study (the RAVE study) that intravenously administered rituximab was non-inferior to cyclophosphamide in induction of remission of AAV and appeared more effective in relapsing disease. The recommended dosing of rituximab is 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for 4 weeks (four infusions in total). Rituximab use is restricted in some countries due to high cost. It has been preferably been used in young patients with reproductive potential, in patients with high cumulative dose of cyclophosphamide and in relapsing cases.

Glucocorticoids have also an established position in the treatment of AAV. The recommended daily dose of glucocorticoids has been 1 mg/kg (with maximum dose of 80 mg) for the first 2-4 weeks

following a gradual tapering of the dose and treatment withdrawal after 6-12 months. A review of the key AAV trials indicated that the mean average daily dose of glucocorticoids was 50 mg after 4 weeks of treatment and 7.5 mg after 21 weeks of treatment.

In life-threatening AAV also intravenous pulse glucocorticoids and plasma exchange have been used.

With the current recommended induction treatment protocol, approximately 60% of the patients will achieve sustained remission at 6 months. Despite the progress achieved, 11% of the AAV patients die within the first year of therapy. Therefore, more effective and safe treatment regimens are still needed.

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

2.2. About the product

Avacopan is an orally administered, small molecule antagonist of the complement 5a receptor (C5aR) that has been shown to block effects of C5a which are believed to be important for the pathogenesis of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV).

Avacopan is also being tested for treatment of patients with C3 glomerulopathy (C3G), atypical haemolytic uremic syndrome (aHUS), and IgA nephropathy (IgAN).

2.3. The development programme/compliance with CHMP guidance/scientific advice

Protocol assistance received from EMA, July 2016 included views on (summarized below):

- *Acceptability to complete the nonclinical carcinogenicity studies post-approval*

  In summary, it was concluded 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 of course provide further support.

- *The applicant's plan to characterise the cardiovascular safety profile of Avacopan*

  In conclusion, an additional TQT study was concluded as probably not necessary. The Applicant was however encouraged to complete the modelling analyses and following this, in case new information emerges about other cardiovascular risks, the strategy was to be reconsidered. It was underlined that it was not possible to draw conclusions on cardiovascular safety profile of Avacopan as the information provided was on the pro-arrhythmic, QT-related potential only, which made it impossible to assess pharmacodynamic effects and other cardiotoxic potential. The Applicant was encouraged to study this further.

- *Adequacy for a Conditional Marketing Authorisation (CMA)*

  It was underlined that adequacy for a Conditional Marketing Authorisation (CMA) can only be assessed definitively in the context of an MAA, depending on the particular unmet medical need / target population to be addressed, the evidence for therapeutic advantages over current standards and overall benefit-risk. There were concerns however that study CL002_168 might not be adequate to support a CMA for the indications of treatment of GPA and treatment of MPA, at least not for the breadth of indication or therapeutic advantages currently targeted.

Considering the criteria for CMA there seemed to be little doubt that the applicant was dedicated and most probably able to provide further data from the additional studies that were planned.

Regarding the fulfilment of unmet medical need, it was agreed that there is room for improvement regarding efficacy in this therapeutic field. It was also agreed that the effect of Avacopan in terms of BVAS response at week 12 which was the primary endpoint in the phase II study CL002_168 was promising. However, as also discussed by the Applicant, the most important limitation of the current therapies was not considered not their lack of efficacy but their lack of an acceptable safety profile. It was stated that besides the characteristic steroid adverse events, much of the strikingly increased risk for serious infections could probably be attributed to the chronic use of high doses of steroids. Accordingly, a large part of the unmet medical need is the need for a steroid-sparing induction agent.

However, it was underlined that, glucocorticosteroid-sparing is difficult to demonstrate unless long-term follow-up of study patients is conducted. Moreover, the study duration and number of patients has to be large enough to assure that the overall safety profile is indeed clearly more favourable for the new drug compared to standard therapy. If for example, the new drug is associated with an increased number of infections or a new safety concern that outweighs its steroid-sparing effect, the unmet need cannot be said to be fulfilled. In this context, the safety data from the phase II study CL002_168 where 67 subjects with ANCA-associated vasculitis were treated for 12 weeks is not sufficient. Even though the serious events in this study were few, the drug exposure is too limited for firm safety conclusions to be drawn. Such conclusions would require a larger number of patients followed for a longer period of time, providing an exposure of the magnitude that is proposed for the planned phase III study. Thus, to judge whether the unmet medical need related to ANCA associated vasculitis is fulfilled by Avacopan, it is anticipated that the full data from the planned phase III study will be required.

It was also stated that it is anticipated that the full data from the planned phase III study will be needed to judge whether the benefit risk balance is overall positive as both data on the duration of remission and long term safety data will be needed for such an assessment. It was not agreed that the benefit to public health of the immediate availability outweighs the risk inherent in the fact that additional data are still required. Even though it was agreed that effective new drugs with a more favourable safety profile are needed, there was not considered to be enough data to assess the probability that Avacopan would fulfil this need.

Still it was not excluded that a CMA in a restricted indication for which a positive benefit-risk could be justified is possible. Such a restricted indication could for example be patients with strictly defined glucocorticoid intolerance or in whom glucocorticoids are contraindicated, or perhaps patient at particularly high baseline risk. The Applicant was invited to identify restricted indications for which a CMA could be justified.

It was finally stated that it should be noted that the orphan designation was only obtained for GPA and MPA which are the focus of the development program. Therefore, the indication ANCA-associated vasculitis (which would include Churg-Strauss syndrome) merits further consideration. However, it was commented that the exact wording of the indication will be determined during the review of a future MAA.

- *Adequacy of the proposed Phase 3 clinical trial CL010_168 (not further discussed here)*

Follow-up Protocol assistance received from EMA, January 2017 included views on (summarized below):

- *The Adequacy of the restricted indication (proposed below) for conditional marketing application:*

  Avacopan (CCX168), in combination with rituximab or cyclophosphamide, is indicated for the treatment of adult patients with granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis who have one or more of the following:

  1. Have developed toxicity associated with glucocorticoid treatment such as osteoporosis, diabetes mellitus, avascular bone necrosis, or peptic ulcer disease;

  2. Have a high risk of developing glucocorticoid-related toxicity such as osteoporosis (low bone density or a family history of osteoporosis), or diabetes mellitus (obesity or impaired glucose tolerance), or

  3. Who have developed resistance to glucocorticoids as indicated by progressive vasculitis despite being treated with optimal glucocorticoid plus rituximab or cyclophosphamide medication.

  It was underlined that CHMP cannot perform a pre-assessment of any type of marketing authorisation. The exact wording of the indication will be determined during the review procedure.

  In was stated that, in the previous advice, the CHMP expressed concerns that the 12-week phase 2 study (CL002_168) might not be sufficient to support a CMA for the proposed indications since the unmet medical need related to GPA and MPA is the need for a vasculitis induction and maintenance agent with more favourable safety profile than high dose steroids and that in this application for CMA are no data to support that avacopan has a more favourable safety profile than steroids in the long-term. Also, with the Applicant's revised proposal, a number of concerns were raised. The Applicant was asked to justify the long-term use of avacopan and to further justify a relevant population in which it is justified to withhold high-dose CS during remission-induction treatment. For use as an induction-remission treatment, the Applicant was further asked to present available data on the time to onset of efficacy of avacopan. These and a few other issues were discussed at a meeting with the Applicant as quoted below:

a) Long-term use of avacopan and handling of patients beyond the induction phase

   The Applicant has presented 12-week data on the efficacy and safety of avacopan. This may cover a short-term treatment, provided a sufficiently rapid onset of avacopan is demonstrated. In practice however, steroids are usually needed far beyond 12 weeks. It seems thus problematic to support an indication that covers the maintenance phase of vasculitis based on the available 12-week data. At the discussion, the Applicant argued that avacopan was well-tolerated in long-term non-clinical studies in rat and monkey, that avacopan has been safe in one patient with C3 glomerulopathy that has been treated for more than 13 months and that avacopan was safe in the phase 2 study. Therefore, the Applicant considered that dosing should not be restricted to 12 weeks if tolerated by the patient. To mitigate the risks, the Applicant suggested that patients could be subject for follow-up every 12 weeks. The CHMP assumes that such follow-up will continue until the phase 3 study informs on what extent of follow-up is needed.

   A restricted short-term use was also discussed, and the Applicant put forward that there would also be a benefit of avoiding high doses of steroids during an induction-remission treatment phase. After 12-weeks of treatment, it may be an option to administer lower doses of steroids (e.g. 7.5-10 mg). The Applicant did however argue for the option to first get the patient in

remission and thereafter replace avacopan with low dose steroids and pointed out that. A 12-week treatment would likely be too short for this.

As previously discussed, the most important limitation of the current therapies is not their lack of efficacy but their lack of an acceptable safety profile. Although the non-clinical data appears clearly to support moving into long-term clinical studies, these together with the 12-week clinical data plus one patient treated for 13 months is not sufficient to support a label that includes long-term treatment. It is still not known whether avacopan, an agent that affects the complement cascade, could potentially be associated with an increased number of infections or new safety concerns that outweighs its steroid-sparing effect if used longer-term. It is thus concluded that, based on the available data, it is very difficult to support a label that includes treatment beyond 12-weeks based on available data.

b) Patient population

The Applicant did provide a detailed overview of the adverse event profile of steroids and its management to justify the now proposed target population. The summary is appreciated, and it is fully agreed that there are major safety issues with regards to the use of steroids, but as discussed above, there is insufficient information to conclude on the safety profile of avacopan.

Thus, the CHMP considers that the indication now proposed is still not sufficiently justified. There are only a few conditions for which withholding high-dose steroids in remissions-induction treatment of GPA and MPA and instead giving the patient a new compound for which only limited (albeit promising) safety and efficacy data can be acceptable.

As discussed during the meeting, these conditions represent circumstances where steroids would be absolutely contraindicated; mainly severe, untreated infections and circumstances where patients have previously suffered from a steroid side effect that cannot be managed by standard care. For patients with an untreated severe infection, the proposed adjunct treatments to avacopan (cyclophosphamide/ rituximab) are also contraindicated so such conditions are not reasonable to include in a restricted indication for avacopan.

It is acknowledged that established diagnoses/high risk of osteoporosis, diabetes or peptic ulcer are severe conditions for which initiating of steroid treatment is problematic (i.e. scenario 2). However, there are effective ways to diminish the consequences of these conditions in routine practice (osteoporosis prophylaxis, glucose monitoring and administration of insulin as needed, proton pump inhibitors and elimination of other risk factors for peptic ulcers) and it is not agreed with the Applicant that, for example, steroid-induced diabetes often is unanticipated. The Applicant's position that the benefit of giving a new compound with limited safety and long-term efficacy data in these situations is greater than the benefit of treating the patients with standard of care high dose steroids can therefore not be supported.

A history of hypersensitivity to steroids, steroid-caused avascular bone necrosis or severe, difficult to treat psychosis may be circumstances for which CCX168 in spite of the limited data available, would be considered instead of further steroid treatment, i.e. a further restriction of the first part of the indication proposed by the Applicant. However, these conditions are rare. Accordingly, applying for a restricted indication with these conditions in mind; the CMA would only come to include a very small number of patients.

The proposal to include patients with "resistance to glucocorticoids as indicated by progressive vasculitis despite being treated with optimal glucocorticoid plus rituximab or cyclophosphamide medication" in a restricted indication also appears problematic. The Applicant refers to data from the rituximab RAVE trial in which the primary outcome measure of disease remission at 6

months was not achieved in 42% of patients. However, it should be noted that the primary outcome measure in the RAVE trial was defined as BVAS/WG score of 0 and no prednisolone treatment at 6 months. Even though 82/197 of enrolled patients did not achieve this primary outcome, only 27/197 patients failed to achieve remission in the first 6 month of therapy. Ten patients had uncontrolled disease, and these were subject to change in therapy (switch to cyclophosphamide, iv steroids, plasma exchange); one of these patients died of septic shock but it was described that the other patients improved. Fifteen patients had AEs that led to discontinuation of therapy; 4 patients had leukopenia and 4 patients had infections (Stone et al, 2010 and Miloslavsky et al, 2013). In summary, the reasons for the 82 patients failing to reach the primary outcome appeared to be either difficulties in tapering the steroids without the patients flaring or adverse events; notably leukopenia and infections. The vast majority in the RAVE trial did thus achieve disease remission with the standard therapy arsenal, in which steroids are an important component.

Consequently, from the references provided by the Applicant it appears difficult to identify any patients that were truly "resistant" to steroids. Thus, no data has so far been provided in support of the existence of such subpopulation with a size that appears reasonable for a CMA. In addition, the patient population in the phase 2 study did not match the now targeted population, particularly with regards to resistance to steroids, and thus, it can also not be concluded on the efficacy of avacopan in these difficult to treat subjects. Therefore, it is problematic also to support the third part of the proposed indication. During the discussion meeting, the Applicant was also asked to elaborate on the option to obtain additional short-term data in a limited number of subjects to support an induction-treatment effect in, for example, subjects resistant to, or where insufficient control is obtained on high-dose steroids. The Applicant argued that an additional study would not provide any meaningful additional data in a reasonable timeframe. This is agreed as likely since the planned phase 3 study is expected to be launched by the end of 2016.

In conclusion, for a further restricted patient population (essentially group 1), it is possible that a conclusion regarding the benefit/risk could be made, the benefit of a rapid access to the market may overrule the limitations with regards to information on the safety profile and an unmet need may be fulfilled, i.e. the conditions for a CMA may be fulfilled. However, this population will likely consist of very few patients.

c) Time to onset of efficacy of avacopan

To support a CMA for short-term treatment, it needs to be demonstrated that the onset of action of avacopan is as rapid as the onset of action of steroids since a rapid disease control is critical for the long-term outcome in GPA and MPA. At the discussion meeting, the Applicant again presented the BVAS data that showed that more subjects on avacopan had reached remission at 4 weeks compared to the group on steroids. The Applicant did however also present support for a rapid onset of action on other inflammatory parameters. For example, albuminuria, neutrophils and eGFR (the latter in combination with high dose steroids from the ongoing Study CL003_168) improved faster than steroids already by week 1 or even earlier. These data are acknowledged. However, it is recommended to thoroughly investigate time to onset for avacopan, and for this purpose also collect ESR, CRP and physician's global assessment frequently after initiation of treatment.

d) Combining avacopan with a low dose steroids

The potential benefits of avacopan as add-on to low dose steroids were discussed. The Applicant argued that the effect profile of avacopan was similar independent on whether

combined with steroids or not. The Applicant proposes to inform in the label that avacopan does not need to be combined with chronic oral steroids. While it is too premature to conclude on the wording of section 4.2 of the SmPC, the strategy could be reasonable. However, in this application for a CMA, especially in the long-term, a risk for an increased number of serious infections or other safety concerns when inhibiting the complement cascade cannot we excluded. Depending on the outcome of the phase 3 trial, further exploration on whether such potential side effects could be mitigated by combining avacopan with low dose steroids, thus enabling the avacopan dose to be lower.

e) Measures taken to keep patients in the phase 3 study in case of a CMA

To keep patients in the phase 3 study in case of a CMA, the Applicant clarified that at least 50% of the patients would be recruited outside Europe. Further, the Applicant aims to support patients and study centres to increase the willingness to remain in the study. Finally, the Applicant considered that with a restricted indication, the majority of patients with AAV will not be eligible for commercial avacopan treatment. The Applicant has also indicated that 80% of patients would be expected to be recruited in the proposed phase 3 study at the time for a potential CMA.

While the efforts are acknowledged, it would nevertheless be a great challenge to retain patients in the study. This would especially be relevant for those with obvious steroid side effects as the side effect profiles are difficult to blind. Thus, there is a risk of a drop-out of control subjects from the EU region and this is a risk even if avacopan is conditionally approved for a restricted indication. This in turn may jeopardise the conduct of the study.

Conclusion

The efforts made by the Applicant to identify a restricted target population were appreciated. However, in theory, there seemed to be only a very limited patient population where treatment could be justified due to the absence of data and for which the CMA requirements would be met. This population would essentially consist of the very small subset of patients who previously have developed very serious steroid toxicities during induction treatment with high doses of steroids but it needs to be justified that the phase 2 data can be extrapolated to this group of patients. The limitations with regards to the lack of long-term data were considered to remain. In addition, with a conditional approval of avacopan, there was a concern that the phase 3 study may be jeopardised, also with the measures taken by the Applicant. Therefore, the strategy to file a CMA based on the currently available data (also considering the Applicant's most recent proposal in the minutes from the discussion meeting) was not encouraged. It was stated that if the Applicant still decides to submit a CMA, there would be a need for a proper a risk-management plan. This plan needs to include a strategy how to minimise off-label use.

Scientific advice/protocol assistance on quality issues:

Protocol assistance received from EMA, July 2016 included views on (summarized below):

- *Acceptability of a starting material*

The CHMP was not able to provide a definitive answer due to the lack of data provided by the applicant on the origin, fate and purge of impurities. However, it was suggested that re-definition may be necessary due to the short synthetic route. Additional advice was given on considerations for one starting material and intermediate specifications, and it was suggested that an additional compound should be defined as a SM. No comment was made on the other starting materials as no data had been provided by the applicant.

Follow-up Protocol assistance received from EMA, January 2017:

- *Acceptability of SM1, SM3 and SM6 as starting materials*

  Again, the CHMP was not able to give a definitive answer due to the lack of data provided on the origin, fate and purge of impurities. Nonetheless, some proposals were made to provide additional data and the applicant was referred to the relevant guidance. For the individual SMs, the following comments were made:

  SM1: the applicant should consider the criticality of the step immediately prior to SM1 including the control of impurities formed (including mutagenic impurities). It was considered that re-definition may be needed to ensure control of that step.

  SM3: it was stated that SM3 is not considered commercially available and that the applicant should address its impurity profile (including regioisomers and different substitution products). Consideration should be given to the instability of SM3. Depending on the origin, fate and purge of impurities, it may be necessary to re-define SM3

  SM6: SM6 is not considered to be commercially available and is separated from the active substance by a single step. Despite the lack of data provided, it was considered that upstream steps were likely critical to the purity of SM6 and in turn, the active substance. Therefore, it may be necessary to re-define SM6.

Conclusion

The applicant chose not to re-define any of the starting materials in the initial submission as had been advised by CHMP. In addition, information on the origin, fate and purge of impurities was not comprehensively provided in the initial submission. Nor was the control of steps immediately upstream of the proposed SMs explained. As a result, major objections were raised in the quality section, and discussed in more detail there.

2.4. General comments on compliance with GMP, GLP, GCP

A QP declaration concerning the drug substance has been provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

Acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the Rapporteur has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the Rapporteur has accepted copies of current GMP Certificates of inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites."

All clinical studies were stated to be performed according to Good Clinical Practice (GCP) principles. However, see later in this AR, there were many uncertainties related to the conduct of the main clinical study CL002_168. For example results of the IIF analyses were missing from many subjects (especially in study center 701), some randomization numbers were lacking from the randomization list, there were high number of major protocol changes made during the study, many patients were enrolled to the trial even though they did not meet all the inclusion/ exclusion criteria, there were many other serious protocol deviations including missed doses of cyclophosphamide/ rituximab. However, due to several Major Objections raised, a GCP-inspection is not requested at this stage of assessment.

2.5. Type of application and other comments on the submitted dossier

- Legal basis: This application concerns a centralized procedure and is submitted in accordance with article 8(3) (NCE) of Directive 2001/83/EC and Regulation 726/2004.

  Avacopan has PRIority MEdicines (PRIME) designation in Europe for AAV.

- Accelerated procedure – Not applicable

- Conditional approval

  The applicant is requesting consideration for an MAA under Conditional Approval (CMA) claiming that the following mandatory criteria are fulfilled:

  1) *The benefit-risk balance is positive*

  In summary, the applicant states that in Phase II studies, avacopan when administered in combination with reduced dose prednisone, or importantly, in the absence of prednisone in patients with AAV on a background of standard cyclophosphamide or rituximab, demonstrated:

  a. Primary endpoint achievement of induction of clinical response, based on BVAS. With avacopan treatment BVAS response was numerically superior and statistically non-inferior at 12 weeks compared to treatment with high dose prednisone standard of care;

  b. More rapid onset of clinical response based on BVAS at 4 weeks, as well as superior improvement in several renal parameters compared with high dose prednisone standard of care;

  c. Superior improvement in health-related quality of life;

  d. Fewer new-onset adverse events attributable to high dose glucocorticoids;

  e. An overall favourable safety profile

  2) It is likely that the applicant will be able to provide comprehensive data

  In summary, the applicant states that a global Phase III trial is ongoing; as of 6 September 2017, 162 of 200 planned sites had been activated, and 64 of the planned 300 patients had been randomized to treatment

  3) Unmet medical needs will be addressed

  In summary, the applicant states that avacopan may address the very high unmet medical need to reduce the mortality and morbidity associated with high dose oral glucocorticoids that are required in current induction treatment regimens

  4) The benefits to public health of the immediate availability outweigh the risk inherent in the fact that additional data are still required

  In summary, the applicant states that Although AAV is uncommon, based on the incidence and relapse rates in the EU, each year approximately 1,000 to 5,000 persons require induction therapy, and are exposed to the morbidity and the risk of mortality associated with high dose oral glucocorticoids. Conditional approval provides an option for these patients in advance of confirmatory data from the Phase III study; the latter is anticipated in late 2019 or early 2020.

- Exceptional circumstances – Not applicable

- Biosimilar application – Not applicable

- 1 year data exclusivity – Not applicable

- Significance of paediatric studies

  According to the application, a deferral was granted by the PDCO for paediatric patients less than 12 years of age. To determine the safety, efficacy, tolerability, pharmacokinetics, and pharmacodynamics of avacopan in adolescents, adolescent subjects will be enrolled into the Phase III study CL010_168.

  Paediatric Investigation Plan (PIP) EMEA-002023-PIP01-16 was originally approved by the Paediatric Committee (PDCO) in May 2017. The modification of the agreed PIP was accepted by PDCO on 23 November 2017. This procedure included modification of the completion dates of two studies and a deferral of one non-clinical pharmacokinetic (PK) study. Finally, a compliance check for two completed PIP studies was finalised with favourable outcome by the PDCO on 15 December 2017.

3. Scientific overview and discussion

3.1. Quality aspects

Introduction

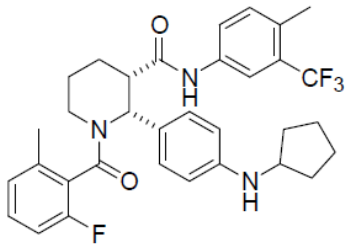
The finished product is presented as hard capsules containing 10 mg of avacopan as active substance. Other ingredients are macrogolglycerol hydroxystearate, macrogols, hard gelatin capsule and gelatin sealing band. The product is available in high density polyethylene (HDPE) bottles with rayon coil and induction sealed child resistant closure.

Active Substance

For the avacopan active substance, full information has been included in the dossier and hence the full assessment of the active substance is included in the day 80 Quality assessment report. Avacopan is not described in any pharmacopoeia and should be considered a New Active Substance (NAS).

General Information

Avacopan, produced as a free amine, is a white to tan crystalline solid which is practically insoluble in water at any pH and physiological media (SGF, FaSSIF). It exhibits polymorphism and is isolated as the anhydrous Form 1. Avacopan includes two stereocentra and is used as a single enantiomer. Its chemical structure is depicted below:



Molecular formula: $C_{33}H_{35}F_4N_3O_2$
Relative molecular mass: 581.64

Manufacture, process controls and characterisation

Manufacturing process

Avacopan development has been performed mainly by ChemoCentryx

The manufacturing process in this application for a CMA defined under cGMP (Figure S.2-1) has been described. The ranges within which the process will be controlled (normal operating ranges) have been defined based on the ranges investigated during process development. The in-process controls and critical process parameters have been described and are considered an adequate part of the control strategy. Isolated intermediates are controlled with specifications that require further revision before considered fully acceptable. Analytical methods used for intermediate testing are described and confirmed validated. A few outstanding issues regarding the validations remain.

Control of materials

The selection of regulatory starting materials was discussed in connection with EMA protocol assistance and pre-submission meetings in 2016 and 2017. The advices given by EMA were initially not followed and major objection was raised at D120 on all starting materials since the documentation provided did not allow full assessment of their suitability. Additional information was provided in the D120 response regarding e.g. starting material syntheses, formation and fate of impurities including potential genotoxic reagents/impurities and analytical methods. Based on the additional information, 2 proposed SMs have been assessed as suitable as starting materials if remaining questions regarding impurity control and analytical methods are addressed. The other 2 starting materials still require redefinition. A redefinition is proposed by the applicant as a post-authorisation measure. This is not acceptable from a quality perspective and adds to the negative benefit/risk of the product.

Acceptable specifications have been provided for most other materials used in the synthesis. Question remains for some solvents used in the process.

Characterisation

Avacopan has been characterised using adequate analytical techniques.

Manufacturing process development

Avacopan was initially manufactured using a route different to the route selected for commercial manufacture. The commercial route has been used with modifications of e.g. reagents, solvents and final isolation, in the manufacture of drug substance to phase 2 (partly) and phase 3 clinical trials as well as preclinical testing.

Adequate manufacturing process development has been conducted. Experiments have been designed on the basis of prior knowledge and risk assessments and summary descriptions of the multivariate studies (DoE) and one variable at a time experiments have been provided in the dossier. The results have been translated into normal operating ranges (NORs) and proven acceptable ranges (PARs) for both critical and non-critical process parameters. The applicant has stated that the process will be operated within the defined NORs but further clarification has been requested regarding the use of PARs. No design space is sought.

Impurities

Potential and actual impurities originating from starting materials or impurities formed in the avacopan process are discussed. The fate of most identified impurities has been studied in impurity tracking experiments and the crystallization steps have been shown to well purge many of the impurities. The information gathered has been used in the development of the control strategy.

Potential mutagenicity of the majority of identified impurities has been assessed but a major objection was raised at D120 concerning the lack of control of the potential mutagenic impurities identified. Based on additional information provided in the D120 response, the control of potential mutagenic

impurities is now largely acceptable. However, a few questions remain, and it should be noted that the control strategy is based on product exposure for up to 10 years. If >10 years treatment, potential mutagenic impurities need to be limited further.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications

The proposed drug substance specifications as presented in Table S.4-1 are acceptable apart from the assay limit. The applicant has confirmed that the specification presented is also applied by the drug product manufacturer. However, the drug product manufacturer's specification should be included in the dossier. The tests omitted from the specification have been justified.

Analytical procedures and reference standards

The analytical methods have been described and validation reports provided. The control of impurities, which is done by HPLC and UPLC, has a critical role in the control of the quality of the drug substance. Additional validation is requested for the newly introduced UPLC method as well as the HPLC method. The lack of validation of analytical method was raised as a major objection at D120. In the D120 response, additional validation data was provided, and the major objection is now considered solved.

Batch analysis

Batch analyses data for representative avacopan batches have been provided.

Stability

The proposed re-test period and storage conditions are supported by the data provided.

3.1.1. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The Vynpenta 10 mg hard capsule drug product is a light orange and yellow opaque bicolor Size 0 hard capsule with a clear gelatine sealing band containing an amorphous solid dispersion formulation.

The description and composition of the drug product is satisfactory. No description of the proposed packaging is given in section 3.2.P.1, but information is provided in other relevant sections of module 3.

The Avacopan 10 mg hard capsule formulation and manufacturing process was developed and characterized in the context of the quality target product profile (QTPP) were a capsule of suitable size to aid patient compliance and acceptability was targeted. The solid state form of avacopan drug substance is not anticipated to have any impact on drug product processing or performance as the drug is dissolved into the excipients to create a solid solutionThe choice and function of the excipients have been described.The applicant should consider the development of an alternate formulation in order to increase drug load in the final dosage form thereby reducing capsule burden and improving patient compliance.

It has been demonstrated that no unacceptable change in enantiomeric purity occurs during the manufacturing process or the proposed shelf-life of the finished product. It is thus considered justified that the analysis for avacopan chiral purity is only determined in the drug substance.

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 commercialization. The color of the capsule shell was changed from white opaque to bicolor yellow opaque body with light orange opaque cap. The clinical lots at were manufactured and tested with processes, analytical procedures, and specifications very similar to those previously employed. The packaging materials are commonly used for oral pharmaceutical dosage forms.

Manufacture of the product and process controls

Manufacturers and responsibilities involved in the manufacture of the finished product are described. The information on manufacturers in module 3 and the application form is consistent. The drug product in bulk is manufactured by Primary/ secondary packaging is performed by Additional sites for secondary packaging and sites responsible for importation and batch release in the EEA are Full addresses of the manufacturing sites are given in the dossier.

The applicant consider the manufacturing process as a standard manufacturing process and robustness of the process have been demonstrated during development by the manufacture of representative batches at the proposed commercial batch size.

Although the manufacturing process is not a new method in the pharmaceutical industry, the manufacturer may have a little experience of this technique and therefore the method of manufacture as standard could be questioned. Nevertheless, the justification provided by the applicant can be considered acceptable if process validation is performed with acceptable results using three production scale batches before the drug product is launched. As the applicant already states, the validation effort should be conducted prospectively and finalized, prior to commercialization, per the approved validation protocol. The applicant confirms that all three validation batches will be placed on stability and will be tested in accordance with the stability protocol.

For the planned manufacturing process validation, an acceptable control strategy should be provided. The protocol for process validation should be updated accordingly, unless otherwise justified.

Product specification, analytical procedures, batch analysis

A risk assessment with respect to the potential presence of elemental impurities in the drug product based on the general principles outlined in Section 5.1 of ICH-guideline Q3D has been presented. The applicant concludes that based on the available data, the elemental impurities concentrations in the drug product are low and below the acceptable threshold, which is considered as relevant for further control strategy. The conclusion is endorsed.

The same analytical methodology is used for the analysis of avacopan 10 mg hard capsules for assay, related substances, content uniformity and identification. The only difference between each of these tests is the sample preparation. Dissolution is performed as described in Ph. Eur. 2.9.3 and using HPLC analysis. Appearance of capsules and contents of capsules is determined by visual inspection. Water content and microbial limits test are determined as described in Ph. Eur. The analytical methods have been described and validation is presented.

Batch analysis data for release testing for the avacopan 10 mg hard capsule batches manufactured are provided. Analytical test methodology has followed Ph. Eur. with the exception of the HPLC analysis for identification/assay/impurities/content uniformity, and dissolution/HPLC. The container-closure system for Avacopan 10 mg capsules is 250 mL HDPE bottles with rayon coil and an induction sealed child-

resistant closure. 180 count capsules are packaged in a white, high density-polyethylene (HDPE) round bottle. The bottle is closed with a white, child-resistant, polypropylene screw cap with an induction sealed, aluminium-faced liner. Specifications and component drawings are provided. Compliance of immediate packaging materials with USP <661> Containers – Plastics is confirmed by the applicant. Compliance with relevant EU and Ph. Eur. requirements for packaging materials for drugs and/or food as applicable has been confirmed.

Stability of the product

The registration stability studies for avacopan 10 mg hard capsules manufactured at commercial-scale by the proposed commercial manufacturer have recently been placed under both long-term (25°C/60% RH, 30°C/65% RH) and accelerated (40°C/75% RH) conditions. These three registration batches will be updated as data at each specified time point becomes available.

The dossier presents the initial two manufactured capsule batches as primary stability data through 6 months at the accelerated condition and to 18 months at the long-term stability conditions for the first primary clinical batch, and through 6 months at the accelerated and 12 months at the long-term conditions for the second and third Registration stability batches. No trends have been observed for assay, individual and total impurities, dissolution or moisture, with the exception noted above for a slight increase in moisture content at the accelerated storage condition, when compared to the initial data.

In use Stability Study

The samples from one batch were packaged in the final configuration and placed into two stability conditions, 25ºC/60% RH (long term) and 40 ºC/75% RH (accelerated). The induction seal will be removed at the state of the in-use stability study. The in-use testing was started after the final packaged capsules were stored at the long-term stability condition for 9 months. All bottles are opened during the actual in-use study for not less than 2 minutes every weekday once per day while inside the stability chamber. The study is planned to continue at both storage conditions for 180 days. Up to date results from 90 days are available and no changes to the capsules have been observed.

Based on the stability data presented the proposed shelf-life of 30 months with no special storage conditions could be considered acceptable.

The applicant has proposed to limit in use shelf-life to 3 months after opening the bottle. The result from the in-use study performed does not show any relevant deterioration. There are therefore no scientific grounds for a limitation regarding use after opening of the bottle. An in-use shelf-life not justified by data should be avoided as it will lead to extra costs for the patient, health insurance systems and environment when drug products fit for use are discarded. See also EMA Q&A on quality "Claims for in-use shelf-life for solid oral dosage forms in multi-dose containers.

