NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

The **final scope** and **final stakeholder list** are available on the NICE website.

The following documents are made available to consultees and commentators:

1. **Company submission** from Vifor Pharma

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Vasculitis UK
   b. British Association of Paediatric Nephrology
   c. Renal Association
   d. UK Renal Pharmacy Group
   e. NHS England & Improvement Specialised Commissioning
   f. NHS England - Commercial Medicines
   g. Dr Peter Lanyon, Commissioning expert, NHS England Specialised Rheumatology Clinical Reference Group

4. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response** from Vifor Pharma

7. **Technical engagement responses & expert statements from experts:**
   a. Zografia Anastasa, patient expert, nominated by Vasculitis UK
   b. Professor Lorraine Harper, clinical expert, nominated by Vifor Pharma
   c. Dr Peter Lanyon, Consultant Rheumatologist – commissioning expert, nominated by NHS England

8. **Technical engagement response from consultees and commentators:**
   a. Renal Pharmacy Group
   b. UKIVAS
   c. NHS England Specialised commissioning: Specialised Rheumatology Clinical Reference Group

9. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews

10. **Evidence Review Group report addendum** prepared by Kleijnen Systematic Reviews

11. Evidence Review Group report addendum post pre-meeting call prepared by Kleijnen Systematic Reviews

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avacopan for treating anti-neutrophil cytoplasmic autoantibody–associated vasculitis [ID1581]

Document B

Company evidence submission

October 2021

File name	Version	Contains confidential information	Date
ID1581_Avacopan Company evidence submission_Document B_101121_ACIC redacted	**2.0**	**Yes**	**10 Nov 2021**

Contents

Tables and figures

STRICTLY CONFIDENTIAL

Abbreviations

AAV	Anti-neutrophil cytoplasmic autoantibody–associated vasculitis
AE	Adverse event
AIS	Aggregate Improvement Score
ANCA	Anti-neutrophil cytoplasmic autoantibody
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
AZA	Azathioprine
BMI	Body mass index
BVAS	Birmingham Vasculitis Activity Score
C-ANCA	Cytoplasmic anti-neutrophil cytoplasmic autoantibody
CD19	Cluster of differentiation 19
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CPRD	Clinical Practise Research Datalink
CRP	C-reactive protein
CT	Computed tomography
CV	Cardiovascular
CWS	Cumulative Worsening Score
CYC	Cyclophosphamide
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EGPA	Eosinophilic granulomatosis with polyangiitis
ELISA	Enzyme-linked immunosorbent assay
ESRD	End-stage renal disease
GC	Glucocorticoid
GPA	Granulomatosis with polyangiitis
GTI	Glucocorticoid Toxicity Index
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
hpf	High-power field
HRQoL	Health-related quality of life
hsCRP	High-sensitivity C-reactive protein
IGRA	Interferon-gamma release assay
ICER	Incremental cost-effectiveness ratio

ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
LFT	Liver function test
LSM	Least squares mean
LY	Life year
MCP-1	Monocyte chemoattractant protein-1
MDRD	Modification of Diet in Renal Disease
MMF	Mycophenolate mofetil
MPA	Microscopic polyangiitis
MPO	Myeloperoxidase
MTX	Methotrexate
NA	Not applicable
NHSE	National Health Service England
OR	Odds ratio
P-ANCA	Perinuclear anti-neutrophil cytoplasmic autoantibody
PD	Pharmacodynamics
PK	Pharmacokinetics
PPD	Purified protein derivative
PR3	Proteinase 3
QALY	Quality-adjusted life year
QoL	Quality of life
QTcF	Fridericia's correction formula
RBC	Red blood cell
RTX	Rituximab
SAE	Serious adverse event
SD	Standard deviation
SEM	Standard error of measurement
SF-36v2	36-Item Short Form Health Survey version 2
SoC	Standard of care
TEAE	Treatment-emergent adverse event
TNF	Tumour necrosis factor
UACR	Urinary albumin-to-creatinine ratio
VDI	Vasculitis Damage Index
WBC	White blood cell
WTP	Willigness to pay

B.1 Decision problem, description of the technology and clinical care pathway

Summary
Avacopan, in combination with a rituximab (RTX) or cyclophosphamide (CYC) regimen, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)

B.1.1 Decision problem

The submission covers avacopan's full marketing authorisation for the treatment of anti-neutrophil cytoplasmic autoantibody (ANCA)–associated vasculitis (AAV) in adults (GPA and MPA), in combination with either CYC (followed by AZA/MMF) or RTX.