Post approval change management protocol(s)

NA

Adventitious agents

NA

GMO

NA

3.1.2. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Three major objections were raised at D120 regarding the start of the drug substance synthesis, lack of validation of analytical method and control of potential mutagenic impurities. Analytical methods have now been adequately validated and the control strategy for potential mutagenic impurities is largely acceptable. To note is that the control strategy is based on product exposure for up to 10 years. If >10 years treatment, potential mutagenic impurities needs to be limited further. The applicant has proposed to redefine two of the proposed starting materials as a post-authorisation measure. This is not acceptable and the major objections regarding the two starting materials remain.

There are remaining other concerns for both drug substance and drug product that need to be resolved before the application can be approved from a quality perspective.

As a post-authorisation measure the applicant should consider the development of an alternate formulation in order to increase drug load in the final dosage form thereby reducing capsule burden and improving patient compliance.

3.2. Non clinical aspects

3.2.1. 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 mobilization 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 0.65 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 has been 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} ~1.4 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} ~1.4 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, a human C5aR knock-in (hC5aR KI) mouse strain in which the mouse C5aR gene was replaced with the human C5aR gene was used for *in vivo* studies. The model seems validated by data indicating that the innate immune cells of these hC5aR KI mice respond 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 0.5 nM in 100% mouse plasma. This value is similar to the IC_{50} of 1.7 nM exhibited by avacopan for hC5a-mediated inhibition of neutrophil migration in human whole blood.

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 necrotizing 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 (Huugen et al, 2007). Moreover, knocking out the C5a receptor makes mice resistant to ANCA disease in this model system (Schreiber et al, 2009).

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, 8 (2x4) or 30 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 8 (2x4) and 30 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 30 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.

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; and weak levels of activity were detected against one protein, a sodium channel (binding site 2, 59% inhibition with 10 µM (~5.8 µg/mL) avacopan. 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; 53% inhibition at cannabinoid receptor type 1, 64% inhibition at sodium channel (binding site 2), and 51% inhibition at GABA-gated chloride channel.

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. Interaction potential with rituximab (other possible co-medication) is considered low.

Safety pharmacology

Safety pharmacology studies to assess the potential effects of avacopan upon the central nervous, cardiovascular, renal and respiratory systems have been conducted in rats and cynomolgus monkeys. However, as avacopan lacks affinity for the rat C5aR, the potential safety pharmacology effects of C5aR antagonism are not considered evaluated in the rat studies.

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 of 29300 ng·h/mL and 9590 ng·h/mL, respectively (44-week study).

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, 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, the maximal concentration of the compound achievable without precipitation. 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 heart rate 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, group mean systolic, diastolic and arterial 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.

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.

Pharmacodynamic drug interactions

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

3.2.2. 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.

Pharmacokinetic studies *in vivo* have been performed in mice, rats, hamsters, rabbits, dogs and monkeys. In mice and rats administration was by both oral and intravenous routes while in dogs only intravenous route was used. In rabbits, hamsters and monkeys avacopan was administered orally.

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 aqueous hydroxypropyl methylcellulose (HPMC) as 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 concentrationswere 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.

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 were also observed, all primarily products of Phase I biotransformations 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. In human plasma, avacopan and metabolite CCX168-M1 accounted for 18% and 11.9% of the total plasma radioactivity, respectively. CCX168-M1 exposure in the rat and monkey toxicology studies was higher than the human exposure.

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.

3.2.3. 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) studies; and *in vitro* phototoxicity studies. A pre- and post-natal study in hamster is ongoing. In addition, 2-year carcinogenicity studies (hamster and rat) are ongoing.

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.

Intended therapeutic route of administration in humans is oral. Same route was used in the toxicology studies. In cynomolgus monkeys in addition the nasogastric intubation was applied.

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)

Avacopan was well tolerated at doses up to 1000 mg/kg/day (500 mg/kg b.i.d.) 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 anatomical pathological correlate(s). As the C5a receptor has been reported to be involved in energy utilization and fat storage in mice (Roy et al. 2013; Bavia et al. 2016), changes in serum triglycerides after 13 weeks of avacopan dosing in hamsters, were reversible and not associated with any adverse histopathological changes in the liver.

No clear 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 maximize exposure, twice daily dosing was used in an attempt to further maximize exposure. Additionally, a saturated absorption was seen in all repeat-dose studies.

Exposures of avacopan reached in the pivotal toxicology studies exceeded the expected exposures reached with 30 mg b.i.d. in humans ($AUC_{0\text{-}24}$ 5593 ng·h/mL based on PoP PK-modeling). The AUC exposure margins relative to the human AUC exposure are approximately 5, 14 and 4 in hamsters, rats and monkeys, respectively.

Genotoxicity and carcinogenicity
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 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. 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.

Two-year carcinogenicity studies in hamsters and rats are ongoing. The study reports are expected to be completed.

Reproductive and developmental toxicity

The reproductive and developmental toxicity of avacopan has been evaluated in a complete study package. The pre- and post-natal development study was submitted in the response to the Day 120 LoQ. Fertility and embryo-foetal development studies were performed in hamsters and in rabbits, and a pre-and post-natal development study in hamsters have been submitted.

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 (2x500 mg/kg/day). 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 fetuses with skeletal variations, principally short thoracolumbar supernumerary rib, at 1000 mg/kg/day (2x500 mg/kg/dose; 33.6% of the fetuses and 100% of the litters in comparison to 14% of foetuses and 70% litters in the control group).

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.

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. On the basis of these data, the maternal NOAEL was 1000 mg/kg/day. At NOAEL, exposure to avacopan and CCX168-M1 corresponds to ~5 and 1-fold clinical AUC exposure, respectively.

In the F_1 generation, there were no findings considered avacopan-related in any of the parameters evaluated with exception of the male sexual maturation. There were seemingly small but dose-related and statistically significant increases in the average day of preputial separation at or above dose levels of 30 mg/kg/day in comparison with the control groups. The study report concludes that these increases were not considered to be avacopan-related because the values were within the historical control range of the Testing Facility. However, as historical control data were not included in the study report, it remains to be concluded whether or not this finding is considered avacopan-related. The effect may indicate a general developmental delay. However, there were no clear effects on body weight gains in the avacopan-treated groups. In general, preputial separation is known to be androgen dependent and consequently delays could potentially indicate an estrogenic or anti-androgenic effect. Thus, the Applicant is asked to provide the historical control data referred to, and to further discuss a relation to avacopan treatment, and potential clinical consequences.

It is noted that the exposure, as assessed by avacopan and metabolite CCX168-M1 (mean C_{max} and AUC_{0-8}), generally increased with the increase in dose from 10 to 100 mg/kg/day but did not increase further with an additional increase from 100 to 1000 mg/kg/day. Thus, avacopan was tested at saturated exposure. The pup:maternal ratios indicate that avacopan and CCX168-M1 is present in pups following maternal administration of avacopan. The pup:maternal ratios for both avacopan and CCX168-M1 indicate that maternal exposure was much higher than pup exposure.

Juvenile toxicity
No juvenile toxicity has been performed which is acceptable as avacopan is currently indicated for use in adult patients only.

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.

Phototoxicity
Avacopan absorbs light within the range of natural sunlight (290 to 700 nm) with a MEC exceeding the threshold of 1000 L $mol^{-1}cm^{-1}$as cited in ICH S10 guideline. 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 validity of this study is questioned. Avacopan shows a peak absorption at 290 nm while the light source used in the study does not emit light at this wavelength. A justification for the selection on the light source used in the in vitro NRU-3T3 test has been provided. 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. As it is well-known that light in the UVB range (280-315 nm) is highly cytotoxic, it is not feasible to test wavelengths covering the peak absorption of avacopan (290 nm). As noted in ICH S10, UVB-induced phototoxicity is rarely a concern for pharmaceuticals with systemic exposure since UVB minimally penetrates beyond the epidermis.

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.

Taken together, although no apparent immunotoxicological concerns have been identified in the performed non-clinical studies, immunosuppression is a potential risk in the clinical situation based on the intended MoA.While the clinical safety base in humans is still limited (73 patients), infections and infestations are proposed to be included as common adverse reactions in SmPC section 4.8 and include

Candida infection (mild to moderate), bronchitis and rhinitis. Serious infections included perirectal and limb abscesses and sepsis. In the clinical trials, avacopan was administered with either cyclophosphamide or rituximab, and most patients also received glucocorticoid treatment.

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 characterized 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. Thus, this major human metabolite is considered adequately qualified from a non-clinical perspective.

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

3.2.4. Ecotoxicity/environmental risk assessment

Avacopan requires a PBT assessment and the applicant has committed towards proving a step-wise PBT assessment. Regarding the log K_{OW} determination, it is requested that if need for a B test arises (which requires a reliable K_{OW} value for the choice of experimental design), the applicant is also requested to provide a more precise log K_{OW} determination. Overall, the available data do not allow concluding definitively on the potential hazard/risk of avacopan to the environment.

3.2.5. Discussion on non-clinical aspects

The non-clinical characteristics of avacopan has been characterised in pharmacology, pharmacokinetic and toxicology studies. Carcinogenicity studies in hamster and rat are ongoing.

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 mobilization 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 rodent 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.

Based on the secondary pharmacology screens, both avacopan and the metabolite CCX168-M1 seem to have low potential for off-target effects.

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.

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, 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, the maximal concentration of the compound achievable without precipitation. Exposure margins for avacopan and CCX168-M1 of about 3500-fold, and 12000-fold, respectively, relative to human $C_{max,unbound}$ 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 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 3.1-fold the C_{max} at MRHD (373 ng/mL).

Additionally, no evidence of electrocardiographic abnormalities was seen *in vivo* in the repeat-dose monkey studies at exposures of up to 2330 ng/mL (avacopan), and 543 ng/mL (CCX168-M1). The plasma concentrations of avacopan evaluated in the *in vivo* CV studies exceeded the expected C_{max} in humans. However, as there are some uncertainties in the avacopan and M1 C_{max} exposure in patients

Pharmacokinetics

Distribution of avacopan to placenta was not investigated. In the pre- and post-natal development study in hamsters, avacopan and CCX168-M1 was present in pups at low levels following maternal administration of avacopan.

Toxicology

The selection of the main toxicology species, hamster and Cynomolgus monkeys is justified based on pharmacology and pharmacokinetic data.

In chronic studies, avacopan was in general well tolerated in repeated dose toxicology studies in hamsters, rat and monkeys. 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.

At Day 120, one major objection was raised regarding unclarities on genotoxicity or mutagenic potential of avacopan, on batches used in the ongoing carcinogenicity studies, and a justification for the lack of available carcinogenic data. From the Quality perspective, one related major objection was raised on the control strategy for potential DNA-reactive impurities (see section 3.1 Quality aspects).

Overall, parts of the major objection are considered largely resolved. It is agreed that avacopan has been tested in a complete package of *in vitro* and *in vivo* genotoxicity studies in agreement with ICH S2(R1) guidance to the extent feasible based on the poor aqueous solubility. Avacopan can thus be regarded as not mutagenic or genotoxic. The Applicant has clarified that avacopan batches used (and will be used) in the carcinogenicity studies closely match the specifications and synthetic route of the intended commercial lots. All of lots have been manufactured using the intended commercial process, with the exception of lot # NJ00001, in which a different solvent was used in the last manufacturing steps. However, one clarification on inconsistent information given is requested.

Regarding the lack of completed carcinogenicity studies, the Applicant is of the opinion that in the absence of a carcinogenicity signal, non-clinical carcinogenicity studies are not needed for the requested short-term treatment in a rare disease indication. The argumentation is partly agreed with. The chronic toxicity of avacopan has been studied to the extent feasible based on the poor solubility, however, as no dose-limiting effects or target organ of toxicity were observed, the chronic toxicity of avacopan is not considered fully explored. Thus, argument that there were also no observations of hyperplasia, premalignant or malignant changes noted after 44 weeks in primate, and 26 weeks in rat general toxicity studies is not considered fully relevant. The lack of carcinogenicity studies is considered a major deficiency in the non-clinical evaluation but may be acceptable in view of the recommended treatment duration of 12 weeks. However, considering the severity and nature of the disease, it seems likely that avacopan, should it be approved, will be used for longer periods than 12 weeks. In SmPC section 4.2, the current recommendation on treatment duration is given; *"The duration of a treatment cycle is 12 weeks (see section 5.1). The patient's physician should perform an individual benefit/risk assessment prior to extending treatment with Vynpenta longer than 12 weeks."* It should also be taken into account that clinical safety data are scarce. Only a limited number of patients have been treated with avacopan for the recommended treatment duration, and there are no unblinded clinical data available on treatment beyond 12 weeks. Thus, the recommendation on treatment duration will be further discussed. In addition, the overall benefit/risk of this CMA is currently regarded as negative (see section 5.7.2).

Taken together, to date, there are not enough data to conclude on the long-term safety of avacopan from a non-clinical perspective. However, the issue not further pursued from a non-clinical perspective. The lack of completed carcinogenicity studies will be taken into consideration in the benefit/risk assessment.

Avacopan has been tested in a complete reproductive and developmental study package in hamster and rabbits. Avacopan–treatment was not associated with adverse effects on either male or female fertility in hamsters. In rabbits, maternal toxicity as seen by an increased incidence in abortions and clinical signs were observed at the highest dose tested. Skeletal abnormalities (increase in short thoracolumbar supernumerary rib) were reported in pivotal embryofoetal development toxicity study in hamsters; findings were in an increased number of litters and foetuses in the 500 mg/kg/dose group (33.6% of the foetuses and 100% of the litters in comparison to 14% of foetuses and 70% litters in control group). The Applicant argues 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. Thus, these variations are considered as adverse. The NOAEL for maternal toxicity is 1000 mg/kg/day, corresponding to 6.4-fold the clinical AUC. Based on the increased incidence of short thoracolumbar supernumerary ribs at 1000 mg/kg/day, the NOAEL for embryo-foetal development is 100 mg/kg/day, corresponding to 6.4-fold the clinical AUC.

In the pre- and post-natal development study, treatment was generally well-tolerated in female hamsters during the gestation and lactation periods. In the F_1 generation, there were seemingly small but dose-related and statistically significant increases in the average day of preputial separation at or above dose levels of 30 mg/kg/day in comparison with the control groups. The study report concludes that these increases were not considered to be avacopan-related because the values were within the historical control range of the Testing Facility. However, as historical control data were not included in the study report, it remains to be concluded whether or not this finding is considered avacopan-related. The effect may also indicate a general developmental delay. However, no clear effects on the body weight was observed in avacopan-treated groups. In general, preputial separation is known to be androgen dependent and consequently delays could potentially indicate an estrogenic or anti-androgenic effect. Thus, the Applicant is asked to provide the historical control data referred to, and to further discuss a relation to avacopan treatment, and potential clinical consequences.

At Day 120, concerns were raised regarding 2 potential mutagenic impurities, SM6 (C0340809) and C0332414. Additional concerns were raised from the Quality perspective. Following clarification from the Applicant, SM6 has been evaluated *in silico* using four software programs, two rule-based (DEREK, Expert Alerts) and two statistical-based (Model Applier, EPA TEST).Three analogs are predicted negative by *in silico* methods, and two compounds, 4-chloro-3- (trifluoromethyl)aniline and 4-fluoro-3-(trifluoromethyl)aniline, are reported as negative for bacterial mutagenicity based on experimental data. Overall, based *in silico* predictions, and on data on SM6 analogs, it is agreed that SM6 should be classified as non-mutagenic, i.e. a class 5 compound.

Regarding C0332414, the Applicant has clarified that this impurity corresponds to the CCX168-M6 metabolite. CCX168-M6 was generated by the Aroclor-induced rat liver S9 fraction, reaching maximum levels at 30 minutes incubation, and is therefore considered evaluated as an *in vitro*-generated metabolite in the avacopan *in vitro* genotoxicity/mutagenicity assays. CCX168-M6 is also a minor metabolite formed *in vivo* in rats, hamster and monkeys. M6 is also a minor (approx. 3% or less) metabolite in humans. The Applicant has discussed the results of the *in silico* assessments and provided further information on the reactivity of the alerting primary amine function. No further testing is therefore assessed needed. C0332414 should be classified as a non-mutagenic impurity.

Regarding the potential for immunotoxicity, although no apparent immunotoxicological concerns have been identified in the performed non-clinical studies, immunosuppression is a potential risk in the clinical situation based on the intended MoA. While the clinical safety base in humans is still limited and the phase III clinical study may provide further insight, infections and infestations are included as common adverse reactions in SmPC section 4.8. Infections are proposed by the applicant in this application for a CMA as an important identified risk. In addition, infections with encapsulated bacteria are proposed to be included as a potential important risk (see section 3.4.1).

3.2.6. Conclusion on non-clinical aspects

The MO regarding genotoxicity and carcinogenic potential of avacopan is considered largely resolved from a non-clinical perspective. However, the lack of completed carcinogenicity studies is considered a major deficiency in the non-clinical evaluation but may be acceptable in view of the recommended treatment duration of 12 weeks. Thus, to date, there are not enough data to conclude on the long-term safety of avacopan from a non-clinical perspective. This deficiency should be taken into consideration in the benefit/risk assessment. Some OCs are still outstanding (see LoQ). Thus, granting of CMA is not currently supported from the non-clinical perspective.

3.3. Clinical aspects

- ***Tabular overview of clinical studies***

The PK and PD profile of avacopan has been evaluated in healthy volunteers in clinical studies CL001_168 (single and ascending dose), CL004_168 (mass balance), CL007_168 (food effect and cardiac safety) and CL008_168 (drug-drug interaction), and in patients with AAV in Phase II studies CL002_168 and CL003_168 (see Table 1 and Table 2).

The efficacy evaluation is based primarily on the results of the Study CL002_168. The safety evaluation is based on the Studies CL002_168 and CL003_168. The assessment of efficacy and safety is also projected on the treatment algorithm used in the ongoing Phase III Study CL010_168 (see Table 1).

Table 1: Clinical phase I studies in the development program of avacopan

Study Number/ Country	Study Phase	Main Study Objectives	Subject Population	Study Size and Dosing Period	Avacopan Dose Form (oral)
CL001_168 / Switzerland	Phase I	Safety and tolerability; pharmacokinetic and pharmacodynamic profiles	Healthy volunteers	48 subjects; single dose (1 – 100 mg) in Period 1; 1 – 10 mg q.d. or 30 / 50 mg b.i.d. dose for 7 days in Period 2	Dosing solutions and 10 mg gelatin capsules
CL004_168 / United States	Phase I	Mass balance	Healthy volunteers	6 males; a single dose of 100 mg / 400 µCi [^{14}C]-avacopan	Dosing solution
CL007_168 / United States	Phase I	Food effects; cardiac safety	Healthy volunteers	16 subjects; 3 – 100 mg in 4 periods	Dosing solution for 3 mg dose; 10 mg capsules for other groups
CL008_168 / United States	Phase I	Drug-drug interaction	Healthy volunteers	32 subjects (16 in each cohort)	10 mg capsules

Table 2: Clinical phase II studies in the development program of avacopan

Study ID	Number of Study Centres Location(s)	Study start Enrollment status, Date Total Enrollment / Enrollment goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. Subjects by Arm entered/ completed	Duration	Gender M / F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
CL002_168	60 sites in Austria, Belgium, Czech Republic, Hungary, France, Germany, Ireland, The Netherlands, Poland, Sweden, and the United Kingdom	Start: 27 Sep 2011 End: 18 Jan 2016	Randomised, double-blind, double dummy, placebo-controlled	Avacopan and matching placebo; Prednisone and matching placebo; 30 mg avacopan twice daily orally For control: 60 mg prednisone once daily, tapered to 0 by week 21	Primary safety: to evaluate the safety and tolerability of avacopan Primary efficacy: to evaluate the efficacy of avacopan based on BVAS.	Entered: Control: 23 Avacopan+low dose prednisone: 22 Avacopan+no prednisone: 22 Completed: Control: 18 Avacopan+low dose prednisone: 19 Avacopan+no prednisone: 18	12 weeks treatment 12 weeks follow-up	47 / 20 59.3 (20-82) years	GPA, MPA, or renal limited vasculitis	Efficacy: BVAS response at Week 12 Safety: Adverse event incidence

Study ID	Number of Study Centres Location(s)	Study start Enrollment status, Date Total Enrollment / Enrollment goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. Subjects by Arm entered/ completed	Duration	Gender M / F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
CL003_168	47 sites in USA and Canada	Start: 4 Feb 2015 End: 19 Jul 2016	Randomised, double-blind, double dummy, placebo-controlled	Avacopan and matching placebo; Prednisone and matching placebo; 10 mg or 30 mg avacopan twice daily orally For all groups: 60 mg prednisone once daily, tapered to 0 by week 21	Primary safety: to evaluate the safety and tolerability of avacopan Primary efficacy: to evaluate the efficacy of avacopan based on BVAS.	Entered: Control: 13 10 mg avacopan: 13 30 mg avacopan: 16 Completed: Control: 13 10 mg avacopan: 12 30 mg avacopan: 15	12 weeks treatment 12 weeks follow-up	19 / 23 58.5 (26-83) years	GPA, MPA, or renal limited vasculitis	Safety: Adverse event incidence Efficacy: BVAS response at Week 12 (descriptive)

In addition to this, a phase 3 study is ongoing (Table 3).

Table 3: An ongoing phase III study of the efficacy and safety of avacopan in subjects with AAV.

Study ID/ Phase	Country	Study Title/Design	Test Product Dosing Regimen, Duration, and Route of Administration	Target Study Population	Study Status
CL010_168/ Phase 3	Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Italy, The Netherlands, New Zealand, Norway, Sweden, Switzerland, United Kingdom, United States	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 plus full dose prednisone (60 mg/day starting dose) or/ Avacopan 30 mg twice daily. All subjects receive cyclophosphamide or rituximab. 52-week dosing period; Oral 8-week follow-up period	**300 subjects with** ANCA-associated vasculitis	Ongoing

3.3.1. 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 11.9% 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.

Bioanalytical methods

Avacopan and metabolite M1 concentrations in human plasma and urine samples were analysed by validated LC-MS/MS methods.

Absorption

The absolute bioavailability is unknown but is a high estimated fraction absorbed is expected based on amount of phase 1 metabolites found in excreta. Regarding solubility, avacopan is practically insoluble across a wide range of conditions (pH 1.1-12.0, SGF and FaSSIF). As a consequence of this property, avacopan is formulated in a solubility enhancing formulation. 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 most Phase I studies e.g. CL001_168 FIH; CL007_168 food effect / cardiac safety; CL008_168 drug-drug interaction.

Based on the poor solubility, avacopan is a BCS 2 or 4 compound.

Avacopan pharmacokinetics profile is approximately dose linear, with an approximate dose-proportional increase in systemic exposure in the dose range of 10 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. 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. The result from the food interaction study is presented below:

Table 4: 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)							

Table 5: 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).							

Across studies a, a modest intra individual (ca 30%) variability is observed.

Distribution

Based on the population PK analysis, mean apparent volume of distribution was 4,990 L. 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. A high degree of binding to albumin and AAG, >99%, was also seen for avacopan and M1. Based on both in vivo data and in vitro data, blood-to-plasma ratios were less than 1, suggesting that both compounds have limited penetration into red blood cells.

Metabolism

Data suggests that 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.

The apparent plasma clearance of avacopan is on average about 52 L/h in healthy subjects, with a terminal elimination half-life of approximately 72 hours. 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 1.2 – 2.2, suggesting a modest degree of time-dependent PK.

Excretion

Based on the ADME study, aapproximately 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.

Following single dose administration and multiple dose administration, avacopan exposure increases approximately proportional vs dose (1-100 mg). Repeat administration for seven days of avacopan resulted in modest accumulation of avacopan (approximately 2-fold at 30 mg b.i.d.).

Special populations

Regarding renally impaired patients, the applicant has not performed a dedicated renal impairment study and does not indicate that such study is planned. The applicant refers to the mass balance study where approximately 0.02% of the dose was excreted unchanged in urine. Following completion of the phase III study which seems to contain a large fraction of patients with severe renal impairment (ca 30 %) there will be an unusual amount of clinical data, including PK, available for renally impaired patients.

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 was not evaluated. 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.

Interactions

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, 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.

Regarding being a perpetrator on CYP-enzymes, the in vitro results indicate a possible CYP3A4 time dependent inhibition. The performed in vitro CYP induction assay is deemed inconclusive. The net effect is described in vivo where avacopan was administered concomitantly with the a CYP3A4

substrate (midazolam). Avacopan increased midazolam AUC with approx. 81% 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.

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.

Also, avacopan seems inactive against 11β-hydroxysteroid dehydrogenases type 1 (11β-HSD1) and type 2 (11β-HSD2).

The ability of M1 to inhibit the common CYP450 isoforms was tested and no effect was seen.

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 P-gp, OATP1B1, OATP1B3 or BCRP in vitro.

Further, M1 seems inactive against 11β-hydroxysteroid dehydrogenases type 1 (11β-HSD1) and type 2 (11β-HSD2).

Pharmacokinetic interaction with the commonly used concomitant medications in AAV patients, namely, prednisone, cyclophosphamide, rituximab, angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers are not expected with avacopan.

3.3.2. Pharmacodynamics

Avacopan is an orally administered small molecule antagonist of the complement 5a receptor (C5aR).

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. Please see the details of the conduct of studies in Table 6 and Table 7.

According to analysis performed by the applicant in study CL001_168, avacopan concentration-dependently block effects of C5a which are believed to be important for the pathogenesis of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV). 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 production of CD11b by the neutrophils. The results of the second assay investigating the chemotaxis of neutrophils indicated a trend towards decreased chemotaxis of neutrophils.

Both in the healthy controls in study CL001_168 and in the subjects with AAV in study CL002_168 and CL003_168, avacopan was associated with a decrease neutrophil count and in the latter group even more pronounced than current standard of care. In study CL002_168 and CL003_168, it was further found that similarly to standard of care, avacopan treatment is associated with a decrease of MCP-1 which is considered a marker for renal inflammation.

In study CL002_168, it was demonstrated that patients with AAV (n=66) had higher levels of complement activation products in circulation than healthy controls (n=20). Overall, the levels of Bb, C3a and C5a were reduced in patients treated with standard of care but did not return to healthy control levels for C3a and C5a. No clear changes were observed in the five analysed complement fragments during the 12 week treatment period, in avacopan only treated patients. According to the applicant, this indicates that avacopan does not alter the production of alternative complement

pathway components. The applicant specifically concludes that avacopan treatment does not affect the plasma sC5b-9 levels, which are needed to protect against encapsulated bacterial infections such as Neisseria meningitides and that this is in contrast to C5 inhibitors, such as eculizumab, which blocks the formation of C5b and therefore C5b-9. However, there appeared to be slight decrease of plasma soluble C5b-9 levels also in the avacopan treated patients, although not statistically significant according to the statistical analysis conducted by the applicant, not more pronounced than in the AAV group treated with standard of care and still resulting in a Day 85 mean value numerically higher than the mean baseline value for the healthy controls, see figures below.

Table 6: Plasma Soluble C5b-9 Levels at Baseline in Subjects with AAV and Healthy Controls in study CL002_168

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.

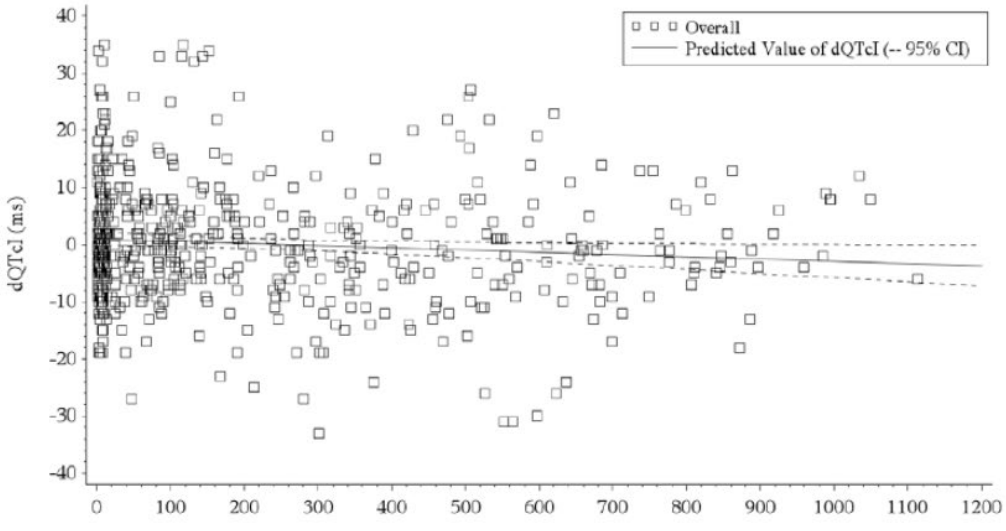
Table 7: Plasma Soluble C5b-9 Levels in Subjects with AAV at Baseline and during the 12-Week Treatment Period and in Healthy Controls in study CL002_168

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

Abbreviations: FD=Full dose, LD=Low Dose

The potential effect of avacopan and its main metabolite CCX168-M1on cardiac safety was evaluated in 16 healthy volunteers in study Study CL007_168. The study included 4 study periods. Subjects received a single oral dose of 30 mg avacopan, given in the fed or fasted state in the first two periods, a single oral dose of 3 mg avacopan in the third period, and a single oral dose of 100 mg avacopan, followed by 100 mg avacopan twice daily for 5.5 days in the fourth study period. Cardiac safety was assessed through electrocardiogram (ECG) measurements of the subjects in the study ranging from a sub-therapeutic dose of 3 mg avacopan up to supratherapeutic doses of 100 mg avacopan twice daily. According to the applicant, results from this ECG study showed that there was no evidence of a detrimental effect from either avacopan or its metabolite CCX168-M1 on the QT/QTc interval or any other ECG parameter. The relationship between plasma avacopan concentrations and QTcI in study CL007_168 is shown in the figure below.

Figure 2: Linear Model Evaluation of avacopan in Study CL007_168: Change From Baseline in QTcI (dQTcI) Versus Time-Matched Plasma Avacopan Concentrations (scatterplot)



Source: CSR CL007_168 Figure 11-6

Results from the categorical outlier analysis for all subjects in study CL007_168 are presented in the table below. None of the subjects had a QTcI >450 msec during the study. Subject 8, receiving 3 mg avacopan, had changes from baseline in QTcI of 32 msec at Hour 4 and 34 msec at Hour 12 following dosing. Subject 9, receiving 30 mg avacopan, had changes from baseline in QTcI of between 32 and 35 msec at 7 of 9 time points following dosing. No subjects had a change from baseline >60 msec. According to the applicant, these effects did not indicate an avacopan dose-dependent relationship and therefore, the results from the categorical analysis suggest no cardiac safety signal with avacopan. The applicant states that in summary, the ECG results from study CL007_168 indicated that across a broad avacopan and CCX168-M1 plasma concentration range there was no evidence of a detrimental effect of avacopan on QTc and that these results are consistent with the nonclinical study findings that showed a large safety margin of avacopan and metabolite CCX168-M1 in the human ether-a-go-go-related gene (hERG) assay, a cardiovascular safety study in cynomolgus monkeys, and the general toxicology studies.

Table 8: Cardiodynamic Outlier Summary for QTcI in Study CL007_168

Outlier Category	30 mg Avacopan (Period 1 or 2) (N=16)	3 mg Avacopan (Period 3) (N=15)	100 mg Avacopan Day 1 (Period 4) (N=15)	100 mg Avacopan Day 7 (Period 4) (N=15)
>450 to ≤480 msec	0	0	0	0
>480 to ≤500 msec	0	0	0	0
>500 msec	0	0	0	0
Change: >30 to ≤60 msec	1	1	0	0
Change: >60 msec	0	0	0	0

Source: CSR CL007_168 Table 14.2.3.3

No specific pharmacodynamic drug interaction studies were reported. The applicant considers that the risk of drug-drug interactions between avacopan and other concurrent medications in the intended patient population is considered low based on a series of biochemical studies conducted in vitro.

3.3.3. Discussion on clinical pharmacology; pharmacodynamics and pharmacokinetics

Pharmacodynamics

The results of the studies assessing the primary PD effect of avacopan support well the proposed hypothesis of mechanism of action. It was shown in the Study CL001_168, that the ability of the neutrophils to functionally respond C5a-induced activation is strongly impaired with simultaneous administration of avacopan. This response was measured by the inhibition of the production of CD11b by the neutrophils. The response correlated well 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 results of the PD part of the pivotal phase II study CL002_168 support the hypothesis that unlike the current standard treatment for AAV including glucocorticoids, the treatment with avacopan with no glucocorticoids does not affect the plasma levels of complement components. This finding has possibly favourable clinical relevance in terms of changes in immune response and host defense related to immunosuppression caused by AAV treatment. However, the significance of the findings from the complement analysis of CL002_168 is somewhat unclear. Given that Neisseria meningitides infection could have serious consequences for the affected individual and since the overall exposure generated in the completed phase II study and the on-going phase III study is still too limited to be able to reliably dismiss a potential over-risk for these infections, more reassurance is needed before the concern can be omitted from the RMP. See later sections of this AR.

According to the study reports for the two phase II studies, CL002_168 and CL003_168, separate PD study reports were to be provided for these studies. Such reports could not be found and were requested in the first LoQ. ***In response to the LoQ, the applicant has clarified that the PD study report for the Phase II study CL002_168 is the CL002_168 Complement Report which was provided in the original submission. The applicant also clarified that no PD assay were performed in study CL003_168. The applicant was also asked to substantially revise the proposed SmPC-text regarding PD data, this has now been done.*** See SmPC-comments in separate SmPC document.

Finally, it is noted that no thorough QT/QTc study appears to have been conducted but that the planned phase 3 study will include further ECG assessments and also that no dedicated phase II dose finding study has been carried out. Instead, the selection of dose, not only for the phase 2 but also for the phase III study, appeared to have been based on data from the phase I study CL001_168, in which the level of C5aR blockade correlated strongly with avacopan plasma concentrations.

The effect of avacopan and its main metabolite CCX168-M1 on QT was investigated by intensive ECG monitoring across different single and multiple doses of avacopan in Study CL007_168. Holter monitors were used to collect continuous 12-lead ECG data from predose until 24 hours postdose within each study period. Triplicate 10-second, 12-lead ECG recordings were extracted from the Holter monitor data. In contrast to the recommendation of IC guidance, the study was not randomized, non-blinded and control group was not used. Since the the upper bound of the two-sided 90% confidence interval around the estimated maximal effect on QTcI was less than 10 ms in all of the subjects receiving the avacopan 30 mg dose (proposed dose for clinical use) and only at one time point (12 hours) on Day 1 with avacopan 100 mg dose), the deficiencies in study design could be accepted. ***The QT analyses were performed by a blinded observer.*** Based on the results of the Study CL007_168, the study can be considered as "negative". It thus is agreed with the applicant that the QT data that has now been submitted do not cause any specific concerns but it is considered that the planned phase 3 study is needed to more reliably assess the risk. Overall, cardiovascular safety is a potential safety issue that needs to be further characterized and it is thus requested to be included in the summary of safety concerns, see later sections of this AR.

The applicant has discussed various genetic aspects possibly affecting either the AAV disease process itself, or the binding and activity of avacopan. It is agreed that the clinical relevance of most of these factors is unclear at this point, and the most relevant aspect of ANCA antigenic specificity has been adequately taken into account in clinical trial design.

Pharmacokinetics

In general, the PK of avacopan is sufficiently addressed. It is however expected that the PK in patients is further described once data from the ongoing phase III study becomes available.

Questions are still raised in the secondary round where some aspects of the bioanalytical validation is still not solved.

The applicant has not been able to define a therapeutic window where efficacy and safety is deemed acceptable. The applicant is specifically requested to present a discussion regarding the upper part of the therapeutic window. Possible side effects which may be seen at a higher frequency or in a more severe form if the avacopan exposure is increased by 100 % (given the proposal to allow concomitant administration with potent CYP3A4 substrates) should be discussed. The plausibly higher risk for adverse events for these patients should also be put in a context of the clinical benefit of avacopan. It should also be discussed whether the criteria stated under "management and dose adjustment" in section 4.2 are effective measures to minimize the plausibly higher risk for adverse events expected at an approximate doubling of the exposure.

Since avacopan is primarily cleared through hepatic metabolism, a hepatic impairment study has been performed. In order to further evaluate the effect of hepatic impairment the applicant should analyse study samples with respect to unbound avacopan and M1 concentrations, if possible. The applicant should also confirm that the included subjects had impairment in the measures indicative of affected elimination capacity and that the subjects are representative of the respective Child Pugh class. Furthermore, Child-Pugh C patients were not included and the applicant is requested to clarify whether such patients are intended to be studied. In the meantime, a restrictive wording regarding use in this population is recommended (**OC**).

3.3.4. Conclusions on clinical pharmacology; pharmacodynamics and pharmacokinetics

Pharmacodynamics

Overall the clinical pharmacology package concerning PD effects of avacopan is judged to be sufficient.

Pharmacokinetics

There are no objections to an approval from a pharmacokinetic point of view, provided that the applicant presents acceptable responses to the other concerns raised.

3.3.5. Clinical efficacy

The clinical efficacy of avacopan has been studied in two phase 2 studies (CL002_168, CL003_168) comprising a total of 109 patients with ANCA-associated vasculitis (AAV), out of which 73 were randomised to treatment with avacopan. A phase 3 study is ongoing, aiming to include 300 subjects.

A summary of the phase 2 studies is presented in Table 9.

Table 9: Description of Completed Avacopan Clinical Efficacy and Safety Studies in ANCA-Associated Vasculitis

Study ID	Number of Study Centres Location(s)	Study start Enrollment status, Date Total Enrollment / Enrollment goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. Subjects by Arm entered/ completed	Duration	Gender M / F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
CL002_168	60 sites in Austria, Belgium, Czech Republic, Hungary, France, Germany, Ireland, The Netherlands, Poland, Sweden, and the United Kingdom	Start: 27 Sep 2011 End: 18 Jan 2016	Randomised, double-blind, double dummy, placebo-controlled	Avacopan and matching placebo; Prednisone and matching placebo; 30 mg avacopan twice daily orally For control: 60 mg prednisone once daily, tapered to 0 by week 21	Primary safety: to evaluate the safety and tolerability of avacopan Primary efficacy: to evaluate the efficacy of avacopan based on BVAS.	Entered: Control: 23 Avacopan+low dose prednisone: 22 Avacopan+no prednisone: 22 Completed: Control: 18 Avacopan+low dose prednisone: 19 Avacopan+no prednisone: 18	12 weeks treatment 12 weeks follow-up	47 / 20 59.3 (20-82) years	GPA, MPA, or renal limited vasculitis	Efficacy: BVAS response at Week 12 Safety: Adverse event incidence

Study ID	Number of Study Centres Location(s)	Study start Enrollment status, Date Total Enrollment / Enrollment goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. Subjects by Arm entered/ completed	Duration	Gender M / F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
CL003_168	47 sites in USA and Canada	Start: 4 Feb 2015 End: 19 Jul 2016	Randomised, double-blind, double dummy, placebo-controlled	Avacopan and matching placebo; Prednisone and matching placebo; 10 mg or 30 mg avacopan twice daily orally For all groups: 60 mg prednisone once daily, tapered to 0 by week 21	Primary safety: to evaluate the safety and tolerability of avacopan Primary efficacy: to evaluate the efficacy of avacopan based on BVAS.	Entered: Control: 13 10 mg avacopan: 13 30 mg avacopan: 16 Completed: Control: 13 10 mg avacopan: 12 30 mg avacopan: 15	12 weeks treatment 12 weeks follow-up	19 / 23 58.5 (26-83) years	GPA, MPA, or renal limited vasculitis	Safety: Adverse event incidence Efficacy: BVAS response at Week 12 (descriptive)

Dose-response studies and main clinical studies

Dose-response study

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. The applicant states that in these assays, 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. According to the applicant, the level of blockade correlated strongly with avacopan plasma concentrations in each cohort in the single-dose period (10, 30, and 100 mg avacopan) and in the multi-dose period (30 mg avacopan twice daily). The 30 mg twice daily dose of avacopan resulted in extended (>12 hr) coverage of C5aR, indicating that this dose regimen provides around-the-clock coverage of the C5aR. The applicant states that therefore, 30 mg avacopan twice daily was selected as the dose regimen to test in the subsequent clinical trial CL002_168 in patients with AAV. This dose regimen, along with 10 mg avacopan twice daily, was also selected for study CL003_168 in patients with AAV.

Main clinical study, phase II study CL002_168

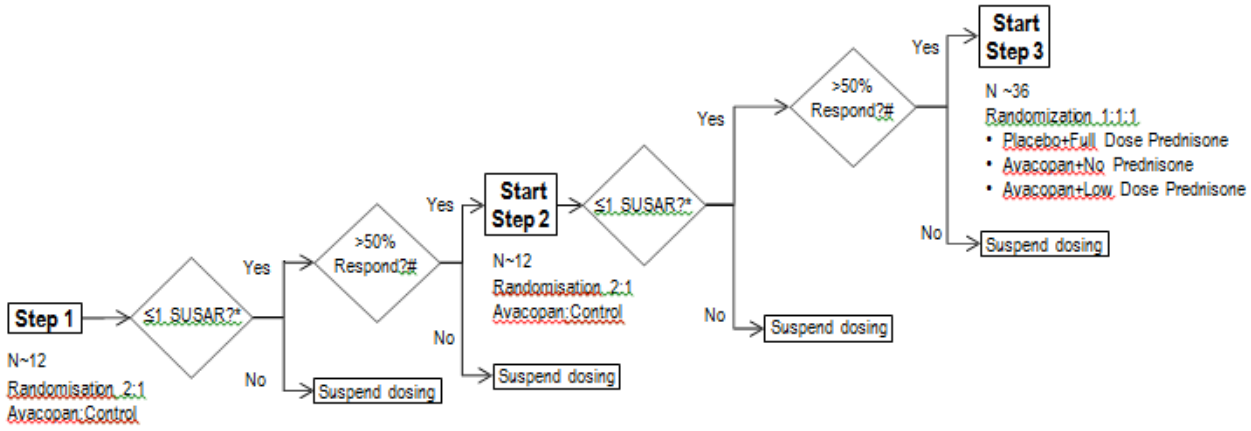
Methods

Study CL002_168 was a phase II, double-blind, randomised, active-controlled study conducted in a step-wise manner in which patients were randomised to either treatment with standard of care including full-dose/high dose prednisone (starting at 60 mg and tapered over 20 weeks to discontinuation), avacopan 30 mg twice daily and reduced dose prednisone (starting at 20 mg and discontinued after 14 weeks) or avacopan 30 mg twice daily without concomitant prednisone (dose recommended in the SmPC).

Subjects included were adult patients with a clinical diagnosis of GPA, MPA or renal limited vasculitis, consistent with Chapel-Hill consensus definitions. They could either have a new or relapsing disease, where treatment with cyclophosphamide or rituximab would be required. Subjects with severe organ involvement (such as renal or pulmonal) were excluded.

The study design is shown below.

Figure 3: Schema for Study CL002_168



Step 1 = Partial glucocorticoid elimination (67% reduced oral dose) (N~12 subjects)
Step 2 = Complete glucocorticoid elimination (100% reduced oral dose) (N~12 subjects)
Step 3 = Include both partial glucocorticoid elimination (67% reduced oral dose), and complete glucocorticoid elimination (100% reduced oral dose) (N ~ 36 subjects)
* Not more than one suspected unexpected serious adverse reaction (SUSAR) most likely related to avacopan, observed in subjects receiving avacopan.
# >50% of subjects maintained on avacopan without need for rescue IV glucocorticoids

Eligible subjects were enrolled and stratified into 2 strata: newly diagnosed (within 4 weeks of screening) or relapsed AAV with renal involvement for Steps 1 and 2, and the 3 stratification factors for Step 3 (i.e., newly diagnosed or relapsing AAV for Step 3, PR3 or MPO ANCA, and cyclophosphamide or rituximab use); and then randomized to one of the 2 treatment groups in a ratio of 2:1, Avacopan + reduced dose prednisone : comparator (full dose prednisone) for Steps 1 and 2, and one of 3 treatment groups in a ratio of 1:1:1, avacopan + no Prednisone : comparator (full dose prednisone) : avacopan + reduced dose prednisone for Step 3.

All subjects, irrespective of treatment group, received standard of care cyclophosphamide 15 mg/kg (up to 1.2 g) IV every 2 to 4 weeks or rituximab 375 mg/m^2 IV once weekly for 4 weeks.

The treatment period of the trial was 12 weeks, with a 12-week follow-up period. During the follow-up period, subjects receiving cyclophosphamide were switched to azathioprine at a target dose of 2 mg/kg/day, starting at Week 15. Subjects receiving rituximab background treatment did not receive any additional treatment during the follow-up period.

Main inclusion criteria:

1. Clinical diagnosis of granulomatosis with polyangiitis (Wegener's) (GPA), microscopic polyangiitis (MPA) or renal limited vasculitis, consistent with Chapel-Hill consensus definitions;
2. Male and postmenopausal or surgically sterile female subjects, aged at least 18 years, with new (within 4 weeks prior to Screening) or relapsed AAV where treatment with cyclophosphamide or rituximab would be required.;
3. Positive indirect immunofluorescence (IIF) test for perinuclear-ANCA (P-ANCA) or cytoplasmic ANCA (C-ANCA), or positive enzyme-linked immunosorbent assay (ELISA) test for anti-PR3 or anti-MPO at Screening. If only the IIF assay was positive at Screening, and none of the ELISA

tests, there must have been documentation in the study records of a positive ELISA assay in the past;

4. Had at least 1 "major" item, or at least 3 non-major items, or at least 2 renal items on the BVAS version 3;
5. Estimated glomerular filtration rate ≥20 mL per minute (MDRD)

Main exclusion criteria:

1. Severe disease as determined by rapidly progressive glomerulonephritis such that commencement of renal replacement therapy could have been anticipated within 7 days, alveolar hemorrhage leading to Grade 3 or higher hypoxia (i.e., decreased oxygen saturation at rest, e.g., pulse oximeter <88% or partial pressure of arterial oxygen ≤55 mmHg), hemoptysis, rapid-onset mononeuritis multiplex (Grade 3 or higher, leading to severe symptoms that limit self-care activities of daily living or requiring an assistive device), or central nervous system involvement;
2. Any other multi-system autoimmune disease including eosinophilic granulomatosis with polyangiitis (Churg Strauss), systemic lupus erythematosus, immunoglobulin (Ig)A vasculitis (Henoch Schönlein purpura), rheumatoid vasculitis, Sjögren's disease, anti-glomerular basement membrane disease, or cryoglobulinemia;
3. Received cyclophosphamide within 12 weeks prior to Screening; if on azathioprine, mycophenolate mofetil, or methotrexate at the time of Screening, these drugs must have been withdrawn prior to receiving the cyclophosphamide dose on Day 1;
4. Received IV corticosteroids, >3000 mg methylprednisolone equivalent, within 12 weeks prior to Screening;
5. Had been taking an oral daily dose of a corticosteroid of more than 10 mg prednisone equivalent for more than 6 weeks continuously prior to the Screening visit. If on an oral corticosteroid at a daily dose of more than 10 mg prednisone equivalent at the time of Screening, the oral dose needed to be reduced to a daily dose not exceeding 10 mg prednisone equivalent prior to Day 1;

Endpoints:

The primary efficacy endpoint of the study was the proportion of subjects achieving disease response at Day 85, defined as BVAS percent reduction from baseline of at least 50% plus no worsening in any body system component.

Other efficacy endpoints included:

1. In subjects with hematuria and albuminuria at baseline, the proportion of subjects achieving renal response at Day 85; renal response was defined as an improvement in parameters of renal vasculitis:

a. An increase from baseline to Day 85 in eGFR (MDRD serum creatinine equation),

b. A decrease from baseline to Day 85 in hematuria (central laboratory microscopic count of urinary RBCs), and

c. A decrease from baseline to Day 85 in albuminuria (first morning UACR);

2. Proportion of subjects achieving disease remission at Day 85, defined as BVAS of 0 or 1 plus no worsening in eGFR and urinary RBC count <10/high power field (hpf)

Calculation of sample size:

Step 1 and 2 sample sizes were justified separately and were based on feasibility. It was calculated that for step 3, a sample size of 36 subjects, 12 in each of the avacopan groups and 12 in the placebo, would provide a total of approximately 60 subjects across all three steps, and approximately 20 subjects in each of the treatment groups. Assuming a control group BVAS response of 44% at Day 85 and avacopan group response of 86%, sample size of 20 in each group would provide approximately 90% power for the primary efficacy analysis.

The sample size calculation does not provide information of used type I error rate, or take into account that the trial was planned to demonstrate non-inferiority, or take into account of having two active treatment groups in the trial. The source of expected BVAS response is not defined. The sample size calculation is not adequate.

Randomization:

In steps 1 and 2, eligible subjects were randomized using one stratification factor: newly diagnosed (within 4 weeks of screening) or relapsed AAV with renal involvement with ratio 2:1 to either avacopan or to placebo.

In step 3, 3 stratification factors were used: 1) new diagnosed or relapsing AAV (with or without renal involvement), 2) PR3 or MPO ANCA, and 3) cyclophosphamide or rituximab use). Subjects were randomized with ration 1:1:1 to either avacopan + No prednisone, avacopan + low dose prednisone or placebo + high dose prednisone.

Randomization was performed centrally via an IVRS using a minimization algorithm.

Blinding:

The study was double-blind, double-dummy. Blinding of the study was achieved by the following measures:

1. The study medication bottles and capsule appearance for avacopan and its matching placebo, as well as prednisone and its matching placebo, were identical;
2. Limited access to the randomization code: study site personnel, study subjects, personnel responsible for study monitoring, and biostatisticians and data managers involved in data analysis of the study remained blinded to treatment assignment for the duration of the study;
3. While laboratory personnel conducting the PK assays were not blinded to treatment assignment, unblinded and plasma concentration results were not shared with the study site personnel or the study staff with direct contact with study sites during the study; and
4. Efficacy data that would have been potentially unblinded, ie, anti-PR3 and anti-MPO antibodies, urinary MCP-1:creatinine ratio, UACR, WBC and neutrophil count data within the normal range, and hsCRP data, were not made available to study site personnel, study subjects, personnel responsible for study monitoring, and biostatisticians and data managers during the study unless for safety monitoring.

Analysis Populations:

The Intent-to-Treat (ITT) Population included all subjects who were randomized, had received at least

1 dose of study medication, and had at least 1 post-baseline on treatment BVAS assessment (used for main analysis).

The All Subjects Randomised / Safety Population included all subjects who were randomized and had received at least 1 dose of study medication.

Statistical methods

The primary analysis was performed across all 3 steps. The proportion of subjects achieving disease response during the 84-day treatment period was calculated to compare each avacopan group against the comparator group (full dose prednisone). If the lower bound of the 1-sided 95% confidence interval (CI) for the difference (avacopan minus comparator group) was greater than -0.20 (20%), the respective avacopan group was considered not inferior to the comparator group. If the lower bound was greater than 0.0, the respective avacopan group was considered superior to the comparator group in achieving the disease response. For the purpose of data presentation, the 2-sided 90% CIs were displayed since the lower bound of the 1-sided 95% CI was identical to the lower bound of the 2-sided 90% CI. The p-values from the hypothesis tests of non-inferiority (H1: p1-p2 >-0.2) and superiority (H1: p1-p2 >0) were also displayed. The primary analysis included all subjects in all 3 steps.

Similar analyses were performed to compare the All avacopan group to the comparator group. In addition, the analyses were repeated for all subjects in Step 3, for subjects in Steps 1 + 2 combined, and for Steps 1 and 2 separately. For these analyses, CIs and p-values were not displayed for Steps 1 and 2 due to the small sample sizes.

Results

Of the 87 subjects screened for the study, a total of 67 subjects were randomised and received at least one dose of study medication. This comprised the All Subjects Randomised population.

A total of 63 subjects were included in the ITT population, defined as all subjects who were randomized, received at least one dose of study drug, and who had at least one post baseline, on-treatment BVAS score. Four subjects, three in the comparator group (full dose prednisone) and one in the avacopan plus no prednisone group did not have any post baseline, on-treatment BVAS assessment, and were excluded from the ITT population according to the pre-specified statistical analysis plan.

Important baseline characteristics are presented in **Error! Reference source not found.**.

Table 10: Demographic and Subject Baseline Characteristics in study CL002_168, Overall All Randomized Subjects

Demographic Characteristic Statistic/Category	Placebo + Full Dose Prednisone (N = 23)	CCX168 + Low-Dose Prednisone (N = 22)	CCX168 + No Prednisone (N = 22)	All CCX168 (N = 44)	Total (N = 67)
Age at Screening (years)					
n	23	22	22	44	67
Mean (SD)	59.1 (13.98)	57.0 (14.22)	57.4 (14.00)	57.2 (13.95)	57.9 (13.88)
Gender, n (%)					
Male	17 (73.9)	14 (63.6)	16 (72.7)	30 (68.2)	47 (70.1)
Female	6 (26.1)	8 (36.4)	6 (27.3)	14 (31.8)	20 (29.9)
Race, n (%)					
White	23 (100.0)	22 (100.0)	22 (100.0)	44 (100.0)	67 (100.0)
ANCA disease status, n (%)					
Newly diagnosed	18 (78.3)	15 (68.2)	16 (72.7)	31 (70.5)	49 (73.1)
Relapsed	5 (21.7)	7 (31.8)	6 (27.3)	13 (29.5)	18 (26.9)

Demographic Characteristic Statistic/Category	Placebo + Full Dose Prednisone (N = 23)	CCX168 + Low-Dose Prednisone (N = 22)	CCX168 + No Prednisone (N = 22)	All CCX168 (N = 44)	Total (N = 67)
Background treatment, n (%)					
Rituximab	3 (13.0)	5 (22.7)	5 (22.7)	10 (22.7)	13 (19.4)
Cyclophosphamide	20 (87.0)	17 (77.3)	17 (77.3)	34 (77.3)	54 (80.6)
Type of AAV, n (%)					
GPA	10 (43.5)	11 (50.0)	12 (54.5)	23 (52.3)	33 (49.3)
Microscopic polyangiitis	10 (43.5)	9 (40.9)	9 (40.9)	18 (40.9)	28 (41.8)
Renal-limited vasculitis	2 (8.7)	2 (9.1)	1 (4.5)	3 (6.8)	5 (7.5)
Unknown	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
ANCA status categorical, n (%)					
Anti-MPO positive	10 (43.5)	12 (54.5)	13 (59.1)	25 (56.8)	35 (52.2)
Anti-PR3 positive	11 (47.8)	10 (45.5)	8 (36.4)	18 (40.9)	29 (43.3)
Both anti-MPO positive and anti-PR3 positive	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
ANCA equivocal	0 (0.0)	0 (0.0)	1 (4.5)	1 (2.3)	1 (1.5)
ANCA negative	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
BVAS total score					
n	23	22	22	44	67
Mean (SD)	13.2 (5.80)	14.3 (5.98)	13.8 (6.38)	14.0 (6.11)	13.7 (5.98)
VDI score					
n	23	22	22	44	67
Mean (SD)	1.2 (1.35)	0.9 (1.46)	0.5 (1.19)	0.7 (1.33)	0.9 (1.35)
Glomerular filtration rate (MDRD) (mL/min/1.73 m^2)					
n	22	22	22	44	66
Mean (SD)	47.6 (15.08)	52.5 (26.70)	54.7 (19.64)	53.6 (23.19)	51.6 (20.92)
Albumin:creatinine ratio (mg/g)					
n	22	22	21	43	65
Geometric mean (range)	353.9 (28-5962)	278.6 (24-2459)	283.4 (25-3051)	280.9 (24-3051)	303.8 (24-5962)

Source: CSR table 10.

Overall, during the 84-day treatment period, the median total cumulative dose of cyclophosphamide received by subjects in the avacopan plus low-dose prednisone group was 4719.0 mg, in the avacopan plus no prednisone group 4336.4 mg, in the pooled avacopan group 4548.5 mg, and in the placebo plus full dose prednisone group 3747.5 mg.

The primary endpoint, the proportion of subjects with BVAS response at day 85, was achieved in 14/20 subjects (70%) in the comparator group that received high dose prednisone, 19/22 subjects (86.4%) in the avacopan + reduced dose prednisone group and 17/21 subjects (81%) in the avacopan + no prednisone group.

After 12 weeks of follow-up (day 169), BVAS response rates for avacopan, with or without prednisone, was lower than for the comparator group with full dose prednisone.

The results of the primary efficacy endpoint response analysis stratified by the study steps are shown in Table 11. In the pooled analysis of steps 1 and 2 of the study, 87.5% (7/8) of the subjects in avacopan plus no prednisolone group were responders compared to 44.4% (4/9) in the standard treatment group. This observed difference between the groups was statistically significant (p=0.0169). In contrast, in the analysis of step 3, 90.9% (10/11) of the subjects in the standard treatment group reached the endpoint. The corresponding proportion of subjects in the avacopan plus no prednisolone group was 76.9% (10/13). It is acknowledged that the study was not designed to show statistically

significant outcomes for each study step but according to the analysis, the p-value for non-inferiority was not significant (p=0.3397).

Table 11: The primary efficacy endpoint analysis stratified by steps of the Study CL002_168

Day Step	Treatment	N'	n	(%)	Difference in percentages versus Placebo	Two-sided 90% CI for Difference	Non-infer. P-value	Superior. P-value
Day 85								
All	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	0.0969
	CCX168 + No Prednisone (N=21)	21	17	(81.0)	11.0	(-11.0, 32.9)	0.0102	0.2061
	All CCX168 (N=43)	43	36	(83.7)	13.7	(-5.5, 33.0)	0.0020	0.1203
3	Placebo + Full Dose Prednisone (N=11)	11	10	(90.9)				
	CCX168 + Low Dose Prednisone (N=14)	14	13	(92.9)	1.9	(-16.3, 20.2)	0.0237	0.4301
	CCX168 + No Prednisone (N=13)	13	10	(76.9)	-14.0	(-37.9, 9.9)	0.3397	0.8318
	All CCX168 (N=27)	27	23	(85.2)	-5.7	(-23.9, 12.4)	0.0980	0.6979
1+2	Placebo + Full Dose Prednisone (N=9)	9	4	(44.4)				
	CCX168 + Low Dose Prednisone (N=8)	8	6	(75.0)	30.6	(-6.5, 67.7)	0.0125	0.0878
	CCX168 + No Prednisone (N=8)	8	7	(87.5)	43.1	(9.7, 76.4)	0.0009	0.0169
	All CCX168 (N=16)	16	13	(81.3)	36.8	(5.2, 68.4)	0.0016	0.0278
2	Placebo + Full Dose Prednisone (N=5)	5	0	(0.0)				
1	Placebo + Full Dose Prednisone (N=4)	4	4	(100.0)				
	CCX168 + Low Dose Prednisone (N=8)	8	6	(75.0)				

The clinically important secondary endpoint of BVAS remission was achieved in 7/20 subjects (35%) in the comparator group (full dose prednisone), 6/22 (27.3%) of the subjects in in the avacopan + reduced dose prednisone group and in 4/21 subjects (19%) in the avacopan + no prednisone group at 12 weeks. After 12 weeks of follow-up (day 169), remission was achieved by 10/20 (50%) in the comparator group, 10/22 (45.5%) in the avacopan + reduced dose prednisone group and 5/21 (23.8%) in the avacopan + no prednisone group. In this study, steroid use was allowed from weeks 12 to 24 in the control group, hence BVAS remission without corticosteroids could not be determined.

In similar analysis of the different steps of the study, the most relevant analysis concerns the step 3 (**Error! Reference source not found.**). According to this analysis, only 15.4% (2/13) of the subjects in the avacopan plus no prednisone group reached clinical remission at Day 85.

Table 12: Clinical remission rate (BVAS 0 or 1 and no decrease in eGFR and urinary RBC count < 10 per hpf) by randomised group and study step at Day 85

Day Step	Treatment	N'	n	(%)	Difference in percentages versus Placebo	Two-sided 90% CI for Difference	Non-infer. P-value	Superior. P-value
Day 85								
All	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	0.7058
	CCX168 + No Prednisone (N=21)	21	4	(19.0)	-16.0	(-38.5, 6.6)	0.3837	0.8782
	All CCX168 (N=43)	43	10	(23.3)	-11.7	(-32.2, 8.8)	0.2538	0.8270
3	Placebo + Full Dose Prednisone (N=11)	11	5	(45.5)				
	CCX168 + Low Dose Prednisone (N=14)	14	4	(28.6)	-16.9	(-48.6, 14.8)	0.4357	0.8096
	CCX168 + No Prednisone (N=13)	13	2	(15.4)	-30.1	(-59.7, -0.4)	0.7116	0.9522
	All CCX168 (N=27)	27	6	(22.2)	-23.2	(-51.2, 4.7)	0.5753	0.9140
1+2	Placebo + Full Dose Prednisone (N=9)	9	2	(22.2)				
	CCX168 + Low Dose Prednisone (N=8)	8	2	(25.0)	2.8	(-31.2, 36.7)	0.1350	0.4465
	CCX168 + No Prednisone (N=8)	8	2	(25.0)	2.8	(-31.2, 36.7)	0.1350	0.4465
	All CCX168 (N=16)	16	4	(25.0)	2.8	(-26.1, 31.7)	0.0976	0.4372
2	Placebo + Full Dose Prednisone (N=5)	5	0	(0.0)				
1	Placebo + Full Dose Prednisone (N=4)	4	2	(50.0)				
	CCX168 + Low Dose Prednisone (N=8)	8	2	(25.0)				

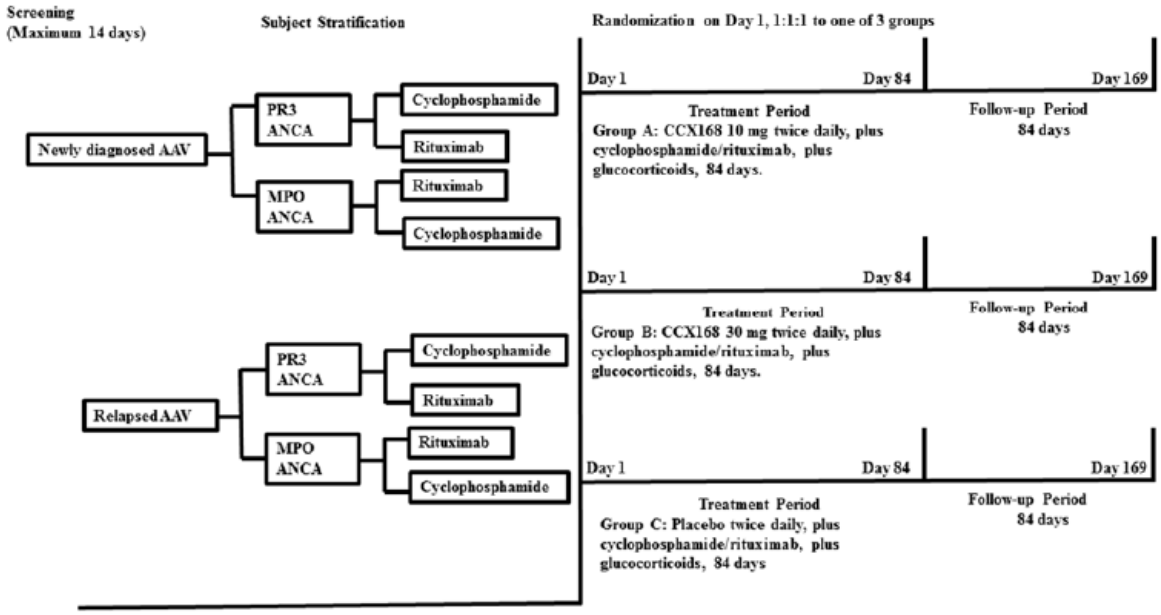
Phase II study CL003_168

CL003_168 was a phase 2, double-blind, randomised, placebo-controlled study comparing the efficacy of two dose levels of avacopan versus placebo, all on top on full dose prednisone. No subjects in this study received avacopan as indicated in the SmPC.

All subjects in the study were adult patients with a clinical diagnosis of GPA, MPA or renal limited vasculitis, consistent with Chapel-Hill consensus definitions. They could either have a new or relapsing disease, where treatment with cyclophosphamide or rituximab would be required. Subjects with severe organ involvement (such as renal or pulmonal) were excluded from the study.

Patients were randomised in a 1:1:1 ratio to treatment with placebo, avacopan 10 mg twice daily or avacopan 30 mg twice daily. All subjects received background therapy of standard of care full dose/high dose prednisone (starting at 60 mg and tapered over 20 weeks to discontinuation), and either cyclophosphamide 15 mg/kg (up to 1.2 g) IV every 2 to 4 weeks or rituximab, 375 mg/m2 IV weekly for 4 weeks. The treatment period of the trial was 12 weeks, with a 12-week follow-up period during which subjects initially receiving cyclophosphamide were switched to azathioprine.