Current standard of care (SoC) for induction of remission in adult AAV patients includes glucocorticoids (GCs) in combination with either CYC, followed by AZA/MMF, or RTX. The standard GC regimen involves a high-dose tapering as remission is achieved but is often then continued at low-dose to sustain remission.

Methotrexate (MTX) and MMF are recommended as alternatives to CYC (followed by AZA/MMF) or RTX for remission induction in patients with localised disease at low risk of suffering organ damage. These patients were not studied in the key avacopan clinical trials and so, in this setting, they are not relevant comparators for avacopan.

Further details of the decision problem are shown in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with newly diagnosed or relapsed AAV	People with newly diagnosed or relapsed AAV	NA
Intervention	Avacopan (as an add-on to SoC)	Avacopan in combination with SoC (i.e., CYC, followed by AZA/MMF, or RTX)	NA
Comparator(s)	Remission induction • Established clinical management without avacopan, including GCs and either RTX, CYC, MTX, or MMF Maintenance treatment • Established clinical management without avacopan, including low-dose GCs and either RTX (in line with the NHSE commissioning policy), AZA, MTX, or MMF	Remission induction • GCs in combination with CYC, followed by AZA/MMF • GCs in combination with RTX Maintenance treatment • Low-dose GCs in combination with AZA/MMF • RTX in combination with low-dose GCs	Current SoC for induction of remission in adult AAV patients includes GCs in combination with either CYC, followed by AZA/MMF, or RTX. The standard GC regimen involves a high-dose tapering as remission is achieved but is often then continued at low dose to sustain remission. MTX and MMF are recommended as alternatives to CYC (followed by AZA/MMF) or RTX for remission induction in patients with localised disease at low risk of suffering organ damage. These patients were not studied in the key avacopan clinical trials and so, in this setting, they are not relevant comparators for avacopan
Outcomes	The outcome measures to be considered include the following: • Mortality • Morbidity, including damage to organs	The outcome measures to be considered include the following: • Mortality • Morbidity, including damage to organs	Avacopan is a targeted therapy, the use of which aims to reduce/replace GCs and avoid associated serious toxicity. Therefore, the following outcomes were considered to be

	• Remission rate and duration of remission • Change in renal function • Use of immunosuppressants and corticosteroids • Adverse effects of treatment (including infection rates) • HRQoL	• Remission rate and duration of remission • GC toxicity (measured with an objective score) • GC-related AEs • Sustained GC-free vasculitis remission • Change in renal function • Use of immunosuppressants and GCs • Adverse effects of treatment • Risk of infection • HRQoL	relevant in addition to the proposed outcomes: • GC toxicity (measured with an objective score) • GC-related AEs • Sustained GC-free vasculitis remission Because infection is such a clinical challenge in AAV, risk of infection was examined separately from overall AEs
Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; AE, adverse event; AZA, azathioprine; CYC, cyclophosphamide; GC, glucocorticoid; HRQoL, health-related quality of life; MMF, mycophenolate mofetil; MTX, methotrexate; NA, not applicable; NHSE, National Health Service England; SoC, standard of care; RTX, rituximab			

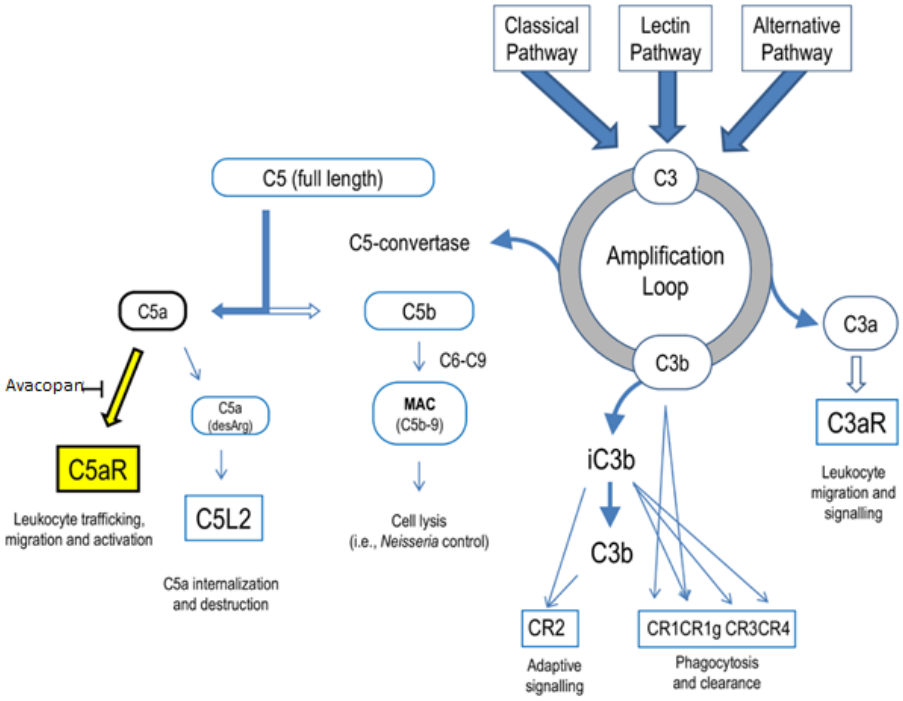
B.1.2 Description of the technology being appraised