Figure 4: Overall study design CL003_168



AAV = anti-neutrophil cytoplasmic antibody-associated vasculitis; ANCA = anti-neutrophil cytoplasmic antibody; MPO = myeloperoxidase; PR3 = proteinase 3.
Source: Study protocol (Appendix 16.1.1)

According to the applicant, the study was primarily a safety study, and was not powered to evaluate efficacy.

Primary endpoint was BVAS response (defined as BVAS percent reduction from baseline of at least 50 %, plus no worsening in any body system component).

Result

A total of 42 subjects were enrolled into the study (13 subjects to the placebo group, 13 subjects to the avacopan 10 mg bid group and 16 subjects to avacopan 30 mg bid group). Of these, 40 subjects remained in the pre-defined modified ITT population (all subjects who were randomized, received at

least 1 dose of study medication, and had at least 1 post-baseline, on-treatment BVAS assessment) that was used for analysis of the primary efficacy endpoint.

The primary efficacy endpoint, the proportion of subjects with BVAS response at day 85, was achieved by 11/13 subjects (84.6%) in the placebo group, 11/12 subjects (91.7%) in the avacopan 10 mg bid group and in 12/15 subjects (80.0%) in the avacopan 30 mg bid group.

The secondary endpoint of renal response at day 85 was achieved by 1/6 subjects (16.7%) in the placebo group, 2/5 subjects (40%) in the avacopan 10 mg group and by 5/8 subjects (62.5%) in the avacopan 30 mg group.

The secondary endpoint of BVAS remission at day 85 was achieved by 7/13 subjects (53.8%) in the placebo group, 8/12 subjects (66.7%) in the avacopan 10 mg group and 7/15 subjects (46.7%) in the avacopan 30 mg group. It should be noted that the placebo group allowed for use of glucocorticoids, which is not the standard definition of remission.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13: Summary of efficacy for trial CL002_168

Title: 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		
Study identifier	Protocol CL002_168; EudraCT 2011-001222-15	
Design	Randomised, Double-Blind, Active-Controlled	
	Duration of main phase: Duration of Extension phase:	12 weeks (Double-blind treatment period) 12 weeks (Follow-up period)
Hypothesis	Non-inferiority	
Treatment groups	Avacopan + No Prednisone:	Number randomised: 22 Number in modified Intent-to-Treat (mITT) population (all patients with at least 1 BVAS assessment while on treatment): 21
	Avacopan + Reduced Dose Prednisone:	Number randomised: 22 Number in mITT population: 22
	Comparator (High Dose Prednisone):	Number randomised: 23 Number in mITT population: 20
	NOTE: All subjects received standard of care with background cyclophosphamide or rituximab.	
Primary Efficacy Endpoint Key Secondary Efficacy Endpoints	Proportion of subjects achieving disease response at Day 85, defined as Birmingham Vasculitis Activity Score (BVAS) percent reduction from baseline of at least 50% plus no worsening in any body system component. 1.In subjects with hematuria and albuminuria at baseline, the proportion of subjects achieving renal response at Day 85, defined as an increase from baseline in eGFR, and a decrease in hematuria, and a decrease from baseline to Day 85 in albuminuria 2.Proportion of subjects achieving disease remission at Day 85, defined as BVAS of 0 or 1 plus no worsening in eGFR and urinary RBC count <10/high power	
Database lock	26 February 2016	

Results and Analysis

Analysis description	**Primary Analysis: Birmingham Vasculitis Activity Score (BVAS) Response**			
Analysis population and time point description	mITT Population 84 days treatment Analysis at Day 85 time point			
Descriptive statistics and estimate variability	Treatment group	Avacopan+ No Prednisone	Avacopan+ Reduced Dose Prednisone	Comparator (High Dose Prednisone)
	Number of subjects	21	22	20
	BVAS response, n (%)	17/21 (81.0%)	19/22 (86.4%)	14/20 (70.0%)
Effect estimate per comparison	BVAS Response	Comparison Groups		Avacopan+No Prednisone vs Comparator (High Dose Prednisone)
		Difference in % Response from comparator		11.0%
		90% CI for Difference		(-11.0%, 32.9%)
		P-value for Non-inferiority		0.0102
		Comparison Groups		Avacopan+Reduced Dose Prednisone vs Comparator (High Dose Prednisone)
		Difference in % Response from comparator		16.4%
		90% CI for Difference		(-4.30%, 37.1%)
		P-value for Non-inferiority		0.0019
Analysis description	**Key Secondary Analyses**			
Analysis population and time point description	mITT population (renal response: subset of mITT Population with hematuria and albuminuria at baseline) Day 85			
Descriptive statistics and estimate variability	Treatment group	Avacopan+No Prednisone	Avacopan+ Reduced Dose Prednisone	Comparator (High Dose Prednisone)
	Number of subjects	21 (18 for renal response analysis)	22 (18 for renal response analysis)	20
	Renal response, n (%)	6/18 (33.3%)	10/18 (55.6%)	8/20 (40.0%)
	BVAS disease remission, n (%)	4/21 (19.0%)	6/22 (27.3%)	7/20 (35.0%)
Effect estimate per comparison	Renal Response	Comparison groups		Avacopan+No Prednisone vs Comparator (High Dose Prednisone)
		Difference in % Response from Comparator		-6.7%
		90% CI for Difference		(-32.3%, 19.0%)
		P-value for Non-inferiority		0.1964
		Comparison groups		Avacopan+Reduced Dose Prednisone vs Comparator (High Dose Prednisone)

		Difference in % Response from Comparator	15.6%
		90% CI for Difference	(-10.8%, 41.9%)
		P-value for Non-inferiority	0.0133
Effect estimate per comparison	BVAS disease remission	Comparison groups	Avacopan+No Prednisone vs Comparator (High Dose Prednisone)
		Difference in %	-16.0
		95% CI for Difference	(-38.5, 6.6)
		P-value for Non-inferiority	0.3837
		Comparison groups	Avacopan+Reduced Dose Prednisone vs Comparator (High Dose Prednisone)
		Difference in %	-7.7
		95% CI for Difference	(-31.2, 15.8)
		P-value for Non-inferiority	0.1950

Table 14: Summary of efficacy for trial CL003_168

Title: 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		
Study identifier	Protocol CL003_168; NCT02222155	
Design	Randomised, double-blind, placebo-controlled	
	Duration of Main phase:	12 weeks (Double-blind treatment period)
	Duration of Extension phase:	12 weeks (follow-up period)
Hypothesis	Descriptive statistics only; no inferential statistics	
Treatment groups	Avacopan 10 mg twice daily	Number randomised: 13 Number in modified Intent-to-Treat (mITT) population (all patients with at last one post-baseline BVAS recorded on treatment): 12
	Avacopan 30 mg twice daily	Number randomised: 16 Number in mITT population: 15
	Placebo	Number randomised: 13 Number in mITT population: 13
	Note: All treatment groups received Standard of Care (SOC) glucocorticoids and either cyclophosphamide or rituximab	
Primary Efficacy Endpoint	Proportion of subjects achieving disease response at Day 85, defined as Birmingham Vasculitis Activity Score (BVAS) percent reduction from baseline of at least 50% plus no worsening in any body system component.	
Key Secondary Efficacy Endpoints	1. In subjects with hematuria and albuminuria at baseline, the proportion of subjects achieving renal response at Day 85. 2. Proportion of subjects achieving disease remission at Day 85	
Database lock	29 August 2016	
Results and Analysis		

Analysis description	**Primary Analysis:** **Birmingham Vasculitis Activity Score (BVAS) Response at Day 85**			
Analysis population and time point description	mITT population Day 85			
Descriptive statistics and estimate variability	Treatment Group	Avacopan 10 mg	Avacopan 30 mg	Placebo
	Number of Subjects	12	15	13
	BVAS response, n (%)	11/12 (91.7%)	12/15 (80.0%)	11/13 (84.6%)
Analysis description	**Secondary Analyses**			
Analysis population and time point description	mITT population (Renal response: Subset of mITT population with hematuria and albuminuria at baseline) Day 85			
Descriptive statistics and estimate variability	Treatment Group	Avacopan 10 mg	Avacopan 30 mg	Placebo
	Number of Subjects	12 (5 for renal response analysis)	15 (8 for renal response analysis)	13 (6 for renal response analysis)
	Renal response, n (%)	2/5 (40.0%)	5/8 (62.5%)	1/6 (16.7%)
	BVAS remission, n (%)	8/12 (66.7%)	7/15 (46.7%)	7/13 (53.8%)

Table 15: 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 (Studies CL002_168 and CL003_168)	25	11	0

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

Since studies CL002_168 and CL003_168 followed a different strategy, i.e., glucocorticoid elimination in study CL002_168 versus add-on to full dose glucocorticoid SOC treatment in study CL003_168, the results from these studies cannot be readily combined or compared.

Supportive study(ies)

Not applicable.

3.3.6. Discussion on clinical efficacy

Design and conduct of clinical studies

In order to support the conditional approval for the proposed indication - "Avacopan, in combination with cyclophosphamide or rituximab, is indicated for the induction of response in adult patients with

granulomatosis with polyangiitis (Wegener's) (GPA) or microscopic polyangiitis (MPA)" – the applicant presented data from two phase II studies. Of these studies, the Study CL002_168 can be considered as pivotal since the treatment scheme analysed (avacopan with no glucocorticoid use) is the one recommended in the SmPC and that will be tested in the ongoing Phase III Study CL010_168.

The Applicant has not conducted any formal dose-finding studies. Despite the low prevalence of AAV in Europe, this is in principle not acceptable. The avacopan dosing of 30 mg twice a day used in the phase II studies is based on the PD results of the Study CL001_168 in healthy subjects. The results after dosing of avacopan 30 mg b.i.d. for seven days are projected to the PK findings of the Study CL002_168 in subjects with AAV. 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. ***The Applicant was in the first RSI requested to discuss and justify that the proposed dose is optimal as no formal dose-finding studies in AAV patients were carried out. The applicant responded that they based the choice of dose both on non-clinical (knock-out mice) and clinical data. Results in knock-out mouse model cannot be directly translated to improvement of clinical condition in patients. Therefore, only the clinical data supports the chosen dose. The dose has been chosen based on PK/PD data on healthy volunteers (study CL001-168). These data support the chosen dose, and the issue is considered solved.***

The first phase 2 study (CL002_168), including 67 patients, aimed to evaluate the efficacy and safety of avacopan plus cyclophosphamide or rituximab in patients with AAV, in the context of reducing or eliminating oral glucocorticoid treatment. The second study (CL003_168), including 42 patients, aimed to evaluate the safety of adding avacopan on top of full dose standard of care treatment consisting of high dose glucocorticoids and cyclophosphamide or rituximab. Both studies were limited to a 12-week treatment period and a 12-week follow-up period. Inclusion and exclusion criteria are acceptable.

The primary efficacy endpoint in both studies was the proportion of subjects achieving disease response at Day 85, defined as BVAS percent reduction from baseline of at least 50 %, plus no worsening in any body system component. Among secondary endpoint were BVAS remission at day 85, percent change from baseline to day 85 in BVAS and proportion of subjects achieving renal response. The choice of the primary endpoint is problematic. In the EULAR recommendation, induction and maintenance of *remission* are preferred primary endpoints. *Response* can be useful secondary endpoint, particularly in studies of refractory disease. Remission was also the primary endpoint in two recent AAV trials, RAVE and RITUXVAS, and is the primary endpoint endorsed by the CHMP in the Protocol Assistance for the on-going avacopan phase 3 study. The clinical relevance of BVAS response is unclear, as the basic principle of acute vasculitis treatment is to induce remission with intensive immunosuppressive therapy, followed by a remission-maintaining phase with milder immunosuppression. If only partial response is achieved during the remission-inducing phase, there is a high risk for relapse during the remission-maintaining phase. The results of the primary endpoint therefore needs to be supported by the secondary endpoint of BVAS remission, and the results from a longer follow-up period which will be available after the ongoing phase 3 study.

In response to the first LoQ, the applicant provided a discussion regarding the relevance of BVAS response as an endpoint for a 12-week study, and its association to future remission. The applicant refers to an analysis on a similar patient population of 303 patients from 4 studies conducted by the European Vasculitis Group (EUVAS). In these patients, who were treated with a variety of therapies, including cyclophosphamide, azathioprine, methylprednisolone, plasma exchange, or methotrexate, 58.9% of the subjects with BVAS response at 3 months went into BVAS remission at 6 months. It is understood that these individuals were on continuous treatment, in contrast to what is proposed in the SmPC for avacopan where subjects should be treated for 12 weeks, and where the response rate

seems to diminish over time (for avacopan + no prednisone, BVAS response at week 12: 81%, BVAS response at week 24: 71.4%).Thus, although these data is of interest, its relevance for this application is somewhat limited.

Study CL002_168

Study CL002_168 was a double-blind, randomised, active-controlled study conducted in a step-wise manner in which patients were randomised to either treatment with standard of care including full-dose/high dose prednisone (starting at 60 mg and tapered over 20 weeks to discontinuation), avacopan 30 mg twice daily and reduced dose prednisone (starting at 20 mg and discontinued after 14 weeks) or avacopan 30 mg twice daily without concomitant prednisone.

All subjects, irrespective of treatment group, received standard of care cyclophosphamide 15 mg/kg (up to 1.2 g) IV every 2 to 4 weeks or rituximab 375 mg/m^2 IV once weekly for 4 weeks.

The treatment period of the trial was 12 weeks, with a 12-week follow-up period. During the follow-up period, subjects receiving cyclophosphamide were switched to azathioprine at a target dose of 2 mg/kg/day, starting at Week 15. Subjects receiving rituximab background treatment did not receive any additional treatment during the follow-up period.

There are several concerns regarding the methods of CL002_168.

Initial primary efficacy hypothesis was related to corticosteroid sparing, and the primary efficacy endpoint was the proportion of subjects without the need for rescue IV or oral corticosteroids. This is not reported.

There were many amendments to the protocol. Changes in the protocol with potential impact on the study results include changes to inclusion/exclusion criteria, order of the secondary endpoints, statistical methods and background therapy.

After amendment 3.0 of the protocol, the primary efficacy endpoint was defined as proportion of subjects achieving disease response at Day 85 defined as BVAS percent reduction from baseline of at least 50% plus no worsening in any body system component. *This change in the protocol was made with knowledge of the outcome from step 1 and 2, why these combined data from all three steps cannot be considered confirmative. The statement that the aim was to review safety signals is not convincing. Only step 3 data should be used in the main analysis. Further, a GCP-inspection could be triggered based on this to clarify that protection of blind has indeed been adequate enough; however, this is not pursued now in light of the several remaining MOs.*

New stratification factors were included for randomisation at Step 3 of the trial. Details of the randomization algorithm have not been provided. *The applicant was in the first LoQ requested to provide the details of the randomization algorithm. The applicant clarified that for all steps, the randomization process was broken, in case the site run out of treatment, and the subject was "randomized" to other treatment. This is not appropriate, as it breaks the randomization. The lack of study drug from some centres could skew the composition of study groups in terms of geographic location, standard of care and other variables. The issue will not be further pursued.*

According to the randomization list, the new stratification factors were only implemented after six patients were randomized to Step 3, and the random allocation for the first 6 patients in Step 3 was only to either Placebo arm or "avacopan + no prednisone" arm. Some of the randomization numbers are lacking from the randomization list (3112, 3114, 3308, 3401, 3402, and 3701). ***The applicant was in the first LoQ requested to explain the reason for the skipped randomization numbers. The applicant explained that this was due to the limitation of maximum number of each treatment arm in total, and the issue is considered solved.***

According to the list of exclusion criteria, up to 3000 mg of methylprednisolone could be permitted within 12 weeks before randomisation. ***The applicant was in the first LoQ asked to present the number of subjects in each group that received IV corticosteroids prior to screening, and this issue could be solved.***

The inclusion and exclusion criteria and the chosen patient population are acceptable and also in line with the previous authorisation studies for treatment of AAV. According to the CRFs, a renal biopsy was taken in 48 out of 67 study subjects to confirm the diagnosis of pauci-immune renal vasculitis. The listed protocol deviations include quite many deviations in the inclusion criteria of the study. Of these deviations, the most common one was that the subject did not fulfil the IIF and ELISA criteria for diagnosis of AAV. In addition, the results of the IIF analysis were missing in many of the subjects (especially in study centre 701). Also in Subject 307-301 with relapsing AAV both IIF and ELISA tests were negative at screening (one necrosis was observed in light microscopy of renal biopsy). ***The Applicant was in the first LoQ requested to provide the number of inclusion of non-eligible subjects to the trial by treatment group, and to discuss the impact of these and other listed deviations to the interpretability of the trial results. The applicant responded that six patients were identified to have significant protocol deviations, and were thus excluded from the per protocol analysis. These patients represent a relatively high proportion of the patients in this small clinical trial (6/67, 9%). The applicant has performed per protocol analyses in response to questions 133 and 134, and the issue is thus resolved.***

The prednisone doses used especially during the first month of treatment were lower than recommended in the guidelines and that were used e.g. in the RAVE study (comparison between oral cyclophosphamide and rituximab) where study subjects received first 1-3 iv pulses of methylprednisolone followed by oral prednisone 1 mg/kg (maximum 80 mg/kg) through the first month of treatment. This could have weakened the efficacy results detected in the standard treatment group without avacopan and with full-dose prednisone. ***The applicant was in the first LoQ requested to discuss this issue, which could then be solved.***

The clinical relevance of one of the secondary endpoints "renal response" is somewhat unclear due to indefinite cut-off values for clinical response in eGFR and urinary findings. ***This was discussed in response to the first LoQ. Although the clinical relevance of detecting small differences in parameters such as urinary blood cell count is not clear, the chosen composite endpoint has benefits such as being a quantitative method, and consisting of individual components which are validated, although the composite endpoint seems not to have been validated. While clinical improvement should be evaluated with caution when the numerical changes in these parameters are small (or the relative changes are largely due to different baseline values), the end point is considered suitable for providing supportive evidence on renal health in the studied population.***

The Applicant engaged international experts in BVAS and VDI to adjudicate, in a blinded manner, all investigator entries on the BVAS and VDI forms prior to data base lock. The purpose of adjudication was to ensure uniform assessment of activity and damage across the study due to partially subjective nature of the assessment. To interpret the effect of this procedure, it would be essential to know how common differences in the scores were, and if they were evenly distributed across the study groups. In addition, the Applicant does not state if the expert committee was independent. The effect of adjudication of BVAS scores cannot be evaluated based on the provided information. In addition, independence of the adjudicating committee is unclear. However, due to the remaining MOs, this issue is not crucial.

There are a number of issues that weaken the statistical confidence in the CL002_168 results. These include risk of bias and insufficient control of the type I error.

- The two Avacopan treatment arms were compared with the comparator (full dose prednisone) arm separately. There is no testing strategy presented to handle the multiplicity resulting from testing two hypotheses.
- The tree subparts (Steps) in the study CL002_168 differ with regards to inclusion criteria (diagnosis), stratification variables and what treatment they were given in addition to randomized treatment. The trial comprised 3 different steps with different randomisation protocols. For the efficacy and safety analyses all 3 steps were pooled and the 3 following treatment groups were compared: 1) High dose prednisone SOC control group; 2) Avacopan plus low dose prednisone group and 3) Avacopan plus no prednisone group. The primary efficacy analysis was performed without taking step into account. There was also no correction for stratification, additional treatment or diagnosis. The resulting effect estimate may therefore be subject to bias.

  Testing of the primary efficacy variable is performed at the 10% level (5% one sided test). This introduces a larger type I error than typically used.
- The primary efficacy analysis was a non-inferiority test performed on the mITT population. In non-inferiority trials the use of the mITT population is however generally not conservative (CPMP/ICH/363/96) and Per Protocol analysis to complement these would be informative.
- Patients were excluded from mITT if they had received nor at least one dose of study drug, or had no post baseline assessment of BVAS. This violates the ITT principle. Out of 67 randomised patients 4 were excluded from mITT. In total 12 out of 67 patients (17.9%) did not complete the study. Sensitivity analyses for missing data were not found in the study report.
- There was no information found on if any approximation was used when calculating confidence intervals for the primary efficacy variable. From the numbers presented it appears as if a chi-square approximation without continuity correction has been used. In the small sample situation at hand the methodology for computing confidence intervals has a large effect on the size of the intervals.
- Unblinded data from step 1 and 2 appear to have resulted in unplanned changes of the study conduct. Revisions include background treatment, inclusion criteria, priority of efficacy endpoints and choice of statistical methods. Such changes make interpretation of the result difficult, and may have resulted in bias and/or inflated type I error.

These issues were discussed by the applicant in response to the first LoQ. The applicant argues that the analyses performed as response to these issues confirm the previously presented efficacy results. However, in the sensitivity analyses non-inferiority was not consistently shown between avacopan+ no prednisone and the comparator with full dose prednisone. Most importantly, for the most appropriate primary analysis including only Step 3 patients, non-inferiority was not shown in any of the avacopan+ no prednisone and the comparator with full dose prednisone.

The applicant argues that the design used in CL002_168 was appropriate for a phase II study, and that the design was chosen since it was not known if avacopan could safely and effectively replace the oral prednisone. It is agreed that the proposed design could be appropriate for a phase II exploratory study. Yet, this is the main study upon which the applicant seeks to make claims of efficacy: therefore the results need to be both statistically and methodologically compelling and the results highly convincing. Hence the exploratory results of CL002_168 need to be confirmed.

Study CL003_168

According to the applicant, the study was primarily a safety study, and was not powered to evaluate efficacy. Since the study does not include the proposed dosing regimen, the result is of limited interest for this assessment.

GCP

There were many uncertainties related to the conduct of the main clinical study CL002_168 (see 2.4/ GCP-aspects section of this AR). However, due to the several Major Objections raised, a GCP-inspection is not requested at this stage of assessment.

Efficacy data and additional analyses

Study CL002_168

A total of 67 subjects were enrolled into the study (23 subjects to the comparator [high dose prednisone] group, 22 subjects to the avacopan + reduced dose prednisone group and 22 subjects to the avacopan + no prednisone group). Baseline characteristics and prior and concomitant corticosteroid treatment were overall balanced between the groups; there were no differences between the groups of such magnitude that they were considered to potentially influence the overall results of the study.

A total of 63 subjects were included in the Per Protocol ITT population, defined as all subjects who were randomized, received at least one dose of study drug, and who had at least one post baseline, on-treatment BVAS score, that was used for the primary analysis of the primary efficacy endpoint. Although this is referred to as the per protocol ITT population, it is rather a modified ITT population. For the primary endpoint, results are also presented for the all-randomised population. No per-protocol analysis has been presented, which should be done for a reliable assessment of non-inferiority.

Concomitant therapy other than corticosteroids was given to almost all patients. There were a larger proportion of subjects in the avacopan + no prednisone group with concomitant mycophenolate mofetil (MMF), 13.6% vs 4.3% in the comparator group and 4.5% in the avacopan + reduced dose prednisone group. According to the protocol, concomitant MMF was prohibited. ***The applicant confirmed in response to the first LoQ that this was withdrawn prior to start of treatment, and this issue was solved.***

All subjects should receive either cyclophosphamide or rituximab. The applicant states (CSR post-text table 14.1.6.1) that 7.5% (n=5) received concomitant cyclophosphamide, and 7.5% (n=5) received concomitant rituximab. ***The applicant has in response to the first LoQ clarified this, and this issue is solved.***

The primary endpoint, the proportion of subjects with BVAS response at day 85, was met as avacopan (both with and without concomitant prednisone) was non-inferior to placebo based on the pre-specified confidence interval of 20%. There are however a number of issues that weaken the statistical confidence in the results. These include risk of bias and lack of control of the type I error. ***Study CL002_168 is considered exploratory.*** *Also, in sensitivity analyses of CL002_168 data, non-inferiority was not consistently shown between avacopan+ no prednisone and the comparator with full dose prednisone. Due to methodological issues, analyses of only Step 3 data are more appropriate than analyses of the full study. Non-inferiority was not shown in any of the analyses between avacopan+ no prednisone and the comparator with full dose prednisone in data from step 3.*

The number of patients eligible for subgroup analyses is small and conclusions are hard to draw, but there are uncertainties regarding the response rate in subjects receiving avacopan + no prednisone on background rituximab, where only 3/5 subjects (60%) achieved BVAS response. More evidence of the efficacy of avacopan without corticosteroids in this important population needs to be provided by the phase 3 study.

After 12 weeks of follow-up (day 169), BVAS response rates for avacopan, with or without prednisone, was lower than for the comparator group with full dose prednisone. As this can put in questions the long-term efficacy of avacopan additional data is needed in order to draw reliable conclusion on the overall efficacy.

As discussed above, the primary endpoint in study CL002_168 is problematic as there is a general consensus that the aim of vasculitis induction therapy is not *induction of response* but rather *induction of remission*. Therefore, the secondary endpoint of BVAS remission is of high importance. BVAS remission was achieved in 7/20 subjects (35%) in the comparator group (full dose prednisone), 6/22 (27.3%) of the subjects in in the avacopan + reduced dose prednisone group and in 4/21 subjects (19%) in the avacopan + no prednisone group at 12 weeks. Avacopan, with or without a reduced dose of prednisone, thus appeared inferior to the comparator. The remission rate at 12 weeks was generally low, which is likely caused by the early time point for the evaluation. Although the remission rate was higher after 12 weeks of follow-up (day 169), both avacopan groups still appeared inferior to the comparator, with a large difference between the avacopan + no prednisone group and the comparator. It is acknowledged that secondary endpoint data were exploratory and not powered to show statistical differences however for the secondary endpoint of renal response among subjects with hematuria and albuminuria at baseline, avacopan + reduced dose prednisone appeared numerically non-inferior to the comparator (full dose prednisone), whereas avacopan + no prednisone appeared numerically inferior to the comparator.

The glucocorticoid use was relatively common also in the avacopan plus no prednisone group where 7 out of 21 subjects were using a median cumulative dose of 500 mg during the treatment period. ***The Applicant was in the first LoQ requested to discuss the importance of this finding in evaluation of corticosteroid-sparing capability and efficacy results related to avacopan use. In response, the applicant provided a discussion where the corticosteroid use in all arms was presented, and this issue could be solved.***

The mean cumulative dose of cyclophosphamide during the 84-day treatment period was 801 mg greater in the pooled avacopan group than the one in the standard treatment group. *The Applicant was in the first LoQ requested to discuss the possible effect of this difference in cumulative dose of cyclophosphamide on the efficacy results. The applicant clarified that there were two reasons for this discrepancy. First, 2/8 patients in the comparator group had a missed cyclophosphamide dose due to infections, compared to no subjects in the avacopan + low dose prednisone group and one subject in the avacopan+ no prednisone group. Second, the starting dose of cyclophosphamide was lower in the comparator group compared to in the avacopan groups because of differences in patient characteristics (the cyclophosphamide dose needed to be adjusted based on subject age, eGFR, and WBC count). Although the differences in cyclophosphamide doses (possibly also reflecting some baseline differences between the treatment groups) may possibly affect the observed treatment effects, this issue cannot be further resolved with the current clinical data, but the issue remains as an additional uncertainty related to the efficacy of avacopan.*

<u>Study CL003_168</u>

As this study was, according to the applicant, not powered to evaluate efficacy, the results are descriptive.

A total of 42 subjects were enrolled into the study (13 subjects to the placebo group, 13 subjects to the avacopan 10 mg bid group and 16 subjects to avacopan 30 mg bid group). One subject in each avacopan group withdrew before day 85 due to adverse events, and 40 subjects remained in the pre-defined modified ITT population that was used for analysis of the primary efficacy endpoint.

The primary efficacy endpoint, the proportion of subjects with BVAS response at day 85, was numerically higher in the avacopan 10 mg group than in the placebo group, but for the intended dose of 30 mg the response rate was lower than for placebo.

For the secondary endpoint of clinical remission, the trend was similar with a higher remission rate in avacopan 10 mg than in placebo, but lower remission rate for avacopan 30 mg than for placebo. Overall, there thus seems to be no gain of adding avacopan 30 mg bid to SOC in terms of increased efficacy however the study was not powered to evaluate remission and the descriptive nature of the results are acknowledged.

3.3.7. Conclusions on clinical efficacy

Although the primary endpoint in CL002_168 was met, as avacopan with or without reduced dose prednisone was non-inferior to the comparator (full dose prednisone) regarding BVAS response at day 85, there are a number of issues that weaken the statistical confidence in the results. These include risk of bias and insufficient control of the type I error. ***It is agreed that the proposed design could be appropriate for a phase II exploratory study. Yet, this is the main study upon which the applicant seeks to make claims of efficacy: therefore the results need to be both statistically and methodologically compelling and the results highly convincing. Hence the exploratory results of CL002_168 need to be confirmed.***

There is also concern on the clinical relevance of the primary endpoint, as there is a general consensus that the aim of vasculitis induction therapy is not *induction of response* but rather *induction of remission*. For the secondary endpoint of BVAS remission, avacopan with or without low-dose prednisone appeared inferior to the comparator. This might have several reasons. One might be that the treatment period is too short. In the ongoing phase 3 study, subjects will be treated with avacopan for 52 weeks.

In response to the first LoQ, the applicant provided a discussion regarding the relevance of BVAS as an endpoint, and its association to future remission. The applicant refers to an analysis on a similar patient population of 303 patients from 4 studies conducted by the European Vasculitis Group (EUVAS). In these patients, who were treated with a variety of therapies, including cyclophosphamide, azathioprine, methylprednisolone, plasma exchange, or methotrexate, 58.9% of the subjects with BVAS response at 3 months went into BVAS remission at 6 months. It is understood that these individuals were on continuous treatment, in contrast to what is proposed in the SmPC for avacopan where subjects should be treated for 12 weeks, and where the response rate seems to diminish over time (for avacopan + no prednisone, BVAS response at week 12: 81%, BVAS response at week 24: 71.4% . Thus, although these data is of interest, its relevance for this application is somewhat limited.

Study CL003_168 did not include the intended dosing regimen (avacopan 30 mg without concomitant prednisone), and the results are or limited value for this assessment.

To conclude, the efficacy of avacopan cannot be considered established, due to severe limitations in the "pivotal" phase II study. It is agreed that the proposed design could be

appropriate for a phase II exploratory study. Yet, this is the main study upon which the applicant seeks to make claims of efficacy: therefore the results need to be both statistically and methodologically compelling and the results highly convincing. Hence the exploratory results of CL002_168 need to be confirmed.

3.3.8. Clinical safety

Patient exposure

Total exposure from clinical trials is limited to exposure from four phase I clinical trials that included in 102 healthy volunteers, of which 89 received avacopan ≤5.5 days and 2 Phase II clinical trials, CL002_168 and CL003_168, that included 109 AAV-patients of which 73 were randomised to receive avacopan. Of the enrolled AAV patients, 60 subjects received 30 mg avacopan twice daily (the currently dose proposed by the applicant) for 12 weeks and 13 subjects received 10 mg avacopan twice daily for 12 weeks i.e. there were no patients with long term safety data.

Adverse events

Adverse events in phase I study

When healthy controls were given avacopan in the phase I studies (n=89) or placebo (n=14), the frequency of subjects that had any treatment-emergent event was 62.9% in the avacopan group and 42.9% in the placebo group.

The most frequently reported adverse event in Phase I studies in healthy volunteers was chromaturia (16.9%). However, this was ascribed to rifampicin dosing in study CL008_168 and not to avacopan. Headache, GI symptoms, infections, dizziness and WBC count decrease, were also reported.

Adverse events and other safety findings in phase II study CL002_168

When safety profile of three different treatment strategies; avacopan +no prednisone, avacopan +reduced dose prednisone group or standard full dose prednisone (comparator group) were compared on top of rituximab or cyclophosphamide in CL0002_168, the frequency of subjects with any TEAEs was >90% in all three treatment groups both during the 84 day treatment period and the 168 day study period. It can be noted that the avacopan + no steroid group corresponds to the posology of the current application and that standard full dose prednisone group (comparator group) corresponds to standard of care.

A summary of the most frequently reported TEAEs (experienced by ≥5% of subjects in the all avacopan group or the standard full dose prednisone group based on preferred term) during the 84-Day Treatment Period for the Safety Population is given in the table below.

Table 16: Summary of Most Common Treatment-Emergent Adverse Events (≥5% of Subjects in the all avacopan group or the standard full dose prednisone group) during the 84-Day Treatment Period for the Safety Population in CL002_168

Step - Overall System Organ Class Preferred Term	Placebo + Full Dose Prednisone (N = 23) n (%)	CCX168 + Low-Dose Prednisone (N = 22) n (%)	CCX168 + No Prednisone (N = 22) n (%)	All CCX168 (N = 44) n (%)
Subjects with any TEAE during the 84-day treatment period	21 (91.3)	19 (86.4)	21 (95.5)	40 (90.9)
Gastrointestinal disorders	10 (43.5)	11 (50.0)	11 (50.0)	22 (50.0)
Nausea	6 (26.1)	6 (27.3)	4 (18.2)	10 (22.7)
Vomiting	0 (0.0)	4 (18.2)	4 (18.2)	8 (18.2)
Constipation	4 (17.4)	3 (13.6)	2 (9.1)	5 (11.4)
Diarrhea	1 (4.3)	3 (13.6)	1 (4.5)	4 (9.1)
Abdominal pain upper	2 (8.7)	1 (4.5)	2 (9.1)	3 (6.8)
Abdominal pain	2 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	9 (39.1)	10 (45.5)	12 (54.5)	22 (50.0)
Nasopharyngitis	3 (13.0)	3 (13.6)	4 (18.2)	7 (15.9)
Rhinitis	1 (4.3)	1 (4.5)	2 (9.1)	3 (6.8)
Viral upper respiratory tract infection	0 (0.0)	2 (9.1)	1 (4.5)	3 (6.8)
Musculoskeletal and connective tissue disorders	9 (39.1)	4 (18.2)	9 (40.9)	13 (29.5)
Arthralgia	1 (4.3)	1 (4.5)	3 (13.6)	4 (9.1)
Muscle spasms	5 (21.7)	1 (4.5)	1 (4.5)	2 (4.5)
Back pain	3 (13.0)	0 (0.0)	1 (4.5)	1 (2.3)
Respiratory, thoracic and mediastinal disorders	7 (30.4)	7 (31.8)	6 (27.3)	13 (29.5)
Cough	2 (8.7)	2 (9.1)	2 (9.1)	4 (9.1)
Epistaxis	2 (8.7)	2 (9.1)	2 (9.1)	4 (9.1)
Dyspnea exertional	2 (8.7)	2 (9.1)	0 (0.0)	2 (4.5)
Skin and subcutaneous tissue disorders	10 (43.5)	5 (22.7)	7 (31.8)	12 (27.3)
Purpura	1 (4.3)	0 (0.0)	3 (13.6)	3 (6.8)
Hyperhidrosis	2 (8.7)	0 (0.0)	1 (4.5)	1 (2.3)
Erythema	2 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	4 (17.4)	5 (22.7)	7 (31.8)	12 (27.3)
Hypertension	2 (8.7)	2 (9.1)	5 (22.7)	7 (15.9)
General disorders and administration site conditions	8 (34.8)	4 (18.2)	7 (31.8)	11 (25.0)
Chills	0 (0.0)	1 (4.5)	2 (9.1)	3 (6.8)
Fatigue	3 (13.0)	0 (0.0)	3 (13.6)	3 (6.8)
Edema peripheral	4 (17.4)	1 (4.5)	2 (9.1)	3 (6.8)
Pyrexia	2 (8.7)	0 (0.0)	1 (4.5)	1 (2.3)
Investigations	10 (43.5)	4 (18.2)	8 (36.4)	12 (27.3)
Alanine aminotransferase increased	1 (4.3)	1 (4.5)	2 (9.1)	3 (6.8)
Blood creatinine increased	2 (8.7)	0 (0.0)	1 (4.5)	1 (2.3)
Nervous system disorders	6 (26.1)	6 (27.3)	4 (18.2)	10 (22.7)
Headache	2 (8.7)	2 (9.1)	4 (18.2)	6 (13.6)
Paresthesia	2 (8.7)	3 (13.6)	1 (4.5)	4 (9.1)
Dizziness	2 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)
Tremor	2 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	4 (17.4)	5 (22.7)	4 (18.2)	9 (20.5)
Nocturia	1 (4.3)	3 (13.6)	0 (0.0)	3 (6.8)
Renal vasculitis	2 (8.7)	0 (0.0)	1 (4.5)	1 (2.3)
Psychiatric disorders	6 (26.1)	2 (9.1)	1 (4.5)	3 (6.8)
Anxiety	2 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	3 (13.0)	1 (4.5)	0 (0.0)	1 (2.3)
Anemia	2 (8.7)	1 (4.5)	0 (0.0)	1 (2.3)

An adverse event was considered treatment-emergent if the start date of the event was on or after administration of the first dose of study medication.
TEAE = treatment-emergent adverse event.
Source: Post-Text Table 14.3.1.3

The most frequently reported TEAEs by SOC during the 168-day study period in the all avacopan group were infections and infestations (26 [59.1%] subjects), gastrointestinal disorders (24 [54.5%] subjects), and musculoskeletal and connective tissue disorders (20 [45.5%] subjects). The most frequently reported TEAEs by SOC during the 168-day study period in the standard full dose prednisone comparator group were gastrointestinal disorders (12 [52.2%] subjects); and infections and infestations, musculoskeletal and connective tissue disorders, skin and subcutaneous tissue disorders, and investigations (11 [47.8%] subjects each).

During the overall 168-day study period, the number of subjects with any treatment-emergent infections in the 168-day study period was 14 (63.6%) in the avacopan +reduced dose prednisone group and 12 (54.5%) in the avacopan + no prednisone group and 11 (47.8%) in the comparator group.

At least 1 TEAE possibly assessed as possibly related to glucocorticoid use during the 84-day treatment period was reported in 11 (50.0%) subjects in the avacopan + reduced dose prednisone group and 8 (36.4%) subjects in the avacopan+ no prednisone group), compared to 13 (56.5%) subjects the comparator group. Only GI-disorders and vascular disorders were reported as TEAEs assessed as possibly related to glucocorticoid use in ≥5% of subjects in the all avacopan group or comparator (based on preferred term) during the 84-day study period. During the whole 168 study period, 11 (50%) subjects in the avacopan+ reduced dose prednisone group and 10 (45.5%) in the avacopan+ no prednisone group had any TEAES assessed as possibly related to corticosteroid use compared to 14 (60.9%) in the comparator group. ***In response to the first LoQ, a summary table of treatment-emergent adverse events assessed as possibly associated with glucocorticoid use during the 168-day study period in the avacopan groups compared to the comparator group was provided. Numerical difference was noted regarding infections with a lower incidence in the avacopan groups compared to prednisone control. However, the numbers are small and the difference thus consists of just a few individuals.***

The applicant summarized treatment-emergent adverse *effects* assessed as possibly associated with glucocorticoid use during the study. ***The definition of this term was provided in the Statistical Analysis Plan of study CL002_168. The term is based on a list of items selected by vasculitis experts and includes serious infections, new-onset diabetes/hyperglycemia, bonefracture, peptic ulcer disease, cataract, new onset/worsening hypertension, weight gain>10 kg and psychiatric disorders.*** At least 1 treatment-emergent adverse effect possibly associated with glucocorticoid use during the 84-day treatment period was reported in 4 (18.2%) subjects in the avacopan + reduced dose prednisone group and 11 (50.0%) subjects in the avacopan+ no prednisone group), compared to 15 (65.2%) subjects with the comparator group. For the 168 day-study period, 6 more subjects in the avacopan+ reduced dose prednisone group had any treatment-emergent adverse effect while the numbers were the same in the other two groups, see table below. ***Using this term, less events (effects) were thus seen in the avacopan groups in study CL002_168 than in the comparator arm but the difference between the groups is small. Comparing the avacopan + no steroid group with the comparator, the largest difference is seen for psychiatric disorders.***

Table 17: Summary of treatment-emergent adverse *effects* possibly associated with glucocorticoid use during the 168-day study period safety population of study CL002_168

Step Adverse Effects Categories	Placebo + Full Dose Prednisone n (%)	CCX168 + Low Dose Prednisone n (%)	CCX168 + No Prednisone n (%)	All CCX168 n (%)
Overall	N=23	N=22	N=22	N=44
Any Treatment-emergent Adverse Effects During the 168-Day Study Period	15 (65.2)	10 (45.5)	11 (50.0)	21 (47.7)
New Onset/Worsening Hypertension	6 (26.1)	5 (22.7)	9 (40.9)	14 (31.8)
Psychiatric Disorders	7 (30.4)	5 (22.7)	1 (4.5)	6 (13.6)
Serious Infections	1 (4.3)	2 (9.1)	2 (9.1)	4 (9.1)
New Onset/Worsening Diabetes Mellitus/Hyperglycemia	3 (13.0)	1 (4.5)	1 (4.5)	2 (4.5)
Weight gain more than 10 kg	3 (13.0)	2 (9.1)	0 (0.0)	2 (4.5)
Cataracts	1 (4.3)	0 (0.0)	1 (4.5)	1 (2.3)
Bone Fracture	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Step 3	N=13	N=14	N=14	N=28
Any Treatment-emergent Adverse Effects During the 168-Day Study Period	8 (61.5)	7 (50.0)	6 (42.9)	13 (46.4)
New Onset/Worsening Hypertension	5 (38.5)	3 (21.4)	5 (35.7)	8 (28.6)
Psychiatric Disorders	5 (38.5)	5 (35.7)	1 (7.1)	6 (21.4)
New Onset/Worsening Diabetes Mellitus/Hyperglycemia	1 (7.7)	1 (7.1)	0 (0.0)	1 (3.6)
Weight gain more than 10 kg	1 (7.7)	1 (7.1)	0 (0.0)	1 (3.6)
Step 2	N= 6	N= 0	N= 8	N= 8
Any Treatment-emergent Adverse Effects During the 168-Day Study Period	5 (83.3)		5 (62.5)	5 (62.5)
New Onset/Worsening Hypertension	1 (16.7)		4 (50.0)	4 (50.0)
Serious Infections	0 (0.0)		2 (25.0)	2 (25.0)
Cataracts	1 (16.7)		1 (12.5)	1 (12.5)
New Onset/Worsening Diabetes Mellitus/Hyperglycemia	2 (33.3)		1 (12.5)	1 (12.5)
Psychiatric Disorders	1 (16.7)		0 (0.0)	0 (0.0)
Weight gain more than 10 kg	2 (33.3)		0 (0.0)	0 (0.0)

Step Adverse Effects Categories	Placebo + Full Dose Prednisone n (%)	CCX168 + Low Dose Prednisone n (%)	CCX168 + No Prednisone n (%)	All CCX168 n (%)
Step 1	N= 4	N= 8	N= 0	N= 8
Any Treatment-emergent Adverse Effects During the 168-Day Study Period	2 (50.0)	3 (37.5)		3 (37.5)
New Onset/Worsening Hypertension	0 (0.0)	2 (25.0)		2 (25.0)
Serious Infections	0 (0.0)	1 (12.5)		1 (12.5)
Weight gain more than 10 kg	0 (0.0)	1 (12.5)		1 (12.5)
Bone Fracture	1 (25.0)	0 (0.0)		0 (0.0)

ECG assessments were performed at screening and day 29 in study CL002_168. Among the patients randomised to avacopan, there were four subjects with ECG findings in that were considered clinically significant by the investigators; for all but one of the subjects, the abnormal findings were present before patients started treatment.

Vital signs and physical findings with regards to changes in mean values from baseline to day 85 are summarized in the table below.

Table 18: Summary of Body Mass Index, Vital Signs, and Weight Changes in Study CL002_168

Parameter Statistic	Placebo + Full Dose Prednisone (N=23)	Avacopan Groups Combined, 30 mg twice daily (N=44)
Body Mass Index (kg/m^2)		
Baseline mean (SD)	27.290 (7.0938)	25.733 (4.3844)
Day 85 mean (SD)	28.190 (7.4800)	26.189 (4.2317)
Mean change (SD)	0.773 (1.4553)	0.356 (1.0669)
Diastolic Blood Pressure (mm Hg)		
Baseline mean (SD)	74.7 (10.99)	76.3 (11.31)
Day 85 mean (SD)	79.5 (8.45)	80.3 (10.90)
Mean change (SD)	5.6 (14.22)	3.9 (11.62)
Heart Rate (bpm)		
Baseline mean (SD)	74.4 (9.28)	72.7 (11.26)
Day 85 mean (SD)	71.8 (14.08)	73.0 (11.11)
Mean change (SD)	-1.3 (14.38)	0.8 (12.70)
Temperature (°C)		
Baseline mean (SD)	36.51 (0.541)	36.36 (0.540)
Day 85 mean (SD)	36.54 (0.773)	36.26 (0.527)
Mean change (SD)	0.04 (0.619)	-0.09 (0.529)
Systolic Blood Pressure (mm Hg)		
Baseline mean (SD)	134.9 (12.61)	129.4 (18.58)
Day 85 mean (SD)	138.8 (20.04)	132.6 (14.02)
Mean change (SD)	4.3 (23.04)	3.8 (19.80)
Weight (kg)		
Baseline mean (SD)	83.00 (21.632)	76.26 (16.195)
Day 85 mean (SD)	85.21 (22.880)	77.86 (16.541)
Mean change (SD)	2.44 (4.783)	1.40 (3.286)

Source: CSR CL002_168 Table 14.3.5.1

Adverse events and other safety findings in phase II study CL003_168

When two doses of avacopan were compared to placebo on top of SOC, (that included full-dose steroids) in patients with acute vasculitis in study CL003_168; 84.6% in the avacopan 10 mg group and 93.8% in the avacopan 30 mg group and 100% of patients in the placebo group, had any TEAE during the 84 day treatment period. The corresponding figures for the 168 day study period were 92.3%, 93.8% and 100%.

A summary of the most frequently reported TEAEs (experienced by ≥5% of subjects in the All avacopan +SOC group or the Placebo +SOC group based on preferred term) overall during the 84-day treatment period for the Safety Population is given in the table below.

Table 19: Summary of the most frequently reported TEAEs (experienced by ≥5% of subjects in the All Avacopan group+ SOC group or the Placebo + SOC group) during the 84-day treatment period for the Safety Population in CL003_168

System Organ Class Preferred Term	Placebo + Standard of Care (N = 13) n (%)	CCX168 10 mg + Standard of Care (N = 13) n (%)	CCX168 30 mg + Standard of Care (N = 16) n (%)	All CCX168 (N = 29) n (%)
Subjects with any TEAE during the 84-day treatment period	13 (100.0%)	11 (84.6%)	15 (93.8%)	26 (89.7%)
General disorders and administration site conditions	3 (23.1%)	4 (30.8%)	7 (43.8%)	11 (37.9%)
Edema peripheral	0	1 (7.7%)	3 (18.8%)	4 (13.8%)
Fatigue	3 (23.1%)	1 (7.7%)	1 (6.3%)	2 (6.9%)
Pain	0	1 (7.7%)	1 (6.3%)	2 (6.9%)
Vessel puncture site bruise	1 (7.7%)	0	0	0
Vessel puncture site hematoma	1 (7.7%)	0	0	0
Skin and subcutaneous tissue disorders	4 (30.8%)	3 (23.1%)	6 (37.5%)	9 (31.0%)
Ecchymosis	1 (7.7%)	1 (7.7%)	2 (12.5%)	3 (10.3%)
Acne	1 (7.7%)	0	0	0
Dry Gangrene	1 (7.7%)	0	0	0
Psoriasis	1 (7.7%)	0	0	0
Rash maculo-papular	1 (7.7%)	0	0	0
Scab	2 (15.4%)	0	0	0
Skin discoloration	1 (7.7%)	0	0	0
Skin ulcer	1 (7.7%)	0	0	0
Splinter hemorrhages	1 (7.7%)	0	0	0
Gastrointestinal disorders	1 (7.7%)	4 (30.8%)	4 (25.0%)	8 (27.6%)
Nausea	1 (7.7%)	2 (15.4%)	1 (6.3%)	3 (10.3%)
Abdominal pain upper	0	1 (7.7%)	1 (6.3%)	2 (6.9%)
Diarrhea	0	0	2 (12.5%)	2 (6.9%)
Flatulence	0	0	2 (12.5%)	2 (6.9%)
Vomiting	0	1 (7.7%)	1 (6.3%)	2 (6.9%)
Vascular disorders	5 (38.5%)	3 (23.1%)	5 (31.3%)	8 (27.6%)
Hypertension	4 (30.8%)	2 (15.4%)	4 (25.0%)	6 (20.7%)
Hot flush	0	1 (7.7%)	1 (6.3%)	2 (6.9%)
Extremity necrosis	1 (7.7%)	0	0	0
Infections and infestations	2 (15.4%)	2 (15.4%)	5 (31.3%)	7 (24.1%)
Cellulitis	1 (7.7%)	0	0	0
Gangrene	1 (7.7%)	0	0	0
Gastroenteritis viral	1 (7.7%)	0	0	0
Herpes zoster	1 (7.7%)	0	0	0
Investigations	4 (30.8%)	3 (23.1%)	4 (25.0%)	7 (24.1%)
Blood creatinine increased	0	0	2 (12.5%)	2 (6.9%)
Amylase increased	1 (7.7%)	1 (7.7%)	0	1 (3.4%)
Lipase increased	1 (7.7%)	0	0	0
Transaminases increased	1 (7.7%)	0	0	0
Weight increased	2 (15.4%)	0	0	0

An adverse event was considered treatment-emergent if the start date of the event was on or after administration of the first dose of study medication.
TEAE = treatment-emergent adverse event.
Source: Post-text Table 14.3.1.3

System Organ Class Preferred Term	Placebo + Standard of Care (N = 13) n (%)	CCX168 10 mg + Standard of Care (N = 13) n (%)	CCX168 30 mg + Standard of Care (N = 16) n (%)	All CCX168 (N = 29) n (%)
Musculoskeletal and connective tissue disorders	5 (38.5%)	1 (7.7%)	6 (37.5%)	7 (24.1%)
Arthralgia	0	0	2 (12.5%)	2 (6.9%)
Back pain	1 (7.7%)	0	2 (12.5%)	2 (6.9%)
Myalgia	0	0	2 (12.5%)	2 (6.9%)
Myopathy	1 (7.7%)	0	1 (6.3%)	1 (3.4%)
Arthritis	1 (7.7%)	0	0	0
Bursitis	1 (7.7%)	0	0	0
Muscle spasms	1 (7.7%)	0	0	0
Muscular weakness	1 (7.7%)	0	0	0
Nervous system disorders	5 (38.5%)	3 (23.1%)	3 (18.8%)	6 (20.7%)
Dizziness	0	0	2 (12.5%)	2 (6.9%)
Headache	2 (15.4%)	0	2 (12.5%)	2 (6.9%)
Lumbar radiculopathy	1 (7.7%)	0	0	0
Neuropathy peripheral	1 (7.7%)	0	0	0
Sinus headache	1 (7.7%)	0	0	0
Tremor	1 (7.7%)	0	0	0
Injury, poisoning and procedural complications	3 (23.1%)	3 (23.1%)	2 (12.5%)	5 (17.2%)
Infusion related reaction	0	2 (15.4%)	1 (6.3%)	3 (10.3%)
Contusion	0	1 (7.7%)	1 (6.3%)	2 (6.9%)
Fall	2 (15.4%)	1 (7.7%)	1 (6.3%)	2 (6.9%)
Pubis fracture	1 (7.7%)	0	0	0
Skin injury	1 (7.7%)	0	0	0
Psychiatric disorders	1 (7.7%)	3 (23.1%)	2 (12.5%)	5 (17.2%)
Insomnia	0	1 (7.7%)	2 (12.5%)	3 (10.3%)
Confusional state	1 (7.7%)	0	0	0
Respiratory, thoracic and mediastinal disorders	5 (38.5%)	1 (7.7%)	4 (25.0%)	5 (17.2%)
Oropharyngeal pain	1 (7.7%)	0	2 (12.5%)	2 (6.9%)
Cough	1 (7.7%)	0	0	0
Epistaxis	2 (15.4%)	0	0	0
Nasal ulcer	1 (7.7%)	0	0	0
Paranasal sinus discomfort	2 (15.4%)	0	0	0
Cardiac disorders	0	0	4 (25.0%)	4 (13.8%)
Tachycardia	0	0	2 (12.5%)	2 (6.9%)
Eye disorders	1 (7.7%)	1 (7.7%)	3 (18.8%)	4 (13.8%)
Scleritis	0	1 (7.7%)	1 (6.3%)	2 (6.9%)
Conjunctival hemorrhage	1 (7.7%)	0	0	0

An adverse event was considered treatment-emergent if the start date of the event was on or after administration of the first dose of study medication.
TEAE = treatment-emergent adverse event.
Source: Post-text Table 14.3.1.3

System Organ Class Preferred Term	Placebo + Standard of Care (N = 13) n (%)	CCX168 10 mg + Standard of Care (N = 13) n (%)	CCX168 30 mg + Standard of Care (N = 16) n (%)	All CCX168 (N = 29) n (%)
Blood and lymphatic system disorders	2 (15.4%)	1 (7.7%)	1 (6.3%)	2 (6.9%)
Neutropenia	0	1 (7.7%)	1 (6.3%)	2 (6.9%)
Increased tendency to bruise	1 (7.7%)	0	0	0
Methemoglobinemia	1 (7.7%)	0	0	0
Renal and urinary disorders	1 (7.7%)	1 (7.7%)	1 (6.3%)	2 (6.9%)
Hematuria	1 (7.7%)	1 (7.7%)	0	1 (3.4%)
Endocrine disorders	1 (7.7%)	0	1 (6.3%)	1 (3.4%)
Hypothyroidism	1 (7.7%)	0	0	0
Metabolism and nutrition disorders	1 (7.7%)	1 (7.7%)	0	1 (3.4%)
Hypoglycemia	1 (7.7%)	0	0	0

An adverse event was considered treatment-emergent if the start date of the event was on or after administration of the first dose of study medication.
TEAE = treatment-emergent adverse event.
Source: Post-text Table 14.3.1.3

The most frequently reported TEAEs by SOC during the 168-day study period in the all avacopan +SOC group were general disorders and administration site conditions (13 [44.8%] subjects), infections and infestations and vascular disorders (11 [37.9%] subjects each), and musculoskeletal and connective tissue disorders and skin and subcutaneous tissue disorders (10 [34.5%] subjects each). The most frequently reported TEAEs by SOC during the 168-day study period in the placebo + SOC group were musculoskeletal and connective tissue disorders; nervous system disorders; and respiratory, thoracic, and mediastinal disorders (6 [46.2%] subjects each); and vascular disorders and investigations (5 [38.5%] subjects each).

The number of subjects with any treatment-emergent infection during the 168 day study period was 4 (30.8%) in the placebo + SOC group, 5 (38.5%) in the avacopan 10 mg + SOC group, 6 (37.5%) in the avacopan 30 mg+ SOC group and 11 (37.9%) in the all avacopan+SOC group.

A majority of the patients had any TEAEs assessed as possibly related to prednisone use during the 168 day study period: 9 (69.2%) in the placebo group, 7 (53.8%) in the avacopan 10 mg group and 13 (81.3%) in the avacopan 30 mg group.

The applicant also summarized treatment-emergent adverse *effects* possibly associated with glucocorticoid use during the study ***(please refer to definition of the term provided above).*** At least 1 treatment-emergent adverse effect possibly associated with glucocorticoid use during the 84-day treatment period was reported in 7 (53.8%) subjects in the avacopan 10 mg + SOC group and 11 (68.8%) subjects in the avacopan 30 mg + SOC group, compared to 5 (38.5%) subjects in the comparator group; placebo + SOC. New-onset or worsening hypertension, psychiatric disorders, serious infections new-onset diabetes mellitus or hyperglycemia weight gain >10 kg possibly associated with glucocorticoid use during the 84-day treatment period was reported. No bone fractures or cataracts possibly associated with glucocorticoid use during the 84-day treatment period were reported. A few new subjects with any Treatment-emergent adverse effects possibly associated with glucocorticoid use were added during the 84 day follow-up period.

Twelve-lead ECGs were acquired during screening and on Days 29 and 85. Three subjects had abnormal ECGs that were considered clinically significant by the Investigators: one had atrial fibrillation on Day 15 (in Avacopan 30 mg + SOC group), one had sinus arrhythmia (anterior infarct [age undetermined] could not be ruled out) on Day 15 (in Avacopan 30 mg + SOC group) and one had abnormal ECG findings of QT lengthening and premature ventricular complexes on Day -9 (in comparator group).

Vital signs and physical findings with regards to changes in mean values from baseline to day 85 are summarized in the table below.

Table 20: Summary of Body Mass Index, Vital Signs, and Weight Changes in Study CL003_168 in ANCA-Associated Vasculitis

Parameter Statistic	Placebo + Full Dose Prednisone (N=13)	Avacopan Groups Combined (N=29)
Body Mass Index (kg/m^2)		
Baseline mean (SD)	30.994 (12.5127)	29.788 (8.2941)
Day 85 mean (SD)	30.742 (9.1735)	30.493 (7.2284)
Mean change (SD)	-0.252 (4.0208)	1.610 (1.5164)
Diastolic Blood Pressure (mm Hg)		
Baseline mean (SD)	78.0 (11.21)	77.4 (8.85)
Day 85 mean (SD)	80.4 (7.16)	79.7 (10.00)
Mean change (SD)	2.4 (8.48)	2.6 (10.58)
Heart Rate (bpm)		
Baseline mean (SD)	75.0 (13.51)	71.7 (9.78)
Day 85 mean (SD)	79.8 (13.48)	72.6 (11.72)
Mean change (SD)	4.8 (15.05)	1.2 (14.05)
Temperature (°C)		
Baseline mean (SD)	36.48 (0.268)	36.59 (0.297)
Day 85 mean (SD)	36.50 (0.383)	36.49 (0.410)
Mean change (SD)	0.02 (0.324)	-0.11 (0.382)
Systolic Blood Pressure (mm Hg)		
Baseline mean (SD)	138.8 (15.10)	132.3 (15.02)
Day 85 mean (SD)	136.8 (15.21)	131.6 (17.12)
Mean change (SD)	-2.1 (13.32)	-1.5 (18.03)
Weight (kg)		
Baseline mean (SD)	84.01 (29.829)	88.99 (31.977)
Day 85 mean (SD)	83.59 (23.193)	91.22 (28.966)
Mean change (SD)	-0.42 (9.473)	4.66 (4.704)

Source: CSR CL003_168 Table 14.3.5.1

Adverse events and other safety findings in the two phase II-studies, CL002_168 and CL003_168, combined

When the data from the two phase II studies were combined, at least one TEAE during the 24-Week study period was reported for 69 (94.5%) subjects in the all avacopan group and for 34 (94.4%) subjects in the comparator group.

There were no deaths (Grade 5 events) but two Grade 4 life-threatening events in the Phase II studies that both occurred in Study CL003_168. The first case was a serious event of sepsis in the Avacopan 30 mg group (likely to be related to a bile duct stricture following a Whipple procedure), and the second case was an event of late-onset neutropenia in the Avacopan 10 mg group (considered probably not related to study medication but possibly related to rituximab). Severe (Grade 3) TEAEs were reported in 4 (11.1%) patients in the High Dose Prednisone Control group and 12 (16.4%) patients in the All Avacopan group. The individual TEAEs occurred as single cases. Overall, there were more Grade 3-4 events in the avacopan groups compared to the control group (14 vs. 4). In Study

CL002_168, however, the number of Grade 1-3 events in the "Avacopan + No Prednisone" group was equal to that in the "Full Dose Prednisone" group (21 vs. 21), and there were no Grade 4-5 events.

The proportion of subjects that reported any infection was higher in the all avacopan group (during the 12 week treatment period and during the complete 24 week period) compared to the comparator group. The same was true for any GI events and any cardiac disorders. Infections and GI-events were considered adverse drug reactions (see below) and included in section 4.8 of the SmPC while cardiac disorders were not. Of the 60 AAV patients that received avacopan 30 mgx2, 7 patients had any TEAE reported as cardiac disorders (3 tachycardia, 1 atrial fibrillation, 1 AV-block, 1 palpitation and 1 restrictive cardiomyopati) during the 12 week treatment period. Of the 36 AAV patients that were included in the comparator groups, 1 had any TEAE reported as cardiac disorder (angina, atrial flutter, bradycardia) during the 12 week treatment period. During the 24 week-study period there were 8 subjects with any TEAEs of cardiac disorders in total (13.3%, 1 extra TEAEs of cyanosis reported since the 12 week treatment period) in the avacopan 30 mgx2 group compared to 2 in the comparator group (5.6%, 1 extra case of tachycardia compared to the 12 week treatment period).

During the 24 week study period, there were 2 subjects with TEAEs in the SOC Neoplasms benign, malignant and unspecified (including cysts and polyps) in the comparator group (5.6%), 1 in the avacopan 30 mgx2 group (1.7%) and one among the avcaopan subjects that received a lower avacopan dose i.e. 2 cases in total among the avacopan treated subjects (2.7%). In the comparator group the 2 subjects were diagnosed with basal cell carcinoma and haemangioma of liver and in the avacopan group the subjects had melanocytic nevus and skin papilloma.

No infections caused by Neisseria meningitidis were been observed in clinical trials with avacopan.

Adverse events were reviewed by the Sponsor and a causality determination was made based on the frequency, severity and seriousness of the adverse events, overall incidence of these adverse events compared to the control group incidence, biological plausibility, medical history and concomitant medications, other factors that more likely explained the adverse event. A summary of the final list of adverse drug reactions (adverse events possibly related to study medication) is shown in the table below.

Table 21: Summary of Adverse Drug Reactions with Avacopan in Phase II Studies CL002_168 and CL003_168 in AAV

Body System	Preferred Term	Number of subjects	%[1]	Serious?	Severity
Common (≥1%, <10%)					
Infections and infestations	Candida infection[2]	4	5.5%	no	1 moderate, 3 mild
	Bronchitis	1	1.4%	no	moderate
	Rhinitis	1	1.4%	no	mild
Gastrointestinal disorders	Abdominal pain upper/abdominal discomfort	4	5.5%	no	mild
	Diarrhoea	2	2.7%	no	1 moderate, 1 mild
Nervous system disorders	Paraesthesia	3	4.1%	no	1 moderate, 2 mild
	Headache	2	2.7%	no	mild
Investigations	Hepatic enzymes increased[3,4]	2	2.7%	1 yes, 1 no	1 severe, 1 mild
Skin and subcutaneous tissue disorders	Rash/Rash pruritic/Drug eruption	4	5.5%	no	mild
Musculoskeletal and connective tissue disorders	Arthralgia/ osteoarthritis	2	2.7%	no	mild
	Myalgia/Pain in extremity	2	2.7%	no	mild
Metabolism and nutrition disorders	Decreased appetite	2	2.7%	no	1 moderate, 1 mild

[1] % calculated as n/N x 100; N = 73 subjects in studies CL002_168 and CL003_168
[2] Including MedDRA preferred terms: Candida infection, oral candidiasis, vulvovaginal mycotic infection
[3] Including MedDRA preferred terms: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, transaminases increased
[4] One of the two cases is an SAE

Serious adverse events and deaths

Serious adverse events and death in phase I study

Among the healthy volunteers in the phase I studies (n=89) or placebo (n=14), there were no death or serious adverse events.

Serious adverse events and death in phase II study CL002_168

There were no deaths in study CL002_168.

At least 1 serious TEAE during the 84-day treatment period was reported in 3 (13.6%) subjects in the avacopan+ reduced dose prednisone group and 8 (36.4%) subjects in the avacopan+ no prednisone group compared to 4 (17.4%) subjects in the comparator group. In total, during the whole 168 day study period, the number of subjects with serious TEAEs were 8 (36.4%) in the avacopan + reduced dose prednisone group and 10 (45.5%) in the avacopan+ no prednisone group compared to 5 (21.7%) in the comparator group. In the avacopan+ reduced dose prednisone group, the reported serious events included vasculitis, musculoskeletal chest pain and haematuria, febrile infection, respiratory tract infection, C-reactive protein increased, pleurisy and ocular hyperaemia and renal impairment. Serious events reported in the avacopan+ no prednisone group included renal impairment, hepatic and

pancreatic enzymes increased, rash, C-reactive protein increased, vasculitis, lung infection and respiratory tract infection. Serious events reported in the comparator group included pneumonia, dehydration, renal vasculitis and back pain, lumbar vertebral fracture, viral infection and pyrexia.

There were 2 subjects with serious treatment-emergent infections in each of the avacopan groups (9.1%) and 1 (4.3%) in the comparator group during the 168 day study period; out of those 1 in each of the avacopan groups were reported to occur during the 84 day treatment period and the event in the comparator group also occurred during the 84 day treatment period.

Serious adverse events and deaths in phase II study CL003_168

There were no deaths in study CL003_168.

At least 1 serious TEAE during the 84-day treatment period was reported in 2 (15.4%) subjects in the avacopan 10 mg group (neutropenia and cellulitis staphylococcal respectively) and 3 (18.8%) subjects in the avacopan 30 mg group (atrial fibrillation, sepsis and urinary tract infection) compared to 2 (15.4%) subjects the placebo group (methemoglobinemia and gangrene). Following the 84-day treatment period, in the avacopan 30 mg group one subject had sepsis, one had a serious event of renal failure and one had a serious event of urinary tract infection while in the placebo group, one subject had a serious event of bronchiolitis and one had nephrolithiasis. During the whole CL003_168 study period, 2 of the 13 subjects in the avacopan 10 mg group (15.4%), 4 of the 16 subjects in the avacopan 30 mg (25.0%) and 3 of the 13 subjects in the placebo group (23.1%) had at least one serious TEAE.