Summary
• Avacopan is a novel and innovative agent that selectively targets a single component of the immune system, complement component 5a (C5a), that is a main contributor to vascular inflammation • Avacopan is taken orally (30 mg; 3 hard capsules of 10 mg each) twice per day with food

C5a, acting on the C5a receptor (C5aR), is a potent neutrophil chemoattractant and agonist and is responsible for chemoattraction and priming of neutrophils and monocytes, as well as their adhesion to vascular endothelium (1, 2). C5a can reduce neutrophil deformability, reducing their capacity to traverse small blood vessels, particularly when ANCA is present (3).

As a first in class, highly selective antagonist of C5aR1, avacopan inhibits the action of C5a (1) (Figure 1). By selectively inhibiting C5aR1, avacopan permits otherwise normal functioning of the complement cascade and preserves important immune defence processes such as the membrane attack complex (C5b-9) and C3a (4), a major advantage with regards to vulnerability for major infections.

Figure 1. Avacopan mechanism of action



More details of avacopan are shown in Table 2. The summary of product characteristics (SmPC) is available in **Error! Reference source not found.**. The European public assessment report is not yet available.

Table 2. Technology being appraised

UK-approved name and brand name	Avacopan (Tavneos®)
Mechanism of action	Avacopan is a first in class, highly selective antagonist of C5aR1. C5a, acting on C5aR, is responsible for the chemoattraction and priming of neutrophils and monocytes, and their adhesion to vascular endothelium, which plays a key role in the inflammatory amplification process in GPA and MPA. By selectively inhibiting C5aR1, avacopan permits otherwise normal function of the complement cascade and preserves important immune defence processes such as the membrane attack complex (C5b-9) and C3a (4)
Marketing authorisation/ CE mark status	Avacopan received marketing authorisation for the treatment of GPA and MPA in Japan in September 2021 and the US in October 2021. EMA and MHRA marketing authorisation are anticipated in [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Avacopan, in combination with a RTX or CYC regimen, is indicated for the treatment of adult patients with severe, active GPA or MPA
Method of administration and dosage	Avacopan is taken orally (30 mg; 3 hard capsules of 10 mg each) twice per day with food
Additional tests or investigations	Not applicable
List price and average cost of a course of treatment	List price: [redacted] capsule of avacopan ([redacted]) [redacted]
Patient access scheme (if applicable)	A simple discount patient access scheme is under fast-track review by NHS England

Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; C3a, complement component 3a; C5a, complement component 5a; C5aR1, complement component 5a receptor 1; CYC, cyclophosphamide; EMA; European Medicines Agency; GPA, granulomatosis with polyangiitis; MHRA, Medicines and Healthcare products Regulatory Agency; MPA, microscopic polyangiitis; RTX, rituximab; SmPC, summary of product characteristics; UK, United Kingdom

B.1.3 Health condition and position of the technology in the treatment pathway

Summary
• AAV is a rare, potentially fatal, remitting-relapsing, autoimmune condition that has a substantial impact on patient morbidity, mortality, and quality of life (QoL) (5) • The overall annual incidence of MPA and GPA in the United Kingdom are 5.9 per million and 11.3 per million, respectively (6) • Guidelines recommend induction of remission with CYC or RTX plus high-dose GCs for patients with organ- or life-threatening disease (7, 8) • Following induction, administration of low-dose GCs as well as AZA administration in place of CYC or RTX for at least 18 months for maintenance of remission is recommended (7) • Although the majority of patients achieve remission with current SoC, they remain at high risk of relapse and require long-term GC treatment, which is associated with significant side effects, causing organ damage and morbidity (9) • Despite current SoC, short- and long-term mortality remain high (10, 11) • There is a clear need for novel and effective treatments to replace current options and which rapidly induce durable remission and reduce the rate of GC-related disease patient experience

B.1.3.1 Nomenclature

AAVs are a collection of relatively rare autoimmune diseases characterised by inflammatory cell infiltration causing necrosis of blood vessels. AAV patients are classified by antibody status or clinical phenotype, which are associated with different disease courses. The three major clinicopathologic variants are GPA (formerly known as Wegener granulomatosis [WG]), MPA, and eosinophilic granulomatosis with polyangiitis (EGPA [formerly known as Churg–Strauss syndrome, or CSS]) (5).