A total of 4 subjects had at least 1 serious infection during the 84-day treatment period: 1 (7.7%) in the avacopan 10 mg group (cellulitis staphylococcal, abscess limb, and perirectal abscess), 2 (12.5%) in the avacopan 30 mg group (sepsis and urinary tract infection respectively) and 1 (7.7%) in the placebo group (gangrene). There was one additional event in the placebo group during the follow-up period i.e. the frequencies for serious infections in the 168-day study period remained the same as during the 84 –day treatment period in the avacopan groups but increased to 15.4% in the placebo group.

Serious adverse events and deaths in the two phase II-studies, CL002_168 and CL003_168, combined

At least one serious TEAE occurred in 24 (32.9%) of the avacopan-treated AAV patients (n=73) and 8 (22.2%) of the AAV subjects in the comparator group (n=36) during the 24-week study period. During the 12-week treatment period, the corresponding figures were 21.9% in the all avacopan group and 16.7% in the control group.

Serious infections occurred in 7 (9.6%) of the avacopan-treated AAV patients and 3 (8.3%) of the AAV subjects in the comparator group during the 24-week study period.

Most SAEs in the avacopan group were reported in one subject only, except for Respiratory tract infection (3 subjects), Renal impairment (2 subjects), Vasculitis (4 subjects) and C-reactive protein increased (2 subjects). In the control group each SAE was reported only once. SAEs related to the SOC "Renal and urinary disorders" were reported in 5 avacopan-treated patients and include two cases of Renal impairment and one Renal failure. No clear differences between the treatment groups could be seen among the most common TEAEs related to Renal and urinary disorders.

According to the Applicant, the rate of TEAEs of vasculitis (including renal vasculitis/ vasculitis/ microscopic polyangiitis/ anti-neutrophil cytoplasmic antibody positive vasculitis (worsening)) was similar between the treatment groups during the 12-week treatment period. There was however some further cases of vasculitis reported as SAE during the 24-week study period.

Laboratory findings

Laboratory findings in phase I study

According to the applicant, no clinically significant mean changes in serum chemistry were observed in the Phase I studies but a in the multi-dose period of study CL001_168, a slight decrease in mean WBC and neutrophil count (~1.5 x 10^9/L) was observed more frequently in subjects receiving avacopan compared to placebo. These WBC and neutrophil counts most often remained within the reference range, were observed within 1 to 2 days after start of dosing, appeared to be most pronounced in subjects with baseline WBC and neutrophil counts at the higher end of the normal reference range, and did not appear to progressively worsen over the 7-day dosing period. The applicant further states that only a few subjects had WBC or neutrophil counts below the lower limit of normal over the course of the study, and these cases were observed in both avacopan and placebo groups.

Regarding individual clinical abnormalities, one subject in phase I study CL001_168, who received a single dose of 10 mg avacopan in the single-dose period and 10 mg once daily for 7 days in the multi-dose period, had an increase in CK and AST on Day 15 of the multi-dose period, 8 days after stopping avacopan treatment. These events were not considered related to avacopan by the investigator.

Laboratory findings in phase II study CL002_168

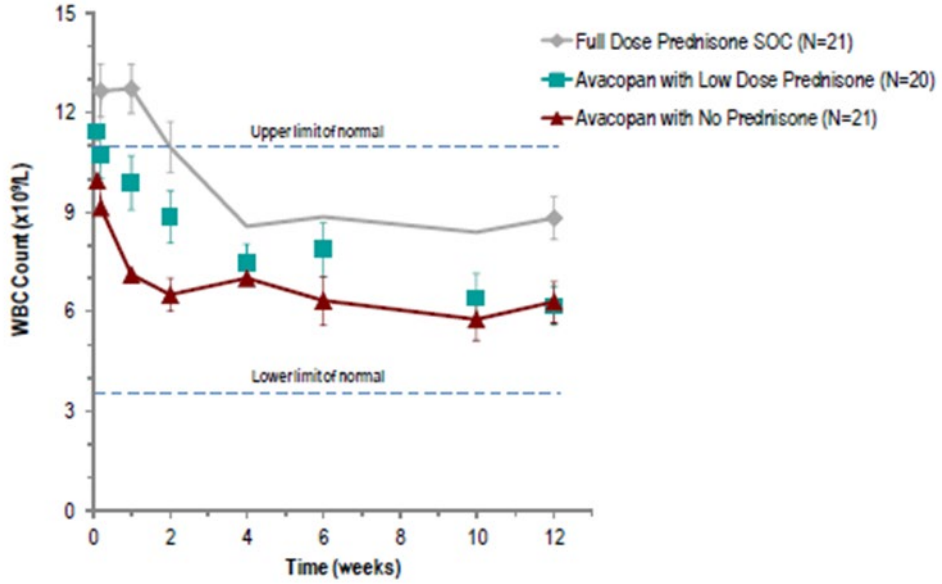
Changes in mean laboratory values throughout the treatment period of CL002_168

Mean CK value increased in the avacopan group in study CL002_168 but not in the comparator group; CK increased from a baseline mean (SD) value of 60.8 (63.02) U/L in the combined avacopan groups to a day 85 mean of 140.3 (149.68) U/L i.e. it was still within the normal reference range (25-210 U/L).

Mean LD increased from baseline to day 85 in the comparator group but not in the combined avacopan groups.

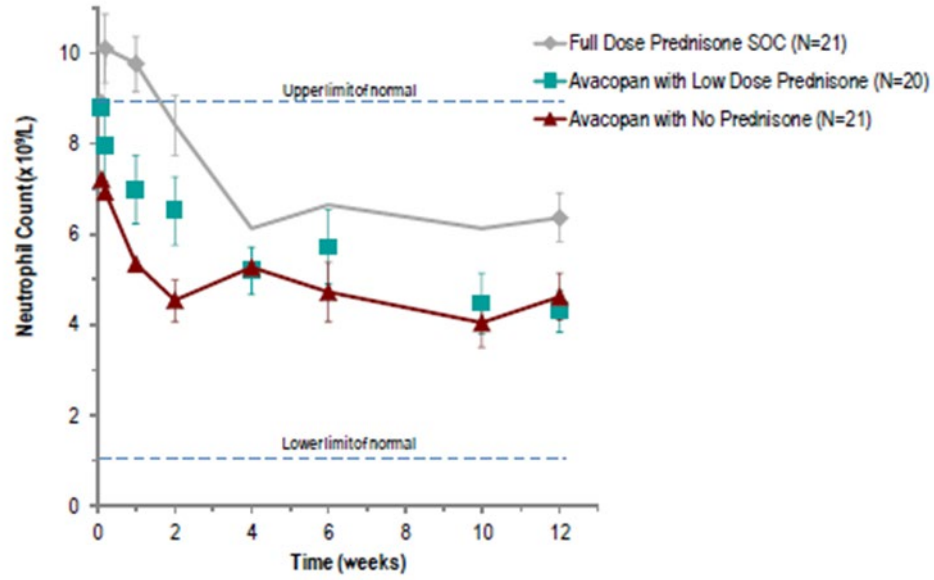
The mean WBC, neutrophil and lymphocyte count over the course of the 12-week treatment period in the two avacopan groups and the comparator group is presented in the three figures below.

Figure 5: WBC Count (Mean ± SEM) Over the Course of the 12-Week Treatment Period in Study CL002_168



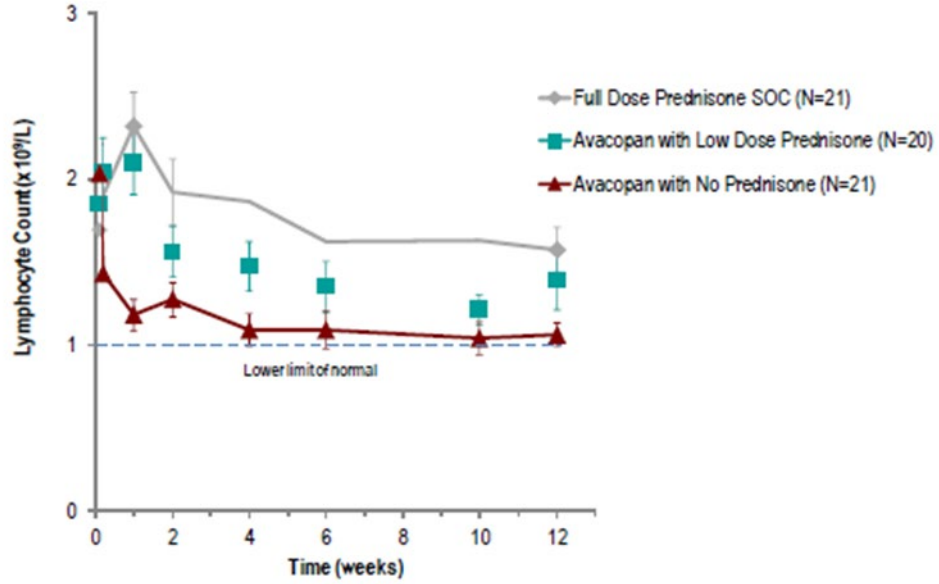
Source: CSR CL002_168 Table 14.3.4.1.

Figure 6: Neutrophil Count (Mean ± SEM) Over the Course of the 12-Week Treatment Period in Study CL002_168



Source: CSR CL002_168 Table 14.3.4.1.

Figure 7: Lymphocyte Count (Mean ± SEM) Over the Course of the 12-Week Treatment Period in Study CL002_168



Source: CSR CL002_168 Table 14.3.4.1.

Individual abnormalities of CL002_168

The Grade 2 or higher abnormalities in ALT, AST, CK, total Bilirubin and Lymphocytes (abnormalities of interest) were more frequent among the avacopan treated subjects than in than in the comparator group and abnormal lymphocytes was most common. One of 23 subjects in the control group had a Grade 2 ALT elevation (>3 to 5-fold upper limit of normal). Three of 44 subjects receiving avacopan had Grade 2 ALT abnormalities during the 12-week treatment period. Two subjects receiving avacopan had a Grade 2 CK abnormality (>2.5 to 5-fold the upper limit of normal) during the 12-week treatment period. It was reported that neither of these two subjects had signs or symptoms of muscle injury.

One subject receiving avacopan plus no prednisone had a Grade 3 ALT elevation (>5 to 20-fold the upper limit of normal) on Day 22 of the study (277 U/L; upper limit of normal [ULN]: 50 U/L), The AST was 210 U/L (ULN 50 U/L) and total bilirubin was 6.20 mg/dL (ULN 1 mg/dL), and pancreatic amylase 62 U/L (ULN 53 U/L). Study medication was discontinued as a result of this event and the event resolved. For the three patients that developed grade 2 ALAT abnormalities on avacopan treatment during the 12-week treatment period, ALAT was reported to decrease/normalize with continued avacopan dosing.

One subject receiving avacopan had a Grade 3 CK abnormality (>5 to 10-fold the upper limit of normal) during the 12-week treatment period, the CK returned to normal on Day 72 with no interruption of avacopan treatment and this subject had an adverse event of mild muscle spasms in the same timeframe as the CK elevation.

No Grade 4 or 5 haematology abnormalities were observed. Grade 2 WBC count decreases (<3 to 2 x 10^9/L) were observed in 2 subjects receiving avacopan in study CL002_168. Grade 2-3 lymphocyte decrease was more common, see table below which summarizes the grade 2-3 lymphocyte decreases in the treatment periods in the two phase II studies and the frequency of infections in these patients.

<u>Laboratory findings in phase II study CL003_168</u>

Changes in mean laboratory values throughout the treatment period of CL003_168

CK increased in both the avacopan group and the comparator group but more in the avacopan group; CK increased from a baseline mean (SD) value of 76.6 (87.48) U/L to a day 85 mean (SD) of 126.8 (234.54) U/L in the combined avacopan groups compare to the comparator group in which CK increased from 58.6 (40.88) U/L to 70.1 (53.30) U/L.

LD increased and reached mean values that were outside the normal reference range at the end of treatment period in both the avacopan and comparator group.

The mean decrease in WBC, neutrophil and lymphocyte count were more pronounced in the avacopan group than the comparator group but the mean count at the end of the treatment period was within the normal range.

Individual abnormalities of CL003_168

Of the grade 2 abnormalities related to ALT, AST, CK, total Bilirubin and Lymphocytes (abnormalities of interest); lymphocyte abnormalities were most common.

Among the avacopan-treated subjects, there was one subject with Grade 3 CK of 1217 U/L on Day 85 (ULN 210 U/L), the elevated CK value persisted until the end of the 12-week follow-up period (1846 U/L on Day 169), while not taking any avacopan and this subject had an adverse event of mild musculoskeletal pain in the same timeframe as the CK elevation. There was one additional case of grade 2 CK elevation among the avacopan treated patients.

One subject in the avacopan group had an ALT of 294 U/L (ULN 52 U/L) and AST of 210 U/L (ULN 39 U/L) on Day 64 (Grade 3), which lowered to an ALT of 67 U/L and AST of 23 U/L by Day 70, while the subject was still taking avacopan. One subject in the control group had a Grade 2 ALT.

No Grade 4 or 5 abnormalities were observed. A total of 2 subjects receiving avacopan had neutropenia. Grade 2 and 3 lymphocyte decreases during the treatment period in study CL003_168 are summarized in the table below.

Table 22: Summary of Lymphocyte Count Decreases During 12-Week Treatment Period in Studies CL002_168 and CL003_168 in ANCA-Associated Vasculitis

Study CL002_168				
Lymphopenia Grade	Prednisone Control N=23	Avacopan plus Low Dose Prednisone N=22	Avacopan plus No Prednisone N=22	All Avacopan N=44
Grade 2	3 (13.0%)	2 (9.1%)	7 (31.8%)	9 (20.5%)
Grade 3	0 (0%)	2 (9.1%)	5 (22.7%)	7 (15.9%)
Study CL003_168				
	Prednisone Control N=13	Avacopan 10 mg N=13	Avacopan 30 mg N=16	All Avacopan N=29
Grade 2	3 (23.1%)	2 (15.4%)	2 (12.5%)	4 (13.8%)
Grade 3	2 (15.4%)	4 (30.8%)	4 (25.0%)	8 (27.6%)
Studies CL002_168 and CL003_168 Combined				
	Prednisone Control N=36			All Avacopan N=73
Grade 2	6 (16.7%)			13 (17.8%)
Grade 3	2 (5.6%)			15 (20.5%)
Grade 2 nadir median (range)	Day 8 (Day 2 to Day 29)			Day 30 (Day 2 to 87)
Grade 3 nadir median (range)	Day 8.5 (Day 2 to Day 15)			Day 15 (Day 2 to 71)
Infections in Grade 2 cases, n (%)	2 of 6 (33.3%)			5 of 13 (38.5%)
Infections in Grade 3 cases, n (%)	0 (0%)			7 of 15 (46.7%)

Source: Table 17

Safety in special populations

The safety profile of avacopan has been studied only in adults to date. The majority of the subjects (94.5%) in the Phase II AAV studies were white. Safety of use of avacopan during pregnancy or breast-feeding has not been evaluated in humans.

Summaries of the safety profile by age, sex and renal function are provided in the tables below.

In the detailed summary of AEs by age category, events that occurred ≥2 subjects in either All Placebo or All avacopan groups were included.

Table 23: Summary of Adverse Event Profile by Age in Phase II Studies CL002_168 and CL003_168

	Age Group					
	<65 years		65-74 years		≥75 years	
Category	Prednisone Control N=22	All Avacopan N=51	Prednisone Control N=9	All Avacopan N=16	Prednisone Control N=5	All Avacopan N=6
Any treatment-emergent adverse event	20 (90.9%)	49 (96.1%)	9 (100.0%)	15 (93.8%)	5 (100.0%)	5 (83.3%)
Any treatment-emergent serious adverse event	4 (18.2%)	14 (27.5%)	2 (22.2%)	8 (50.0%)	2 (40.0%)	2 (33.3%)
Discontinuation of study drug due to adverse events	3 (13.6%)	4 (7.8%)	1 (11.1%)	3 (18.8%)	0 (0%)	1 (16.7%)

Source: Table 2.7.4.30

Table 24: Detailed Summary of Treatment-Emergent Adverse Events During the 168-day Study Period in by Age Group in Phase II studies (CL002_168 and CL003_168)

MedDRA Terms	**Age <65 number (percentage)**		**Age 65-74 number (percentage)**		**Age≥ 75-number (percentage)**	
	All Placebo n=22	All Avacopan n=51	All Placebo n=9	All Avacopan n=16	All Placebo n=5	All Avacopan n=6
Total AEs	20 (90.9%)	49 (96.1%) 9	9 (100%)	15 (93.8%)	5 (100%)	5 (83.3%)
Serious AEs – Total	4 (18.2%)	14 (27.5%)	2 (22.2%)	8 (50.0%)	(40.0%) 2	2 (33.3%)
- Fatal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- Hospitalization/prolong existing hospitalization	NA	NA	NA	NA	NA	NA
- Life-threatening	0 (0.0%)	1 (2.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)
- Disability/incapacity	Not presented	Not presented	Not presented	Not presented	Not presented	Not presented
- Other (medically significant)	NA	NA	NA	NA	NA	NA
AE leading to discontinued study medication	3 (13.6%)	4 (7.8%)	1 (11.1%)	3 (18.8%)	0 (0.0%)	1 (16.7%)
Psychiatric disorders	5 (22.7%)	7 (13.7%)	2 (22.2%)	2 (12.5%)	1 (20.0%)	2 (33.3%)
Nervous system disorders	9 (40.9%)	8 (15.7%)	2 (22.2%)	9 (56.3%)	2 (40.0%)	3 (50.0%)
Injury, poisoning and procedural complications	2 (9.1%)	7 (13.7%)	3 (33.3%)	1 (6.3%)	2 (40.0%)	1 (16.7%)
Cardiac disorders	0 (0.0%)	5 (9.8%)	1 (11.1%)	3 (18.8%)	1 (20.0%)	0 (0.0%)
Vascular disorders	5 (22.7%)	13 (25.5%)	2 (22.2%)	9 (56.3%)	3 (60.0%)	3 (50.0%)
Cerebrovascular disorders	Not presented	Not presented	Not presented	Not presented	Not presented	Not presented
Infections and infestations	8 (36.4%)	25 (49.0%)	5 (55.6%)	9 (56.3%)	2 (40.0%)	3 (50.0%)
Anticholinergic syndrome	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Quality of life decreased						
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	2 (9.1%)	2 (3.9%)	3 (33.3%)	4 (25%)	2 (40.0%)	2 (33.3%)

NA=Not Available (according to Applicant)
TEAE with frequency of ⩾ 2 in All Placebo or All avacopan presented
"Anti-cholinergic syndrome" Includes preferred term of "anticholinergic syndrome" and medical review of subject listings for occurrences of combination of preferred terms that could represent anticholingergic syndrome (e.g., anhidrosis, hyperthermia, pyrexia, blindness, blurred vision, delirium, hallucinations, urinary retention

Table 25: Summary of Adverse Event Profile by Sex in Phase II Studies CL002_168 and CL003_168

	Sex			
	Male		Female	
Category	Prednisone Control N=21	All Avacopan N=45	Prednisone Control N=15	All Avacopan N=28
Any treatment-emergent adverse event	19 (90.5%)	44 (97.8%)	15 (100.0%)	25 (89.3%)
Any treatment-emergent serious adverse event	4 (19.0%)	16 (35.6%)	4 (26.7%)	8 (28.6%)
Discontinuation of study drug due to adverse events	3 (14.3%)	6 (13.3%)	1 (6.7%)	2 (7.1%)

Source: Table 2.7.4.29

Table 26: Summary of Adverse Event Profile by Baseline Estimated Glomerular Filtration Rate in Phase II Studies CL002_168 and CL003_168

	Estimated Glomerular Filtration Rate			
	<60 mL/min/1.73 m^2		≥60 mL/min/1.73 m^2	
Category	Prednisone Control N=25	All Avacopan N=43	Prednisone Control N=10	All Avacopan N=30
Any treatment-emergent adverse event	24 (96.0%)	41 (95.3%)	10 (100.0%)	28 (93.3%)
Any treatment-emergent serious adverse event	6 (24.0%)	15 (34.9%)	2 (20.0%)	9 (30.0%)
Discontinuation of study drug due to adverse events	2 (8.0%)	5 (11.6%)	2 (20.0%)	3 (10.0%)

Source: Table 2.7.4.32

Immunological events

Not reported by the applicant. This is not a biological drug and issues with anti-drug antibodies are not foreseen.

Safety related to drug-drug interactions and other interactions

No pharmacodynamic drug interaction studies were reported.

The applicant considers that the risk of drug-drug interactions between avacopan and other concurrent medications in the intended patient population is considered low based on a series of biochemical studies conducted in vitro.

See pharmacokinetic section of this AR for more data on interactions.

Discontinuation due to AES

In study CL002_168, the number of subjects that discontinued study medication due to adverse events was: 1 (4.5%) subject in the avacopan+ reduced dose prednisone group (due to vasculitis), 3 (13.6%) subjects in the avacopan+ no prednisone group (reported to be due to renal impairment, hepatic enzyme increased, pancreatic enzymes increased and microscopic polyangiitis), and 2 (8.7%) subjects in the full dose comparator group (due to vasculitis and renal vasculitis).

In study CL003_168, the number of subjects that discontinued treatment due to an adverse event were 2 (15.4%) in the placebo group (due to maculopapular rash and gangrene respectively), 1 (7.7%) in the avacopan 10 mg group (due to abscess limb and perirectal abscess) and 3 (18.8%) in the avacopan 30 mg group (atrial fibrillation, sepsis and pain in leg, arm, abdomen, jaw)

Thus, in total, the number of subjects that discontinued study medication due to TEAES during the study period in the two phase studies was 8 (11.0%) in the all avacopan group and 4 (11.1%) in the comparator group.

3.3.9. Discussion on clinical safety

Avacopan is an orally administered small molecule antagonist of the complement 5a receptor (C5aR) that has been shown to concentration-dependently block effects of C5a which are believed to be important for the pathogenesis of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV). Both in healthy controls and in subjects with AAV, avacopan appears to decrease neutrophil count and in the latter group even more pronounced than current standard of care (see further comments below). Just as standard of care, avacopan treatment is associated with a decrease of MCP-1 which is considered a marker for renal inflammation. No clear changes were observed in the levels of five analysed complement fragments in avacopan-only treated patients which could, as the applicant put forwards, indicate that avacopan does not alter the production of alternative complement pathway components. The applicant specifically concludes that avacopan treatment does not affect the plasma sC5b-9 levels, which are needed to protect against encapsulated bacterial infections such as Neisseria meningitides and that this is in contrast to C5 inhibitors, such as eculizumab, which blocks the formation of C5b and therefore C5b-9. Moreover, the applicant states that no infections caused by Neisseria meningitidis were been observed in clinical trials with avacopan. However, the findings from the complement analysis are somewhat difficult to interpret, the clinical data is so far too limited to be reassuring, infections with encapsulated bacteria should thus be considered for inclusion as a safety concern in the RMP, see RMP sections of this AR.

Safety concerns related to infections in general and possibly also malignancies cannot be excluded in this application for a CMA, especially if avacopan is used during longer periods, beyond the 12 weeks stipulated by the current SmPC. Carcinogenicity studies in animals are lacking. It is noted that malignant melanoma and myelodysplastic syndrome is included in section 4.8 of the eculizumab SmPC (with the frequency rare). Clinical data for avacopan is so far limited (see discussion below). ***To handle the issue, the applicant proposes to include the term "Carcinogenicity" in the Summary of Safety Concerns (as missing information). This proposal is acceptable to the CHMP Rapporteur.***

It is noted that no thorough QT/QTc study appears to have been conducted but that the planned phase 3 study will include further ECG assessments and that no dedicated phase II dose finding study has been carried out. Instead, the selection of dose, not only for the phase 2 but also for the phase III study, appeared to have been based on data from the phase I study CL001_168, in which the level of C5aR blockade correlated strongly with avacopan plasma concentrations. Regarding the assessment of cardiovascular safety in the phase II studies, these studies included an ECG assessment at screening and day 29 in both studies and additional assessment at 85 in study CL 003_168. In study CL002_168, four subjects randomised to avacopan had ECG findings that were considered clinically significant by the investigators; for all but one subject the abnormalities were present before patients started treatment. In study CL003_168 there were two subjects with clinically significant ECG findings in the avacopan group; atrial fibrillation and sinus arrhythmia (+anterior infarct of undetermined origin). The importance of this is difficult to assess due to the limited amount of data available but does not cause any immediate concern. The current database of this CMA is small but from the total phase II data there seemed to be a slight imbalance in subjects with cardiac adverse events (a difference of two subjects) disfavouring avacopan compared to the comparator. Even though none of the events were reported as serious or related, this stresses the need to further characterize cardiovascular safety in a disease that itself carries a 65% increase in cardiovascular risk.

Total exposure from clinical trials is limited to exposure from 4 phase I clinical trials that included in 102 healthy volunteers, of which 89 received avacopan ≤5.5 days (and the rest probably received placebo although there is question regarding this group) and 2 Phase II clinical trials that included 109 AAV-patients of which 73 were randomised to receive avacopan. Of the enrolled AAV patients, 60 subjects received 30 mg avacopan twice daily (the dose currently proposed by the applicant) for 12 weeks and 13 subjects received 10 mg avacopan twice daily for 12 weeks i.e. there were no patients with long term safety data. The 12-week treatment period was in both phase II studies followed by a 12-week follow-up period. Both the very restricted number of AAV patients exposed and the complete lack of long-term safety data on AAV patients are considerable limitations of this application. This limitation was pointed out both in the Protocol Assistance July 2016 and the Follow-up Protocol Assistance Jan 2017. It was commented that a large part of the unmet medical need for the indication of interest (which is a prerequisite to demonstrate fulfilment of, for Conditional Approval), is the need for a steroid-sparing agent and that steroid-sparing is difficult to demonstrate unless long term follow-up of study patients is conducted. Moreover, the study duration and number of patients has to be large enough to assure that the overall safety profile is indeed clearly more favourable for the new drug compared to standard therapy with steroids. If for example, the new drug is associated with an increased number of infections or a new safety concern that outweighs its steroid-sparing effect, the unmet need cannot be said to be fulfilled. In this context, it was questioned whether the phase II safety data presented by the applicant would be sufficient. It was commented that data on the duration of remission and long-term safety data would be of importance.

The assessment of the overall safety profile of avacopan as it emerges from the conducted clinical trials is thus complicated by rather small number of included subjects -especially as two doses of

avacopan were tested in the phase II study-and the relatively short study durations. Moreover, the background treatment in the avacopan group varied between and within the studies. Patients in the control groups of both the phase II studies (n = 36; n=23 in study CL002_168 and n=13 in study CL003_168) received SOC treatment (placebo plus a full starting dose of 60 mg prednisone tapered over 20 weeks to discontinuation + either cyclophosphamide→ azathioprine or rituximab). In study CL003_168 (conducted in US and Canada), patients in the active group received either 10 mg x 2 (n=13) or 30 mg x2 (n=16) avacopan on top of SOC. In contrast, in study CL002_168 (conducted in Europe), patients in the active group received 30 mg avacopan on top of reduced SOC; either a reduced starting dose of 20 mg prednisone per day discontinued after 14 weeks + cyclophosphamide→ azathioprine /rituximab (n = 22 subjects) or no prednisone+ cyclophosphamide→ azathioprine /rituximab (n = 22). Thus, in CL003_168, two doses of avacopan are compared to placebo and the comparison is carried out on top of SOC. Consequently, the difference in safety profile between the avacopan and the comparator group in study CL003_168 would be expected to be more or less completely attributable to the avacopan drug in itself. A limitation is that the interpretation could be obscured by an overall expected large number of AEs overall in this severely ill population with heavy background medication. CL0002_168 is instead a comparison between two concepts; SOC or SOC with reduced steroid dose but with added avacopan. The safety question in this trial is thus whether it is more or less favourable from a safety perspective to receive an extra 60-30 mg prednisone as starting dose (gradually tapered down during 20 weeks or 14 weeks respectively) in induction therapy for AAV compared to receiving avacopan (during 12 weeks). Especially, the comparison between SOC (including high dose steroids) and SOC without any steroids but with 30 mgx2 avacopan is of interest as this is the comparison between the existing routine treatment and avacopan treatment as proposed in the current PI. It should be noted that one would expect this comparison to be favour of avacopan to fulfil the unmet need as stipulated in the criteria for conditional approval. In conclusion, there is a very limited material (subjects exposed) available for assessment of a rather extensive set of interesting safety aspects of this new drug; 1) the effect of dose (10mgx2/30 mgx2), 2) the safety profile of the drug vs placebo when compared on top of SOC, 3) the safety profile of the drug as compared to +30 mg prednisolone on top of rituximab/cyclophosphamide and 4) the safety profile of the drug as compared to +60 mg prednisolone on top of rituximab/ cyclophosphamide. For the current application, the last aspect is of most interest since it concerns the comparison between the safety profile of avacopan prescribed in line with the proposed PI (without corticosteroids) compared to current SOC. However, it should be noted that in even in the avacopan+ no prednisone group, a substantial proportion of subjects were also using non-study supplied glucocorticoids.

When healthy controls were given avacopan in the phase I studies (n=89) or placebo (n=14), there were no serious adverse events. The proportion of subjects with any treatment-emergent event was 62.9% in the avacopan group and 42.9% in the placebo group. Headache, GI symptoms and infections were reported.

When two doses of avacopan were compared to placebo on top of SOC in patients with acute vasculitis in study CL003_168, practically all patients had at least one TEAE. The number of serious adverse events, infections and adverse events that could be associated with corticosteroid use is of special interest and some observations and comments on the data from study CL003_168 are presented below.

> At least 1 serious TEAE during the 84-day treatment period was reported in 2 (15.4%) subjects in the avacopan 10 mg group (neutropenia and cellulitis staphylococcal respectively) and 3 (18.8%) subjects in the avacopan 30 mg group (atrial fibrillation, sepsis and urinary tract infection) compared to 2 (15.4%) subjects the placebo group (methemoglobinemia and gangrene). Following the 84-day treatment period, serious events of renal failure and

infections were reported among patients randomized to avacopan while events of bronchiolitis and nephrolithiasis were reported in the placebo group. During the whole CL003_168 study period, 2 of the 13 subjects in the avacopan 10 mg group (15%), 4 of the 16 subjects in the avacopan 30 mg (25%) and 3 of the 13 subjects in the placebo group (23%) had a serious TEAE. Thus, although the numbers in each of the groups were low, the proportion of subjects in each group that experienced serious adverse events appeared overall roughly comparable.

The number of subjects with at least one treatment-emergent infection during the 168 day study period was 5 (38.5%) in the avacopan 10 mg group, 6 (37.5%) in the avacopan 30 mg group and 4 (30.8%) in the placebo group while the corresponding figures for serious treatment-emergent infections were 1 (7.7%), 2 (12.5%) and 2 (15.4%). Thus, although the frequency of subjects with infections was somewhat higher in the avacopan groups, overall the number of subjects with infections and serious infections appeared comparable between the groups with the important limitation that the each of the groups included a very limited number of individuals.

Only a few individuals in each group discontinued due to adverse events.

The majority of subjects in all three groups had adverse events that were assessed as possibly related to corticosteroid use which is not surprising given that all three groups received the same SOC treatment that included relatively high doses of steroids. The applicant also reported the number of subjects with at least 1 treatment emergent "adverse *effect*" possibly associated with glucocorticoid use during the 84-day treatment period; 7 (53.8%) subjects in the avacopan 10 mg group and 11 (68.8%) subjects in the avacopan 30 mg group, compared to 5 (38.5%) subjects in the placebo group. A few new subjects with "treatment-emergent adverse effects" possibly associated with glucocorticoid use, were added during the 84 day follow-up period.

The safety profile of three different treatment strategies were compared in CL002_168 and thus an extra 60 or 30 mg prednisone as starting dose (tapered down during 20 weeks or 14 weeks respectively) was indirectly compared to receiving avacopan (12 weeks) on top of rituximab → azathioprine /cyclophosphamide. Regarding the three comparisons, the comparator group corresponds to standard of care and the avacopan + no steroid group corresponds to the posology of the current application. The frequency of subjects with at least one TEAE was around 90% in all three treatment groups both during the 84 day treatment period and the 168 day study period. The numbers of serious adverse events, infections and adverse events that could be associated with corticosteroid use are of special interest and some observations and comments on the data from study CL002_168 are presented below.