GPA and MPA are the main forms of the disease that also carry the most severe complications (see Table 3 for detailed definitions), with EGPA the rarer variant, having a distinctive clinical phenotype and treatment pathway (5).

Note: EGPA is not a proposed indication for avacopan. Further reference to AAV patients within this dossier pertains only to those with GPA and MPA, as an avacopan-based regimen targets the treatment of these two forms of the disease.

Table 3. Chapel Hill Consensus definitions (2012) for GPA and MPA (12)

GPA (formally WG)	Necrotising granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotising vasculitis predominantly affecting small to medium vessels (e.g., capillaries, venules, arterioles, arteries, and veins). Necrotising glomerulonephritis is common.
MPA	Necrotising vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotising arteritis involving small and medium arteries may be present. Necrotising glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.
Abbreviations: GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; WG, Wegener granulomatosis	

B.1.3.2. Clinical manifestations and diagnosis

GPA and MPA patients typically present with nonspecific symptoms, including fever, malaise, anorexia, weight loss, myalgias, and arthralgias (6, 13-15). Prodromal symptoms may last for weeks to months without evidence of specific organ involvement (13, 16). As a result, GPA and MPA are frequently misdiagnosed as infections, malignancies, or inflammatory joint disease (17). When lesions involve the ear, nose, and throat, other symptoms may include rhinosinusitis, cough, dyspnoea, and haemoptysis. Other typical findings may include urinary abnormalities (haematuria, proteinuria, an active urine sediment) with or without kidney function impairment, purpuric lesions in the skin, or evidence of neurologic dysfunction (particularly foot or wrist drop). Occasionally, patients may present more explosively over a period of days (6, 13-15, 17).

Organ damage is common in AAV, with renal involvement being the most common severe manifestation. Chronic kidney disease (CKD) resulting from renal vasculitis occurs in up to 90% of MPA patients and 80% of GPA patients (18). Typically presenting as glomerulonephritis, renal dysfunction is often diagnosed at disease presentation and a high rate of end stage renal disease (ESRD) is observed in the AAV population; 15% to 38% of AAV patients develop ESRD within 5 years (19-22)

with prognosis particularly poor in elderly patients (23). The absence of kidney involvement does not imply benign disease, given that involvement of other organs such as the lungs, heart, gastrointestinal tract, and central nervous system may be serious and life threatening (24). Some patients may present with manifestations limited to a single organ (e.g., kidneys, upper respiratory tract) and then may later evolve to include other organ involvement (24). In a subset of patients, the disease will be limited to a single organ (e.g., renal-limited vasculitis) (25).

Approximately one-fourth of patients present with clinical features such as migratory polyarthropathy, nasal crusting, or other findings that do not include organ-threatening manifestations (26). Compared with those who have severe organ-threatening involvement, such patients have the following characteristics (26):

- They are younger at disease onset and more likely to be women
- They are more likely to have chronic, recurring disease and destructive upper respiratory tract disease (saddle nose deformity)

B.1.3.3. Epidemiology

Assessing the epidemiology of AAV can be challenging because of its rarity, and currently available data are relatively limited.

The prevalence of GPA in the United Kingdom ranges from 2.3 to 146.0 cases per million persons, with an incidence of 0.4 to 11.9 cases per million person-years. By comparison, the prevalence of MPA in the United Kingdom ranges from 9.0 to 94.0 cases per million persons, with an incidence of 0.5 to 24.0 cases per million person-years (6).

The incidence of GPA and MPA varies widely depending on geography. GPA mainly affects regions of the world in which the population is predominantly of European ancestry and is rarely observed in East Asia. By contrast, MPA is more commonly observed in Asian countries such as China and Japan (27, 28). The incidence of GPA also appears to correlate with latitude and is lower toward the equator (29, 30). Studies of multi-ethnic populations in France and in the United States report at least

a 2-fold higher incidence of GPA and MPA among white populations compared with other ethnicities (31, 32).

The UK prevalence of MPA and GPA were estimated to be 63.1 and 145.9 per million, respectively (33). The same epidemiological study reported the overall annual incidence of MPA and GPA in the United Kingdom as 5.9 per million and 11.3 per million, respectively (33).

GPA and MPA most commonly occur in older adults, although these diseases have been reported at all ages. Males and females are equally affected. GPA and MPA are rare among children (6).