At least 1 serious TEAE during the 84-day treatment period was reported in 3 (13.6%) subjects in the avacopan+ reduced dose prednisone group and 8 (36.4%) subjects in the avacopan+ no prednisone group compared to 4 (17.4%) subjects in the comparator group. In total, during the whole 168 day study period, the number of subjects with serious TEAEs were 8 (36.4%) in the avacopan + reduced dose prednisone group and 10 (45.5%) in the avacopan+ no prednisone group compared to 5 (21.7%) in the comparator group. Serious events reported in the avacopan groups included: vasculitis, musculoskeletal chest pain, haematuria, infections, renal impairment, hepatic and pancreatic enzymes increased, rash, pleurisy and ocular hyperaemia. Serious events reported in the comparator group included infections, dehydration, vasculitis and back pain and lumbar vertebral fracture. Thus, although the reported TEAEs, including the serious TEAEs, appeared to be a mix of true AEs and signs/symptoms related to the underlying conditions that obscures the interpretation of these safety results, the number

of subjects with any serious TEAE appeared somewhat higher in the avacopan groups, especially in the group that was not treated with steroids.

At least 1 treatment-emergent infection during the 84-day treatment period was reported in 10 (45.5%) subjects in the avacopan + reduced dose prednisone group and 12 (54.5%) subjects in the avacopan+ no prednisone group compared to 9 (39.1%) subjects in the comparator group. During the overall 168-day study period, the number of subjects with any treatment-emergent infections in the 168-day study period was 14 (63.6%) in the avacopan+ reduced dose prednisone group and 12 (54.5%) in the avacopan+no prednisone group and 11 (47.8%) in the comparator group. There were 2 subjects with serious treatment-emergent infections in each of the avacopan groups (9.1%) and 1 (4.3%) in the comparator group during the 168 day study period. Thus, also for the comparison regarding infections, the numbers are small, but there seemed to be a trend disfavouring the avacopan groups when compared to the comparator group.

The number of subjects that discontinued study medication due to TEAE was: one in the avacopan+ reduced dose prednisone group (due to vasculitis), 3 the avacopan+ no Prednisone group (reported to be due to renal impairment, hepatic enzyme increased, pancreatic enzymes increased and microscopic polyangiitis), and 2 in the comparator group (due to vasculitis and renal vasculitis).

At least 1 TEAE assessed as possibly related to glucocorticoid use during the 84-day treatment period was reported in 11 (50.0%) subjects in the avacopan + reduced dose prednisone group and 8 (36.4%) subjects in the avacopan +no Prednisone group), compared to 13 (56.5%) subjects the comparator group. Only GI-disorders and vascular disorders were reported as TEAEs assessed as Possibly Related to Glucocorticoid Use in ≥5% of Subjects in the all avacopan group or comparator based on preferred Term. During the follow-up period, a few more subjects reported these TEAEs.

The applicant also reported that at least 1 treatment-emergent "adverse *effect* possibly associated with glucocorticoid use" during the 84-day treatment period was reported in 4 (18.2%) subjects in the avacopan + reduced dose prednisone group and 11 (50.0%) subjects in the avacopan+no Prednisone group), compared to 15 (65.2%) subjects with the comparator group. During the 84 day-follow up, 6 more subjects in the avacopan+ reduced dose prednisone group had any treatment-emergent adverse effect while the numbers were the same in the other two groups. The differences were mainly seen regarding the number subjects reporting of psychiatric disorders.

Thus, both for adverse events and adverse effects assessed as possibly related to steroids, the differences between the groups were small. Moreover, the reported difference in adverse effects could be driven by psychiatric disorders and is of unclear clinical significance. Overall, the small sample size renders the comparisons susceptible to chance.

Regarding vital signs and physical findings, it is noted that in study CL002_168 in which patients in the avacopan group received no corticosteroids or a reduced dose compared to the control group, there were slight differences between the two groups regarding the mean changes in BMI/weight and blood pressure throughout the study. These changes were in favour of avacopan. This pattern was not replicated in study CL003_168 in which patients received avacopan on top of full dose steroids. The metabolic finding in CL002_168 study, potentially in favour of avacopan use, was modest and not reflected in the number of subjects in each group in study CL002_168 that experienced new/worsening of hypertension as an adverse effect (on the contrary hypertension was reported more frequently in

the avacopan group than in the control group and thus could be considered to be included among the ADRs). Nonetheless, this observation could be regarded as some support for the benefit of steroid sparing associated with avacopan.

Regarding laboratory findings, it is noted that the mean CK value increased in the avacopan group in study CL002_168 but not in the comparator group. In study CL003_168, CK increased in both the avacopan group and the comparator group but markedly more in the avacopan group. Even though the mean value at the end of treatment period was still within the normal range for both treatment groups in both studies, the observation is of interest. Especially, as it is also noted that adverse events of elevated CK were somewhat more frequent in the avacopan groups than the comparator groups in the phase II studies. There were two grade 3 CK elevations in two patients randomised to avacopan, but none in patients in the comparator group. In one of these patients, the CK returned to normal with no interruption of avacopan treatment and this subject had an adverse event of mild muscle spasms in the same timeframe as the CK elevation. In the other patient, the elevated CK value persisted until the end of the 12-week follow-up period, while not taking any avacopan and this subject had an adverse event of mild musculoskeletal pain in the same timeframe as the CK elevation. *In response to the first LoQ, the applicant was asked to provide all data available on creatine phosphokinase levels in avocapan studies, including phase 1 study data and comparative data between avacopan alone versus high dose prednisone, and elucidate the reasons and the potential risk of the elevated CK levels. Regarding the phase I studies, plausibility of the relatively modest CK elevation caused by physical exertion such as catching a train by running or carrying a heavy box remains weak. In the phase II studies, modest or significant CK elevations took place in 3 patients not receiving avacopan (associated with muscle spasms in 1 patient) and 15 patients receiving avacopan (associated with muscle spasms or muscle pain in 4 patients). These findings do not support the conclusion of the Applicant on the lacking safety risk of avacopan for CK elevation and consequences. Preliminary data from the phase III study show 14 post-baseline moderate to severe CK-elevations so far, also leading to one discontinuation.* Whilst it is acknowledged that the study was blinded, this does not allow to give leeway on the current conclusions based on the provided partial Phase III dataset. *No cases have, according to the applicant, so far been associated with rhabdomyolysis or cardiac adverse events.*

CK increases in this application for CMA are included in section 4.8 of the SmPC which is considered acceptable to the CHMP Rapporteurs (please refer to separate SmPC document for specific SmPC comments). However, clinical conditions associated with CK-elevations are also proposed to be included in the RMP, see later sections of this AR.

In study CL002_168, the WBC count decreased in the two avacopan groups within days after starting avacopan treatment and then subsequently levelled off. The mean decrease in WBC count over the course of the study was more prominent in the avacopan group than the comparator group but the mean value was not below the lower limit of normal at any time point. A similar pattern was seen for the neutrophil and lymphocyte count. The decrease of WBC, neutrophils and lymphocytes was most pronounced in the avacopan+ no prednisone group, followed by avacopan+ reduced dose prednisone group and comparator group. Also in study CL003_168, the mean decrease in WBC, neutrophil and lymphocyte count were more pronounced in the avacopan group than the placebo group but the mean count at the end of the treatment period was within the normal range. Grade 3 lymphocyte abnormalities were more frequent in the avacopan groups compared to the comparator groups in the phase II studies. For approximately half of the avacopan treated subjects that had grade 3 lymphocytopenia, infections were reported; this frequency is similar to the frequency of infections reported in the overall group of avacopan treated subjects. The decrease in lymphocyte count typically occurred within the first 2 weeks of treatment. This may reflect the anti-inflammatory effect of avacopan. For the interpretation of these data, it also has to be remembered that all patients in the

phase 2 studies received either cyclophosphamide or rituximab, two drugs that often affect WBC/leucocyte count (including number of neutrophils and lymphocytes). Not only lymphocyte count decreased should be included in the SmPC but also neutrophil count decreased/WBC count decreased. Recommendation for monitoring should address why, when and how the monitoring should be conducted in clinical practice, and justification should be provided for the proposed updated recommendation. The SmPC still requires some further revisions with regards to these issues; please refer to comments in separate SmPC document. *In particular, the timing of blood counts has to be justified.* LoQ Finally, it is considered that the phase III data, once available, will be of utmost importance for a reliable characterization the new drug's effect on WBC, neutrophil and lymphocyte count.

Elevations in liver tests appeared to occur more often among avacopan treated subjects than in the comparator groups in the phase II studies; information is included in the SmPC which is endorsed**.** The number of reported hepatobiliary AEs and SAEs is small. But taking into account the small study populations, the hepatobiliary safety of avacopan cannot be fully assessed and would require additional analysis from phase III data. With sufficient precautionary measures (e.g., monitoring the hepatobiliary laboratory parameters and avoiding concomitant hepatotoxic treatments) the safety could however be improved in this respect. *The timing of monitoring of elevation of liver enzymes (i.e., prior to initiating the treatment with Vynpenta, two weeks after initiation of treatment, monthly thereafter) needs to be further justified. LoQ The RMP-wording related to this issue is assessed in the RMP-sections of this AR (see later sections of this AR).*

Regarding the pooled analysis of the two phase II studies, these are difficult to interpret as the background treatment in the avacaopan groups is not uniform and neither is the avacopan dose. That being said some reflections are made and commented below.

> At least one TEAE is reported for almost all patients during the 24-week time period irrespectively of treatment group. The frequency of discontinuations due to TEAEs is similar between the groups.
>
> The number of subjects with serious TEAEs is numerically higher in the avacopan groups. Most SAEs in the avacopan group were reported in one subject only, except for Respiratory tract infection (3 subjects), Renal impairment (2 subjects), Vasculitis (4 subjects) and C-reactive protein increased (2 subjects). In the control group each SAE was reported only once. SAEs related to the SOC "Renal and urinary disorders" were reported in 5 avacopan-treated patients and include two cases of Renal impairment and one Renal failure. No clear differences between the treatment groups can be seen among the most common TEAEs related to Renal and urinary disorders. *The number of urinary system SAEs appears low and there is no significant difference between three treatment groups in this respect. In the data presented so far, there are no changes in the creatinine clearance in any of the study groups.*
>
> *There have been no cases of newly onset vasculitis during the phase II studies. Vasculitis related adverse events have been reported from similar number of patients from all three treatment groups in study CL002_168.*
>
> Infections and GI-events appeared more frequent in the avacopan treated groups compared to the comparator groups; these events are considered by the applicant as adverse drug reactions and included in section 4.8 of the SmPC. *It is noted that in this application for CMA the incidences of both serious and all infections increase in the treatment groups in following order: standard prednisone, avacopan + low dose prednisone, avacopan without prednisone. The number of serious infections is small, but the analysis based on the submitted dataset*

(final data from the phase 3 study report missing) appears clear and consistent. . Cardiac adverse events seemed to be somewhat more frequent among avacopan-treated than among AAV-patients that did not receive avacopan in the phase II studies. The small patient population exposed to avacopan during a very limited time period and the fact that patients with symptomatic congestive heart failure/clinically significant cardiovascular disease were excluded from these studies influences the reliability of the results. It is however considered that this is potential safety concern that needs to be further characterized and it is thus requested to be included in the summary of safety concerns, see later sections of this AR.

A dose-dependent increase could be observed for several AEs in the phase II studies (higher frequencies in the 30 mg group compared to the all avacopan group).

During the 24-week study period of the two phase II studies, there were in total 2 subjects with TEAEs in the SOC Neoplasms benign, malignant and unspecified (including cysts and polyps) in the comparator group (5.6%) and 2 in total among the avacopan treated subjects (2.7%). Given the total exposure and especially the short follow-up, the data cannot be considered reassuring, especially as use beyond 12 weeks is foreseen in clinical practice- despite the currently proposed label, and the fact the carcinogenicity studies in animals are lacking. *To handle the issue, the applicant proposes to include the term "Carcinogenicity" in the Summary of Safety Concerns, this proposal is acceptable is acceptable to the CHMP Rapporteur.*

Regarding AE profile summarized according to age, sex and GFR, it is agreed with the applicant that there was no clear pattern although the analysis is considerably hampered by the low number of individuals in the different categories.

It was stated by the applicant that safety of use of avacopan during pregnancy or breast-feeding has not been evaluated in humans; this is reflected in the SmPC. For further discussion on the implication on this for the RMP, see following sections.

In response to the RSI, the applicant was requested to provide an overall integrated discussion on the safety of avacopan alone (with no prednisone) compared to the high dose prednisone group, taking also into account patients that were using non-study supplied glucocorticoids in the avacopan alone group. It can specifically be concluded that overall, avacopan alone, without prednisone, increases infections and lymphopenia, that these are appropriately described in the SmPC 4.8 and finally that there is no evidence to conclude on any therapeutic advantage over corticosteroids on safety grounds based on these provided responses.

The Applicant is also asked to provide a summary of ADRs for which a causal relationship between avacopan and the adverse event is at least a reasonable possibility, as the current categorization of the TEAEs as ADRs is not fully endorsed.

Additional expert consultation

Not applicable.

Assessment of paediatric data on clinical safety

Not applicable.

3.3.10. Conclusions on clinical safety

With this application, a conditional approval for induction treatment of acute vasculitis based on only phase I and phase II clinical data, is sought for avacopan, a new drug that targets the complement 5

receptor and selectively blocks the interaction between C5aR and the anaphylatoxin C5a, thereby reducing the pro-inflammatory effects of C5a. Considering its mode of action and especially as avacopan, according to the proposed indication, is to be given in combination with cyclophosphamide and rituximab (although not with steroids), infections; and potentially infections with encapsulated bacteria, are considered safety concerns. Theoretically one could also expect other safety concerns associated with sustained immunosuppression such as malignancies. These issues are in this application for CMA considered necessary for inclusion as safety concerns in the RMP. Patient exposure to avacopan in the completed clinical studies are too limited to exclude the risk of malignancies. Animal carcinogenicity studies are ongoing to provide further information on a potential long-term risk. Based on the results of the Study CL007_168 it is agreed with the applicant that the QT data, that has now been submitted, do not cause any specific concerns but it is considered that the planned phase 3 study is needed to more reliably assess the risk.

Cardiac safety is overall not sufficiently characterized in this application for CMA by the limited available data and moreover additional data on this in relation to the observed CK elevations are warranted, thus these issues should be considered for inclusion as safety concerns in the RMP. See further comments on the RMP in the following sections of this AR.

In total, the safety population includes only 73 AAV patients randomised to avacopan and of those 60 patients were exposed to the dose currently proposed by the applicant. Only 22 patients received avacopan alone with no prednisone. Patients were exposed to the drug for only 12 weeks with an additional 12 week off-drug follow-up i.e. there are no long-term safety data.

When two doses of avacopan were compared to placebo on top of SOC in patients with acute vasculitis in study CL003_168, practically all patients had at least one TEAE and more than half of the subjects in all three groups had adverse events that were assessed as possibly related to corticosteroid use. This latter is not surprising given that all three groups received the same SOC treatment that included relatively high doses of steroids. The proportion of subjects in each group that experienced serious adverse events and the number of infections and serious infections appeared roughly comparable between the groups with the important limitation that the each of the groups included a very limited number of individuals.

When the safety profile of three different treatment strategies for acute vasculitis were compared in CL002_168, of which the comparator group corresponds to standard of care and the avacopan + no steroid group corresponds to the posology of the current application, again almost all patients had at least one TEAE. Although the reported TEAEs, including the serious TEAEs, appeared to be a mix of true adverse events and signs/symptoms related to the underlying conditions which together with the small sample size makes the interpretation of the safety results difficult, the number of subjects with serious TEAEs appeared somewhat higher in the avacopan groups, at least in the group that was not treated with steroids. Also for the comparison regarding infections, there seemed to be a trend disfavouring the avacopan groups when compared to the full dose steroid group. This imbalance between the Avacopan group and steroid group, with regard to infections, appeared to be driven by mild nasopharyngitis and viral upper respiratory tract infections. Regarding adverse events and adverse *effects* assessed as possibly related to steroids, the differences between the groups were small and when clear differences in favour of avacopan were noted, it appeared to be driven by psychiatric disorders.

Relevant safety issues identified in the submitted data for avacopan, are related to infections, decreased lymphocyte count, increase in liver function tests and increased CK levels. These events of interest are being monitored in ongoing studies.

For conditional approval of the drug, the benefit-risk balance has to be demonstrated to be positive but the applicant also show that an unmet need will be addressed (i.e. that the product will provide major therapeutic advantage over the authorised methods) and that the benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. As previously pointed out in Protocol Assistance, it is questionable that the very limited clinical data available from the phase II would be sufficient to address these issues, regardless of how convincing they were to be.

Regarding the requirement to demonstrate positive benefit-risk, the low total number of patients exposed to avacopan (73, out of which 60 patients were exposed to the dose currently proposed dose) and the fact that none was exposed to more than 12 weeks treatment or followed for more than 24 weeks seem to preclude a reliable risk assessment.

Regarding the major therapeutic advantage over the authorized methods and whether the immediate availability can be said to outweigh the risks inherent in the fact that additional data are still required i.e. two requirements for conditional approval, it is agreed that the steroid-sparing potential of this drug may potentially confer patient benefits as compared to standard of care treatment for acute vasculitis. No advantage in efficacy compared to authorized methods is expected but a safety benefit is hoped for. However, this is not indisputably demonstrated by the limited phase II data (in fact, as there was rather a trend for more serious adverse events and infections in subjects treated with avacopan 30 mg x2 without steroids as compared to standard of care data from the phase 3 clinical trial would be of critical importance for the assessment. In addition, and more important, even if the short time safety profile of avacopan as emerged from the data that can be extracted from the now presented phase II studies, was to appear more favourable than the safety profile of standard of care, it would still be very questionable if an overall safety benefit of avacopan over authorized methods could be claimed without any long-term data. In summary, a safety advantage over established treatment (including steroids that are authorized for systemic vasculitis) has not been demonstrated and thus the benefits to public health of the immediate availability of the drug cannot be said to outweigh the risks inherent in the fact that additional data are still required unless an efficacy benefit for avacopan over existing therapies is demonstrated.

3.4. Risk management plan

3.4.1. Safety Specification

The ***applicant's initial*** proposal for summary of safety concerns

Initially, the applicant proposed the following summary of safety concerns in the RMP:

Table 27: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Infections
Important potential risks	None
Missing information	• Long-term use • Paediatric population • Pregnancy

Summary of safety concerns	
	• Women who are breastfeeding • Women of childbearing potential • Patients with hepatic impairment • Patients on renal dialysis • Patients with severe disease

The ***CHMP's*** comments on the proposed summary of safety concerns in the ***first round*** (LoQ) were**:**

The following items were proposed, by the applicant, to be missing information and agreed by the CHMP:

1. Patients with severe disease, rationale: treatment of (at least some of) these patients must be considered "on label" according to the currently proposed indication, use in this patient population can be anticipated but as these patients were excluded from the clinical trials it is not known whether use in this very ill patient population is associated with increased risks. As it is not unlikely that such use is associated with significantly increased risks, the issue should be further evaluated. However, the applicant should discuss whether this safety concern can be better defined.

2. Patients with hepatic impairment, rationale: patients with evidence of hepatic disease were excluded from the clinical trials (i.e. there is a lack of data), increases in hepatic enzymes were noted in the clinical studies and there is no firm contraindication against use in patients with hepatic impairment (although recommendations and warnings/precautions are included in SmPC section 4.2 and 4.4 respectively). A hepatic impairment study is planned.

3. Long-term use, rationale: according to the currently proposed SmPC, the duration of a dosing cycle is 12 weeks (which corresponds to the duration of the treatment period in the clinical trials). However, it is not unlikely that avacopan, should it be approved, will be used for a longer time period and such use has not at all been characterised due to the very limited data available.

The following items were proposed, by the applicant, to be missing information and but are not considered by the CHMP to be missing information:

1. Pregnancy, rationale: Although data is missing, the risks to pregnancy of the concomitant medication (included in the currently proposed 4.1-wording) make it unlikely that avacopan will be prescribed to patients at risk of being pregnant. A need for precautions in addition to the precautions that the concomitant medication warrants and the SmPC for avacopan confers, is not foreseen neither is it likely that a clinical study to address the issue is feasible.

2. Women of childbearing potential, rationale: see rationale for pregnancy.

3. Women who are breastfeeding, rationale: see rationale for pregnancy and women of childbearing potential.

4. Paediatric population, rationale; use in the paediatric population is off-label according to the proposed indication. AAV is very infrequent in children so although theoretically one could expect a use in this population, in practice this use is expected to very seldom occur.

6. Patients on renal dialysis, rationale: the SmPC specifically advice against use in patients on dialysis and it is not very likely that patients on dialysis will be treated with avacopan, it could happen in the

scenario of a severe, rapidly progressing AAV but this is considered covered by the item "Patients with severe disease" (see above).

The following items were not proposed by the applicant to be an important potential risk but are considered by the CHMP to be an important potential risk:

1. Malignancies, rationale: given that avacopan through its mechanism of action (immune-modulator/suppressor) could potentially be associated with malignancies, that reassuring data is at the moment scarce (patients with current/history of malignancies were excluded from the clinical trials, there are no long term data whatsoever for any AAV patients and the nonclinical carcinogenicity studies are not completed, see comments in non-clinical parts of the AR) and that use beyond 12 weeks is not considered unlikely, this risk needs to be further evaluated and characterized as it could potentially have an impact on the benefit-risk balance.

2. Infections with encapsulated bacteria, rationale; given that avacopan's mode of action it's influence on complements a potential increased risk for infections with encapsulated bacteria, the potentially severe consequences for the individual patients and that the clinical experience with avacopan so far generated from the clinical trials could be too limited to detect this safety concern, it is considered an important potential risk that needs to be further characterized and could influence the benefit-risk balance.3. Cardiovascular safety, rationale: cardiac adverse events appeared numerically more frequent among avacopan-treated AAV-patients than among AAV-patients that did not receive avacopan in the data from the phase II trials. The small patient population exposed to avacopan during a very limited time period and the fact that patients with symptomatic congestive heart failure/clinically significant cardiovascular disease were excluded from these studies affects the reliability of the results. It is however considered that this is potential safety concern that needs to be further characterized as it could influence the benefit risk balance of this new drug.

4. Clinical conditions associated with elevated CK such as rhabdomyolysis, cardiac disorders and myositis, rationale: given that avacopan-treatment was associated with elevated CK in the phase 2 studies but that the exposure gained from these studies (small number of patients, short study duration) was very limited and thus also the number of events, this potential risk needs to be further characterized. Frequency and reversibility of CK elevations during avacopan treatment should be further characterized and most importantly, it needs to be evaluated to what extent these CK elevations are associated with clinical symptoms and conditions.

The following items were proposed by the applicant as important identified risk and agreed by the CHMP:

1. Infections (in general), rationale: the findings in the clinical studies, the potential consequences for the individual patients, this is an important identified risk,(Phase III data missing) information about the risk is included in the product information but the magnitude of the risk should be further evaluated as it could be important for the benefit risk balance. It should also be further evaluated what role the decreases in WBC, neutrophil and lymphocyte count that have been observed during Avacopan treatment, play when it comes to the risks for infections.

The ***CHMP's*** additional comments on the proposed safety specification in the ***first round*** were**:**

In addition to the comments to the summary of safety concerns, revisions of the safety specification regarding the description of the following issues are needed:

Epidemiology:

The following sentence should be deleted since it does not concern the applied indication: *"An early study in patients with polyarteritis nodosa showed early efficacy, with 95% of patients receiving cortisone surviving at 3 months compared to 73% in untreated patients (Pickering et al., 1960). However, after 3 years, there was no difference in survival between groups, likely due to the toxicity of chronic glucocorticoid use, including peptic ulceration, fractures, and hypertension-related adverse events."*

The following sentence should be deleted unless further justified i.e. supported by scientific data: *"Patients with GPA and MPA appear to be more sensitive to the detrimental effects of glucocorticoids compared to patients with other auto-immune diseases such as rheumatoid arthritis."*

Populations not studied in clinical trials:

The reasoning regarding data on patients with a history of cancer, stated to be missing information but still not included in the summary of safety concern as missing information needs to be revised in order to provide consistency throughout the text.

Potential for harm from overdose, transmission of infectious agents, medication errors and off-label use:

The applicant's view on these issues is absent in the relevant sections of the RMP and should be included.

The applicant's current proposal for summary of safety concerns (in second round of the procedure):

Summary of safety concerns	
Important identified risks	• Infections
Important potential risks	• Hepatic transaminases (ALT/AST) increase
Missing information	• Carcinogenicity • Long-term use • Patients with severe hepatic impairment • Use in patients with severe vasculitis (e.g. rapidly progressive glomerulonephritis, alveolar hemorrhage, hemoptysis, rapid-onset mononeuritis multiplex, or central nervous system involvement)

The CHMP's comments on the proposed summary of safety concerns in this application for a CMA (in the second round) LoQ:

The following issues remain regarding the Summary of Safety Concerns: 1) "Clinical conditions associated with elevated CK such as rhabdomyolysis, cardiac disorders and myositis" and "Cardiovascular Safety" should be included in the Summary of Safety Concerns (as important potential risks), 2 "Hepatic transaminase (ALT/AST) increase" should be re-worded to reflect the clinic concern, 3) "Patients with severe vasculitis (e.g. rapidly progressive glomerulonephritis, alveolar hemorrhage, hemoptysis, rapid-onset mononeuritis multiplex, or central nervous system involvement)" should be re-worded to "Patients with rapidly progressive glomerulonephritis, alveolar hemorrhage, hemoptysis, rapid-onset mononeuritis multiplex, or central nervous system involvement" and 4) The applicant's

view on the potential for harm from overdose, transmission of infectious agents, medication errors and off label use should be included in Module SVI in the Safety Specification.

Further, the applicant is requested to re-consider including the risk "Infections with encapsulated bacteria" in the RMP or provide an Expert Overview summarizing available data regarding C5-R blockade and the potential risk for infections with encapsulated bacteria, in particular Neisseria meningitides. The Overview should include references to relevant published literature. (LoQ)

3.4.2. Pharmacovigilance Plan (PRAC Rapporteur's assessment second round)

The RMP versions 1.1 dated 9 October 2018 is under assessment.

Routine pharmacovigilance activities

All safety information will continue to be monitored in accordance to Good Pharmacovigilance practices including regular review and evaluation of data. No specific adverse reaction follow-up questionnaires have been proposed.

Summary of additional PhV activities

Table Part III.3: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None.				
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				
None.				
Category 3 - Required additional pharmacovigilance activities				
Carcinogenicity	To determine the effects of avacopan, on the incidence and morphology of tumours in rats and hamsters	Carcinogenicity potential of avacopan in rats and hamsters	Study start	July 2017
			Study finish	
			Final study report	

The pharmacovigilance plan should be updated to reflect the amendments requested to the safety specification (see assessment of Q147). The Applicant should discuss appropriate (additional) pharmacovigilance activities for each of the (newly added) safety concerns, especially since very limited data has been available from clinical trials. **LoQ**

Feasibility of using EU disease registries

The Applicant discussed the need and feasibility of collecting data in the post-marketing setting. The Applicant described their ongoing initiatives to collaborate with European Vasculitis Study Group (EUVAS) and European Network on Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases Network (ERN RITA) to link existing disease registries from seven EU countries to further study the safety profile of avacopan in the post-marketing setting. These initiatives to set up a collaborative approach in EU are supported but at the moment only limited information could be

provided by the Applicant, and more information is necessary for a careful assessment of this possible PASS. From the information provided by the Applicant it remains unclear which safety concerns will possibly be further studied with the EU Register study and no study has been included in the pharmacovigilance plan. In addition, the applicant is not able to provide any timelines for harmonized data collection for such a study.

Considering the very limited safety information available for avacopan, there is a need for further additional pharmacovigilance activities in the post-marketing setting which should be reflected in the pharmacovigilance plan. In addition, further information about the collaborative approach with EUVAS and ERN RITA and the possible EU registry study should be provided. The Applicant should address the topics as listed in **LoQ.**

Other PASS

The Phase I Pharmacokinetic study in hepatic impaired patients (CL013_168) that was included as additional pharmacovigilance activity with previous assessment round (D94 PRAC Rap AR) has been completed, and therefore removed as ongoing or planned study from the pharmacovigilance plan in RMP version 1.1. , *please refer to the pharmacokinetic sections for the assessment of data from this study.* It should be noted that this study did not include patients with severe hepatic impairment. The safety concern "patients with severe hepatic impairment" remains included as an area of missing information, the Applicant should discuss how data on the safety in this population will be obtained.

Further, the Applicant is requested to use "carcinogenicity" in Table Part III.3, in line with summary of safety concerns and remove "Carcinogenicity potential of avacopan in rats and hamsters".

Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is not sufficient to identify and characterise the risks of the product. The pharmacovigilance plan should be updated to reflect the amendments requested to the safety specification. The Applicant should discuss appropriate (additional) pharmacovigilance activities for each of the (newly added) safety concerns.

Apart from the carcinogenicity study, no additional pharmacovigilance activities have been proposed by the Applicant for the safety concerns listed in the RMP version 1.1. Since other important potential risks to be included in the RMP ("Clinical conditions associated with elevated CK such as rhabdomyolysis, cardiac disorders and myositis", "Cardiovascular Safety" and "liver toxicity") and areas of missing information (long term safety) also require further evaluation during the post-marketing setting, the Applicant should provide further details about the collaborative approach with EUVAS and ERN RITA and the possible EU registry study to ensure that it will provide meaningful information about the safety concerns of interest.

3.4.3 Plans for post-authorisation efficacy studies (PRAC Rapporteur's assessment second round)

Summary of Post authorisation efficacy development plan

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
A Randomized, Double-Blind, Active-Controlled, Phase III 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 CL010_168	The primary objective is to evaluate the efficacy of CCX168 (avacopan) to induce and sustain remission in patients with active anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), when used in combination with cyclophosphamide followed by azathioprine, or when used in combination with rituximab. For a list of secondary objectives, refer to CL010_168.	Longer term efficacy of Avacopan-ChemoCentryx in patients with AAV.	1. Protocol submission	December 2016
			2. Study (enrolment) start	March 2017
			3. Study finish	
			4. Final study report	
			Blinded interim Phase III study results reported at the 120-day clock stop of conditional marketing authorisation application review.	October 2018

3.4.4 Risk minimisation measures (PRAC Rapporteur's assessment second round)

Summary of additional risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		
Infections	Routine risk minimisation measures: SmPC section 4.2, 4.4 and 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: Information regarding complete blood cell count	None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	monitoring is included in SmPC Section 4.2 and 4.4 Information regarding detection of signs and symptoms of infection is included in SmPC Section 4.4 Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medication. Treatment with Vynpenta should be initiated and monitored by healthcare professionals experienced in the diagnosis and treatment of GPA and MPA.	
Important potential risk		
Hepatic transaminases (AST/ALT) increase	Routine risk communication: SmPC Sections 4.2, 4.4, and 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: Information regarding liver function test monitoring, awareness for patients with liver disorders and alcohol abuse is included in SmPC Section 4.2 and 4.4 Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medication. Treatment with Vynpenta should be initiated and monitored by healthcare professionals experienced in the diagnosis and treatment of GPA and MPA.	None
Missing information		
Carcinogenicity	Routine risk communication: SmPC Section 5.3 Other routine risk minimisation measures beyond Product Information: Legal status: Prescription only medication. Treatment with Vynpenta should be initiated and monitored by healthcare professionals	Additional pharmacovigilance activity: carcinogenicity

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	experienced in the diagnosis and treatment of GPA and MPA.	
Long-term use	Routine risk communication: SmPC Section 4.2 Other routine risk minimisation measures beyond Product Information: Legal status: Prescription only medication. Treatment with Vynpenta should be initiated and monitored by healthcare professionals experienced in the diagnosis and treatment of GPA and MPA.	None
Patients with severe hepatic impairment	Routine risk communication: SmPC Section 4.2, 4.8 and 5.2 Routine risk minimisation activities recommending specific clinical measure to address the risk: Information regarding liver function monitoring is included in SmPC Section 4.2 and 4.4 Other routine risk minimisation measures beyond Product Information: Legal status: Prescription only medication. Treatment with Vynpenta should be initiated and monitored by healthcare professionals experienced in the diagnosis and treatment of GPA and MPA.	None
Patients with severe vasculitis (e.g. rapidly progressive glomerulonephritis, alveolar hemorrhage, hemoptysis, rapid-onset mononeuritis multiplex, or central nervous system involvement)	Routine risk communication: SmPC Section 4.4 Other routine risk minimisation measures beyond Product Information: Legal status: Prescription only medication. Treatment with Vynpenta should be initiated and monitored by healthcare professionals experienced in the diagnosis and treatment of GPA and MPA.	None

No additional risk minimisation measures are proposed by the Applicant.

The discussion on the need to include infections with encapsulated bacteria, in particular Neisseria meningitides in the RMP has not been finalised, and the Applicant has been requested to reconsider including the risk in the RMP or provide an Expert Overview summarizing available data regarding C5-R blockade and the potential risk for infections with encapsulated bacteria, in particular Neisseria meningitides. Depending on the discussions of the safety concerns by the CHMP, the Applicant should discuss the need for aRMM for avacopan (and other updates of the above table) again.

Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

Depending on the discussions of the safety concerns by the CHMP, the Applicant should discuss the need for aRMM for avacopan.

3.4.5 Summary of the risk management plan (PRAC Rapporteur's assessment second round)

The public summary of the RMP requires revision based on the comments made throughout the report.
LoQ

3.4.6 Overall conclusion RMP

The CHMP and PRAC considered that the risk management plan version 1.1 is not acceptable. Details are provided in the Rapporteur assessment report and in the list of questions in section 7 of this overview AR.

3.4.7 PRAC outcome on RMP version 1.1

The PRAC fully supported the assessment of the pharmacovigilance plan and risk minimisation measures as detailed in the assessment report as well as the suggestions made on the summary of safety concerns and agreed that the RMP could be acceptable provided that an update to RMP version 1.1 and satisfactory responses to questions detailed in the joint CHMP-PRAC D150 overview assessment report (AR) are submitted.

3.5. Pharmacovigilance system

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

Please note: Applicants are encouraged to request a PSMF number (MFL EVCODE) assigned by the extended EudraVigilance Medicinal Product Dictionary (XEVMPD) for their PSMF in order to include in their application; the applicant is asked to provide the MFL EVCODE in future applications, if available.

Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the {EBD} or {IBD} to determine the forthcoming Data Lock Points. 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.

4. Orphan medicinal products

Orphan designation

According to the conclusion of the COMP (Opinion dated 09/10/2014) the prevalences of the two components of AAV, microscopic polyangitis (MPA) and granulomatosis with polyangitis (GPA) are 1.0 and 1.6 per 10000 individuals, respectively, in the European Union (EU).

Orphan Designations, EMA/OD/149/14 for treatment of MPA and EMA/OD/150/14 for treatment of GPA, were granted on 19 Nov 2014.

Similarity

The application did not contain a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products, as no such authorised orphan medicinal products exist.

The applicant states that *"There are no similarity concerns at this time".*

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

The proposed indication in this application for CMA is:

Vynpenta is indicated for induction treatment of adult patients with organ or life-threatening granulomatosis with polyangiitis (Wegener's) (GPA) or microscopic polyangiitis (MPA) in combination with cyclophosphamide (CYC) or rituximab (RTX).

Granulomatosis with polyangiitis (GPA) (previously named Wegener's granulomatosis) and microscopic polyangiitis (MPA) are forms of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) that affect small to medium vessels and share a number of clinical, pathologic, and laboratory features (Falk and Jennette, 2010).

The proposed indication concerns subjects with various activity and severity of GPA or MPA. The indication concerns both newly diagnosed and relapsed GPA or MPA.

The aim of the therapy with avacopan is to increase the efficacy and safety of current standard induction treatment for GPA and MPA by eliminating (ultimate goal, as in the pivotal phase II trial and in the ongoing phase III trial) or reducing the need for concomitant corticosteroid treatment.

5.1.2. 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 milder immunosuppressive drugs

Cyclophosphamide plus glucocorticoids or rituximab plus glucocorticoids are considered the standard of care induction therapy for organ or life-threatening AAV (Jayne et al, 2003; Jones et al, 2010; Stone et al, 2010).

Maintenance treatment includes immunosuppressive drugs such as azathioprine, mycophenolate mofetil, or methotrexate. Glucocorticoid treatment is also often used during maintenance, even though long-term side effects such as osteoporosis, diabetes mellitus, and hypertension are common with its use (Little et al, 2010). In life-threatening AAV also intravenous pulse glucocorticoids and plasma exchange have been used.

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

5.1.3. Main clinical studies

The clinical efficacy of avacopan has been studied in two phase 2 studies (CL002_168, CL003_168) comprising a total of 109 patients with ANCA-associated vasculitis (AAV), out of which 73 were randomised to treatment with avacopan. Subjects included in both studies were adult patients with a clinical diagnosis of GPA, MPA or renal limited vasculitis, consistent with Chapel-Hill consensus definitions. They could either have a new or relapsing disease, for which treatment with cyclophosphamide or rituximab would be required. Subjects with severe organ involvement (such as renal or pulmonal) were excluded from the studies.

A phase 3 study is ongoing, aiming to include 300 subjects.

CL002_168 was a phase 2, double-blind, randomised, active-controlled (although referred to by the applicant as placebo-controlled) study comparing the efficacy and safety of avacopan 30 mg bid, with (n=22) and without (n=22) a reduced dose of prednisone versus standard-of-care with high dose prednisone (n=23). The treatment period was 12 weeks, followed by 12 weeks follow up.

CL003_168 was a phase 2, double-blind, randomised, placebo-controlled study comparing the efficacy of avacopan10 mg bid (n=13) and avacopan 30 mg bid (n=16) versus placebo (n=13), all on top on full dose prednisone. No subjects in CL003_168 received avacopan without concomitant steroids as proposed in the SmPC. The treatment period was 12 weeks, followed by 12 weeks follow up.

All subjects in both studies received background treatment with cyclophosphamide or rituximab. During the follow-up period, subjects receiving cyclophosphamide were switched to azathioprine at a target dose of 2 mg/kg/day, starting at Week 15. Subjects receiving rituximab background treatment did not receive any additional treatment during the follow-up period.

Primary endpoint in both studies was BVAS response (defined as BVAS percent reduction from baseline of at least 50 %, plus no worsening in any body system component). Important secondary endpoints were BVAS remission (in CL002_168 defined as BVAS of 0 or 1 plus no worsening in eGFR and urinary RBC count <10/high power field, and in study CL002_168 as BVAS of 0) and renal response (defined as an improvement in three renal parameters). It is important to note that the control group subjects all received glucocorticoids at Week 12. Therefore, BVAS remission without glucocorticoids could not be assessed in these studies.

Since the Study CL003_168 was not powered for formal efficacy analyses, the results of the Study are only supportive from the efficacy point of view. The safety assessment is based on both Phase II studies, although the main emphasis should be placed on the comparison between the "Avacopan + no

prednisone" and "Full dose prednisone" groups in the Study CL002_168, reflecting the sought indication.

5.2. Favourable effects

CL002_168

The primary endpoint, the proportion of subjects with BVAS response at day 85, was achieved by 14/20 subjects (70%) in the comparator group that received high dose prednisone, 19/22 subjects (86.4%) in the avacopan + reduced dose prednisone group (90% CI: -4.3-37.1, non-inferiority p-value:0.002) and 17/21 subjects (81%) in the avacopan + no prednisone group (90% CI: -11.0-32.9, non-inferiority p-value:0.01).

Renal response at day 85 (secondary endpoint) was achieved by 8/20 subjects (40.0%) in the comparator group, 10/18 subjects (55.6%) in the avacopan + reduced dose prednisone group (90% CI:-10.8-41.9, non-inferiority p-value: 0.01) and 6/18 subjects (n=33.3%) in the avacopan + no prednisone group (90% CI:-32.3-19.0, non-inferiority p-value: 0.20).

In this study, steroid use was allowed from weeks 12 to 24 in the control group, hence BVAS remission without corticosteroids could not be determined. The clinically important secondary endpoint of BVAS remission was achieved in 7/20 subjects (35%) in the comparator group (full dose prednisone), 6/22 (27.3%) of the subjects in in the avacopan + reduced dose prednisone group (90% CI: -31.2-15.8, non-inferiority p-value: 0.20) and in 4/21 subjects (19%) in the avacopan + no prednisone group (90% CI: -38.5-6.6, non-inferiority p-value: 0.39) at 12 weeks. After 12 weeks of follow-up (day 169), the remission rate increased to 50% (n=10/20) in the comparator group, 45.5% (n=10/22) in the avacopan + reduced dose prednisone group and 23.8% (n=5/21) in the avacopan + no prednisone group.

CL003_168

According to the applicant, this study was not powered to evaluate efficacy and the results is therefore descriptive. The study does not include the proposed dose regimen.

The primary efficacy endpoint, the proportion of subjects with BVAS response at day 85, was achieved by 11/13 subjects (84.6%) in the placebo group, 11/12 subjects (91.7%) in the avacopan 10 mg bid group and in 12/15 subjects (80.0%) in the avacopan 30 mg bid group.

The secondary endpoint of renal response at day 85 was achieved by 1/6 subjects (16.7%) in the placebo group, 2/5 subjects (40%) in the avacopan 10 mg group and by 5/8 subjects (62.5%) in the avacopan 30 mg group.

The secondary endpoint of BVAS remission at day 85 was achieved by 7/13 subjects (53.8%) in the placebo group, 8/12 subjects (66.7%) in the avacopan 10 mg group and 7/15 subjects (46.7%) in the avacopan 30 mg group.

5.3. Uncertainties and limitations about favourable effects

There are major uncertainties with regards to the efficacy of avacopan.

First, the available data for the proposed posology of avacopan is limited with one pivotal phase 2 study (CL002_168) including 67 patients and a treatment period of 12 weeks. This limits the possibility to draw reliable conclusions. The sought indication is broad, including both GPA- and MPA-patients, patients with newly diagnosed and relapsed disease, also regardless of severity/ activity of the disease and use with both rituximab or cyclophosphamide, even though data are extremely limited or non-existing and inconsistent in these different patient subgroups.

The primary endpoint in study CL002_168 is problematic as there is a general consensus that the aim of vasculitis induction therapy is not *induction of response* but rather *induction of remission*. Therefore, the secondary endpoint of BVAS remission is of high importance. For this endpoint, Avacopan, with or without a reduced dose of prednisone, appeared inferior to the comparator but it is acknowledged that BVAS remission may require longer term treatment.

Also, after 12 weeks of follow-up (day 169), BVAS response rates for avacopan, with or without prednisone, was lower than for the comparator group with full dose prednisone.

This questions the long-term efficacy of avacopan and further stresses the importance of gaining access to the upcoming phase 3 result for the overall efficacy assessment**.**

Primary efficacy endpoint was changed from the use of rescue corticosteroids to BVAS response at Day 85 with protocol amendment 3.0. The change of the primary endpoint seems to be driven by results of Steps 1 and 2 of the study, i.e. the data from Step 1 and 2 have been used as hypothesis creator, and therefore should not be included in the primary analysis. Hypothesis should have been tested with the new data, i.e. Step 3 data. *Non-inferiority was however not shown in any of the analyses between avacopan + no prednisone and the comparator with full dose prednisone for Step 3.*

There are a number of issues that weaken the statistical confidence in the CL002_168 results, these issues include the design of the study with different "steps", the population analysed, the handling of missing data, as well as multiplicity issues. Sensitivity analyses addressing these issues did not show consistency of results. CL002_168 is the main study upon which the applicant seeks to make claims of efficacy: therefore the results need to be both statistically and methodologically compelling and the results highly convincing. This was however not achieved.

5.4. Unfavourable effects

Adverse events in the phase I studies

When healthy controls were given avacopan in the phase I studies; there were no serious adverse events. The frequency of subjects with at least one treatment-emergent event was 62.9% in the avacopan group and 42.9% in the placebo group. Headache, GI symptoms and infections were reported.

Adverse events in phase II study CL002_168

Almost all patients had one or more TEAE. Both gastrointestinal disorders and infections were reported in approximately half of the patients and occurred more often among patients that received avacopan compared to patients in the comparator group. During the overall 168-day study period, the frequency of subjects with at least one treatment-emergent infection was 14 (63.6%) in the avacopan + reduced dose prednisone group, 12 (54.5%) in the avacopan + no prednisone group and 11 (47.8%) in the comparator group.

During the 168-day study period, 11 (50%) subjects in the avacopan+ reduced dose prednisone group and 10 (45.5%) in the avacopan+ no prednisone group had at least one TEAE that was assessed as possibly related to corticosteroid use compared to 14 (60.9%) in the comparator group. The applicant also reported that at least 1 treatment-emergent "adverse *effect* possibly associated with glucocorticoid use" during the 168 day study period was reported in 10 (45.5%) subjects in the avacopan + reduced dose prednisone group, 11 (50.0%) subjects in the avacopan + no Prednisone group), compared to 15 (65.2%) subjects with the comparator group.

At least 1 serious TEAE during the 84-day treatment period was reported in 3 (13.6%) subjects in the avacopan+ reduced dose prednisone group and 8 (36.4%) subjects in the avacopan+ no prednisone

group compared to 4 (17.4%) subjects in the comparator group. During the whole 168-day study period, the number of serious TEAEs were 8 (36.4%) in the avacopan + reduced dose prednisone group and 10 (45.5%) in the avacopan+ no prednisone group compared to 5 (21.7%) in the comparator group. Serious events in the avacopan group included: vasculitis, haematuria, infections, renal impairment, hepatic and pancreatic enzymes increased, musculoskeletal chest pain, rash pleurisy and ocular hyperaemia. Serious events in the comparator group included: pneumonia, dehydration, lumbar vertebral fracture, renal vasculitis and back pain.

There were 2 subjects with serious treatment-emergent infections in each of the avacopan groups (9.1%) and 1 (4.3%) in the comparator group during the 168-day study period.

The number that discontinued study medication due to TEAEs was: 1 (4.5%) subject in the avacopan+ reduced dose prednisone group (due to vasculitis), 3 (13.6%) subjects in the avacopan+ no prednisone group (reported to be due to renal impairment, hepatic enzyme increased, pancreatic enzymes increased and microscopic polyangiitis), and 2 (8.7%) subjects in the full dose comparator group (due to vasculitis and renal vasculitis).

Adverse events in phase II study CL003_168

Almost all patients had one or more TEAEs. Gastrointestinal disorders and infections were reported somewhat more often among patients that received avacopan in any of the two investigated doses as compared to patients that received placebo. The number of subjects with treatment-emergent infections during the 168-day study period was 5 (38.5%) in the avacopan 10 mg, 6 (37.5%) in the avacopan 30 mg group and 4 (30.8%) in the placebo group.

A dose-dependent increase could be seen in some AEs.

A majority of patients had adverse events or adverse *effects* that were assessed as possibly related to medication with steroids.

At least 1 serious TEAE during the 84-day treatment period was reported in 2 (15.4%) subjects in the avacopan 10 mg group (neutropenia and cellulitis staphylococcal respectively) and 3 (18.8%) subjects in the avacopan 30 mg group (atrial fibrillation, sepsis and urinary tract infection) compared to 2 (15.4%) subjects the placebo group (methemoglobinemia and gangrene). Following the 84-day treatment period, in the avacopan 30 mg group one subject had sepsis, one had a serious event of renal failure and one had a serious event of urinary tract infection and in the placebo group, one subject had a serious event of bronchiolitis and one had nephrolithiasis. During the whole CL003_168 study period, 2 of the 13 subjects in the avacopan 10 mg group (15%), 4 of the 16 subjects in the avacopan 30 mg (25%) and 3 of the 13 subjects in the placebo group (23%) had a serious TEAE.

A total of 4 subjects had at least 1 serious infection during the 84-day treatment period: 1 (7.7%) in the avacopan 10 mg group (cellulitis staphylococcal, abscess limb, and perirectal abscess), 2 (12.5%) in the avacopan 30 mg group (sepsis and urinary tract infection respectively) and 1 (7.7%) in the placebo group (gangrene). There was one additional event in the placebo group during the follow-up period i.e. the proportion of subjects with serious infections in the 168-day study period remained the same as during the 84 –day treatment period in the avacopan groups but increased to 15.4% in the placebo group.

The numbers of subjects that discontinued treatment due to a TEAE were 2 (15.4%) in the placebo group (due to maculopapular rash and gangrene respectively), 1 (7.7%) in the avacopan 10 mg group (due to abscess limb and perirectal abscess) and 3 (18.8%) in the avacopan 30 mg group (atrial fibrillation, sepsis and pain in leg, arm, abdomen, jaw).

Adverse events and laboratory findings in the pooled analysis of the phase II data

The proportion of subjects with serious TEAEs was numerically higher in the avacopan groups compared to the group not treated with avacopan. Infections and GI-events were considered by the applicant as adverse drug reactions and included in section 4.8 of the SmPC.

There were two grade 3 CK elevations in two patients randomised to avacopan, but none in patients in the comparator group. In one of these patients, the CK returned to normal with no interruption of avacopan treatment and this subject had an adverse event of mild muscle spasms in the same timeframe as the CK elevation. In the other patient, the elevated CK value persisted until the end of the 12-week follow-up period, while not taking any avacopan and this subject had an adverse event of mild musculoskeletal pain in the same timeframe as the CK elevation. ***However, it was clarified that no cases have been associated with rhabdomyolysis or cardiac adverse events.***

There were more avacopan-treated patients with elevated liver enzyme levels.

Upon initiation of avacopan treatment, a rapid decrease in mean WBC, neutrophil and lymphocyte count is evident during the first two weeks of treatment. In particular Grade 3 lymphopenia (<0.5 to 0.2 x 10^9/L) was seen in 22.7% of patients in the avacopan alone (without prednisone) group compared to 0% in the high dose prednisone group in the pivotal Study CL002.

Overall, there were more Grade 3-4 events in the avacopan groups compared to the control group (14 vs. 4). However, the number of Grade 1-3 events in the avacopan + no prednisone group was equal to that in the comparator group (21 vs. 21), and there were no Grade 4-5 events.

5.5. Uncertainties and limitations about unfavourable effects

The low total number of vasculitis patients exposed to avacopan (73, out of which 60 patients were exposed to the currently proposed dose) and the fact that none was exposed to more than 12 weeks treatment or followed for more than 24 weeks seems to preclude a reliable overall risk assessment. In particular, the population available for comparison of avacopan alone and standard of care treatment with high dose prednisone in Study CL002 is limited (22 and 23 patients, respectively).

Another limitation when the safety data are to be interpreted is that the background treatment in the avacopan groups varied between and within the studies. Moreover, the understanding of the data is obscured by the fact that the number of AEs is overall expected to be large in this severely ill population with heavy background medication, rendering it very difficult to distinguish which of the negative effects observed that are in fact related to the new drug itself and not to confounding factors. The impact of these limitations is enhanced because of the small sample size, making it difficult to conduct meaningful subgroup analysis or stratification to further explore the issue. A summary of ADRs for which a causal relationship between avacopan and the adverse event is at least a reasonable possibility is ***still requested.***

From a non-clinical perspective, a complete package of *in vitro* and *in vivo* genotoxicity studies in agreement with ICH S2(R1) guidance have been performed with negative results. The chronic toxicity of avacopan has been studied to the extent feasible based on the poor solubility, however, as no dose-limiting effects or target organ of toxicity were observed, the chronic toxicity of avacopan is not considered fully explored. Carcinogenicity studies with avacopan are not yet available; these studies are on-going in hamster and rat (estimated finalisation date 2020). The lack of completed carcinogenicity studies is considered a major deficiency in the non-clinical evaluation but may be acceptable in view of the recommended treatment duration of 12 weeks. Overall, to date, there are not enough data to conclude on the long-term safety of avacopan from a non-clinical perspective.

It is uncertain whether the steroid-sparing potential of avacopan can be translated into any measurable clinical effects in the available clinical data.

Some further data on monitoring of liver enzymes and blood count are requested LoQ . See also separate SmPC document.

5.6. Effects Table

Please note that in the effects table, the data from the treatment arm in CL002_168 that corresponds to the currently proposed posology; avacopan 30 mgx2 with no prednisone on top of cyclophosphamide or rituximab is presented in the treatment column and the data from the comparator arm of CL002_168 that corresponds to current standard of care including standard full dose prednisone on top of cyclophosphamide or rituximab, is presented in the control arm.

The reason why this comparison was selected for the presentation in the Effects Table is that it is the comparison considered most relevant for the current application.

Table 28: Effects Table for Avacopan for induction of response in PGA and MPA

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
BVAS response	50% reduction from baseline to day 85	n(%)	17/21 (81.0%)	14/20 (70.0%)	Concerns on statistical methods. Small study size. Unclear relevance of endpoint.	CL002_168
Renal response at day 85	Improvement in parameters of renal vasculitis from baseline to day 85	n(%)	6/18 (33.3%)	8/20 (40.0%)	Short treatment period (12 weeks).	CL002_168
BVAS remission	BVAS score of 0 or 1 at day 85	n(%)	4/21 (19.0%)	7/20 (35.0%)	Short treatment period (12 weeks). Relevant endpoint.	CL002_168
Unfavourable Effects						
Subjects with any TEAE	During 12 weeks treatment period and 24 weeks study period	n(%)	21 (95.5%) both at 12 weeks and 24 weeks	21 (91.3%) both at 12 weeks and 24 weeks	1. Limited number of patients: n=22 treatment arm, n=23 control/comparator arm 2. Short study period: 12 weeks treatment+12 weeks follow-up)	CL002_168
Subjects with any Serious TEAE	See above	n(%)	8 (36.4%) 12 weeks 10 (45.5%) 24 weeks	4 (17.4%) 12 weeks 5 (21.7%) 24 weeks	See above	CL002_168
Subjects with any infections	See above	N (%)	12 (54.5%) 12 weeks 12 (54.5%) 24 weeks	9(39.1%) 12 weeks 11 (47.8%) 24 weeks	See above	CL002_168

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Subjects with any serious Infections	See above	n(%)	1 (4.5%) 12 weeks 2 (9.1%) 24 weeks	1 (4.3%) 12 weeks 1(4.3%) 24 weeks	See above	CL002_168
Subjects with any TEAE assessed as possibly related to glucocorticoid use	See above	n(%)	8 (36.4%) 12 weeks 10 (45.5%) 24 weeks	13 12 weeks 14 (60.9%) 24 weeks	See above	CL002_168
Subjects with any Adverse *Effect* possibly related to glucocorticoid use	See above	n(%)	11 (50.0%) 12 weeks and 24 weeks	15 (65.2%) 12 weeks and 24 weeks	See above	CL002_168

Abbreviations: TEAE=Treatment Emergent Adverse Event
Notes: Data from the treatment arm in CL002_168 that corresponds to the currently proposed posology (avacopan 30 mgx2 with no prednisone on top of cyclophosphamide or rituximab) is presented in the treatment column and the data from the comparator arm of CL002_168 that corresponds to current standard of care (including standard full dose prednisone on top of cyclophosphamide or rituximab), is presented in the control arm.

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

The most important effect put forward by the applicant is the primary endpoint, non-inferiority of avacopan regarding BVAS response, compared to standard of care with full dose prednisone. The relevance of this endpoint is not agreed on, since BVAS remission is the clinically more relevant endpoint. There is a general consensus that the aim of vasculitis induction therapy is *induction of remission.* The relevance of clinical response was not addressed.

It is acknowledged that patients in the control group were still receiving prednisone at Week 12, the timepoint of the efficacy assessment, which complicates the interpretation of the endpoint BVAS remission (patients should be off glucocorticoids). However, for this endpoint, avacopan with or without low-dose prednisone appeared inferior to the comparator. This uncertainty in the efficacy of avacopan is further supported by the results for BVAS response after 24 weeks where avacopan, with or without prednisone, had a lower response rate than the comparator group with full dose prednisone. This could be a consequence of not achieving remission in the induction phase.

In response to the first RSI, the applicant provided a discussion regarding the relevance of BVAS as an endpoint, and its association to future remission. The applicant refers to an analysis on a similar patient population of 303 patients from 4 studies conducted by the European Vasculitis Group (EUVAS). In these patients, who were treated with a variety of therapies, including cyclophosphamide, azathioprine, methylprednisolone, plasma

exchange, or methotrexate, 58.9% of the subjects with BVAS response at 3 months went into BVAS remission at 6 months. It is understood that these individuals were on continuous treatment, in contrast to what is proposed in the SmPC for avacopan where subjects should be treated for 12 weeks, and where the response rate seems to diminish over time (for avacopan + no prednisone, BVAS response at week 12: 81%, BVAS response at week 24: 71.4%) . Thus, although these data is of interest, its relevance for this application is somewhat limited.

There are a number of issues that weaken the statistical confidence in the CL002_168 results, these issues include the design of the study with different "steps", the population analysed, the handling of missing data, as well as multiplicity issues. Sensitivity analyses addressing these issues did not show consistency of results. CL002_168 is the main study upon which the applicant seeks to make claims of efficacy: therefore the results need to be both statistically and methodologically compelling and the results highly convincing. This was however not achieved.

Thus, based on the presented data, it cannot be concluded that the documented effect would be of relevant importance for the proposed target population.

Importance of unfavourable effects

When two doses of avacopan were compared to placebo on top of SOC in patients with acute vasculitis in study CL003_168, practically all patients had at least one TEAE and more than half of the subjects in all three groups had adverse events that were considered to be possibly related to corticosteroid use (not surprising given that all three groups received high doses of steroids). Although gastrointestinal disorders and infections were reported somewhat more often among patients that received avacopan in any of the two investigated doses as compared to patients that received placebo, the differences were small. Overall, the proportion of subjects in each group that experienced serious adverse events as well as the number of infections and serious infections appeared comparable between the groups with the important limitation that the each of the groups included a only a small number of individuals.

When the safety profile of three different treatment strategies for acute vasculitis were compared in CL002_168, of which the comparator group corresponds to standard of care and the avacopan + no steroid group corresponds to the posology of the current application, again almost all patients had at least one TEAE. Although the reported TEAEs, including the serious TEAEs, appeared to be a mix of true AEs and signs/symptoms related to the underlying conditions which together with the small sample size makes the interpretation of the safety results difficult, the proportion of subjects with serious TEAEs appeared somewhat higher in the avacopan groups, at least in the group that was not treated with steroids. Also for the comparison regarding infections, there seemed to be a trend disfavouring the avacopan groups when compared to the full dose steroid group (Mostly caused by mild nasopharyngitis and viral upper respiratory tract infections). Regarding adverse events adverse *effects* possibly related to steroids; the differences between the groups were small and when differences in favour of avacopan were noted, it appeared to be driven by psychiatric disorders. Overall, it appears doubtful that a possible increase in serious events and infections in avacopan treated subjects as compared to standard of care treated subjects could be considered outweighed by a potential decrease in the group of adverse events/effects that were assessed as possibly related to steroids.

In both the phase II studies, the numbers of subjects that discontinued treatment due to TEAE were rather low and comparable between the treatment groups.

AE profile was summarized according to age, sex and GFR. It is agreed with the applicant that there was no clear pattern although the analysis is considerably hampered by the low number of individuals in the different categories and that some data are still lacking**.**

Thus in conclusion, based on the limited data presented, the importance of unfavourable effects associated with the use of avacopan has not been reliably documented. The benefit of administering a new novel compound with limited safety and efficacy data for 12 weeks and thereafter stopping the treatment (as currently the data is too premature to allow longer administration) compared to the benefit of treating a patient with SOC high dose steroids for 12 weeks does not outweigh the unknown risks and uncertainties related to avacopan treatment and complement cascade inhibition.

There may be few conditions (e.g. previous major AEs due to corticosteroids), where individual patient benefit/risk assessment could imply that withholding high-dose steroids in induction of remission and instead giving a new compound for 12 weeks with only limited safety and efficacy data could be acceptable. But for these patients no data exist (corticosteroids could have been used in all patients in the two studies according to the inclusion/ exclusion criteria) and therefore all data has to be fully extrapolated from other patients. At the moment such extrapolation is considered too premature and unjustified. Finally, as no clinical benefit nor safety advantages have been demonstrated in the clinical trials, the importance of carcinogenicity studies in the context of overall benefit/risk-evaluation is emphasized.

From a quality perspective, the GMP control of the drug substance manufacture is not sufficient. A redefinition of starting materials further back in the synthesis is needed to assure the quality of avacopan. To address this, the applicant proposes a re-definition of the two starting materials as a post-authorisation measure. This is not acceptable and adds to the negative benefit/risk of the product. Major objections are raised regarding these two starting materials.

5.7.2. Balance of benefits and risks

The applicant presents in this application the results from two phase 2 studies with a 12 week treatment period and a 12 week follow-up period. Only one of these studies includes the proposed posology. The assessment of the benefit-risk is at this stage based on a very limited amount of data. The intended dose of avacopan, 30 mg twice daily on top of cyclophosphamide or rituximab without concomitant prednisone, has only been studied in 22 subjects (out of which 21 were included in the primary efficacy evaluation) in study CL002_168, which is considered the pivotal study for this assessment.

From the limited data presented by the applicant, it cannot be concluded that the favourable effects of avacopan as induction of response in adult patients with GPA or MPA outweighs the risks associated with this treatment. The Benefit/Risk balance is thus considered to be currently negative for this application for CMA.

5.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation (CMA)

A conditional marketing authorisation has been applied for.

Medicines for human use are eligible for CMA if they belong to at least one of these categories:

- aimed at treating, preventing or diagnosing seriously debilitating or life-threatening diseases;
- intended for use in emergency situations (also less comprehensive pharmaceutical and non-clinical data may be accepted for such products);
- designated as orphan medicines.

Avacopan meets two of the above criteria, i.e. the orphan drug designation was granted to Avacopan for the following conditions: treatment of microscopic polyangitis and treatment of granulomatosis with polyangitis, for which the number in the community register of orphan medicinal products are EU/3/14/1372 and EU/3/14/1373. In addition, ANCA-vasculitis can be considered to be a seriously debilitating or life-threatening disease.

CMA may be granted if all of the following requirements are met:

1. *The risk-benefit balance of the product is positive.*

   This requirement is not considered fulfilled (please see discussion above).

2. *It is likely that the candidate will be able to provide comprehensive data.*

   This requirement can be considered fulfilled.

3. *Fulfilment of unmet medical need*.

4. *The benefit to public health of the immediate availability outweighs the risk inherent in the fact that additional data are still required*.

   These last two requirements are linked to each other and none of them are considered fulfilled. These issues have been thoroughly discussed by the CHMP during previous Protocol Assistance. Regarding the fulfilment of unmet medical need, it was agreed that there is room for improvement regarding efficacy in this therapeutic field but it was also agreed that the most important limitation of the current therapies is not their lack of efficacy but their lack of an acceptable safety profile. Accordingly, a large part of the unmet medical need is the need for a safe steroid-sparing induction agent that can be used for long-term treatment/ maintenance phase, where the steroid-sparing effect is considered to be of utmost importance.

   On the contrary to what the Applicant claims, there are (according to the Article 57 database) some corticosteroids formally approved for the indication of vasculitis in all EU Member States (either for the indication of vasculitis, MPA, GPA, or generally as an anti-inflammatory therapy, or for immunosuppression or autoimmune disorder). Therefore, evidence should suggest that avacopan provides major therapeutic advantage over corticosteroids in this indication to meet the requirements for CMA.

   For Avacopan, no clear advantage in efficacy compared to authorized methods was expected and neither has this been demonstrated by the limited available data; rather it can be questioned whether even non-inferiority as regards to standard of care has been demonstrated, especially beyond 12 weeks. A safety benefit was hoped for. However, this is not indisputably demonstrated by the limited phase II data. In summary, neither an efficacy advantage nor a safety advantage over established treatment (including steroids that are authorized for systemic vasculitis) has been demonstrated for avacopan. Thus the benefits to public health of the immediate availability of the drug cannot be said to outweigh the risks inherent in the fact that additional data are still required.

Thus, overall the specific requirements for conditional approval have not been fulfilled.

As commented in other parts of this AR, it should be noted that in the Protocol Assistance received by the applicant, the strategy to file a CMA based on phase II data was not encouraged.

<u>Regulatory status of rituximab and cyclophosphamide – impact on avacopan indication</u>

The indication includes the use of avacopan in combination with rituximab or cyclophosphamide. Rituximab has the formal indication for induction treatment of GPA and MPA throughout the EU. Cyclophosphamide has been approved for the treatment of Wegener's granulomatosis throughout the EU, but not specifically for the treatment of MPA. However, according to the Article 57 database, cyclophosphamide has been approved in all EU-Member States for a more unspecific indication (autoimmune disorder, immunosuppressant drug, and/or vasculitis), and therefore also MPA is considered to be included in the cyclophosphamide indications. In conclusion, no special consideration is required related to the add-on indication with regard to rituximab and cyclophosphamide, as both can be considered to already include GPA and MPA in their formal indications.

5.8. Conclusions

The overall B/R of Vynpenta for this CMA is currently negative in the sought indication for treatment of MPA or GPA.