B.1.3.4. Aetiology and risk factors

The cause of AAV is not fully understood, with genetic factors, environmental exposures, medication history, and infection all contributing to the disease aetiology and initial loss of immune tolerance (34-37). Three different genome-wide association studies have confirmed that AAV is a polygenic disease with approximately 20% of the disease risk due to genetic factors, which also differ between patients who are proteinase-3 (PR3) ANCA positive or myeloperoxidase (MPO) ANCA positive (34, 38, 39). Infections, seasonal variations, geographic location, ultraviolet radiation, and silica/chemical exposure are all environmental influences that have been repeatedly reported as risk factors for the development of AAV (40).

Patients with incident GPA and MPA often have symptoms for a long time before diagnosis, a factor associated with worse long-term clinical outcomes (41). Although AAV can affect both younger and older people, it is much more common in the older population, with the average age of diagnosis being 57 years, and incidence increasing with age (42, 43).

B.1.3.5. Vasculitis pathophysiology

The binding of ANCA to target proteins activates neutrophils and causes them to adhere and migrate through the endothelium. Neutrophils in the blood vessel wall release toxic substances that cause vessel damage (degranulation) (44).

In addition, neutrophils release several mediators, including properdin, that activate the alternative complement pathway. The terminal effector protein C5a acts through its C5a receptor (C5aR1, or CD88) to play a central role in the pathogenesis of AAV (45-47). The heart of the vasculitis process in AAV is the C5a neutrophil priming effect driving an inflammatory cycle mediated by the complement-neutrophil interaction, acting as a powerful chemoattractant for further neutrophils. The resulting necrotising inflammation leads to damage and loss of organ function (47).

B.1.3.6. Quality of life

AAV is a debilitating disease that substantially impairs patients' physical and emotional well-being, reducing their QoL compared with population norms at diagnosis both physically (odds ratio [OR], 7.0; 95% confidence interval [CI], 4.4-11.1) and mentally (OR, 2.5; 95% CI, 1.7-3.6) (48). The chronic relapsing and remitting nature of AAV, and requirement for prolonged treatment, significantly impacts patients' physical and emotional well-being, reducing their QoL (48-56). AAV affects all aspects of patient's QoL, with patients reporting significantly worse QoL than population controls (49, 52). Benarous et al. assessed QoL using the 36-Item Short Form Health Survey (SF-36) in a French cohort of 189 AAV patients; they reported altered physical health in 19% of patients and altered mental health in 14% of the study population (52). In another study, sleep impairment, assessed using the Pittsburgh Sleep Quality Index, was significantly worse in AAV patients ($p \leq 0.001$). Anxiety and depression, assessed using the Hospital Anxiety and Depression Scale, were present in significantly more patients with AAV than healthy controls (anxiety, $p=0.001$; depression, $p=0.003$) (57). Fatigue is a major issue for AAV patients, with up to 58% developing severe fatigue (58). European Vasculitis Society data show that although fatigue improves after induction remission, it remains higher than that measured in controls ($p<0.001$) (59).

In a study by Herlyn et al., 264 AAV patients across 3 countries (the United States, Germany, and the United Kingdom) were assessed for their perspective of the burden of disease using a validated questionnaire (60). Patients ranked the severity of their symptoms on a scale from 0 to 5, with 5 being the most severe. Fatigue (3.5), loss of energy (3.4), weight gain (3.1), joint pain (3.0), and sinusitis (3.0) were the

highest ranked symptoms, experienced by at least 50% of the study cohort. Ninety-five percent of all patients experienced both fatigue and energy loss and rated these manifestations as severe. However, severe organ manifestations (seizures, kidney failure, and oxygen dependency) were perceived as lower in terms of burden (<3.0). Saddle nose deformity and thrombosis were relatively rare but were rated as severe. Patients from different nationalities rated their burdens similarly. Patients in self-declared remission estimated their disease manifestations as less severe, with lower mean scores than patients who rated their disease as active or very active (60).

B.1.3.7. Current management

AAV is a relatively rare condition and NICE has not published clinical guidelines or patient pathways on AAV or related vasculitis conditions. NICE has published a technology assessment on the use of RTX in AAV (8), the recommendations of which have led to the commissioning of RTX by NHS England (61). Evidence-based clinical guidelines have been published jointly by the British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) in 2014 (7). These guidelines are NICE accredited and are also closely aligned with guidelines from the European League Against Rheumatism (EULAR), published in 2016 (62). The management strategy of AAV consists of 2 principal phases: induction of remission and maintenance. Treatment of relapses or refractory disease may also be necessary.

Induction treatment

Upon presentation of a person with newly diagnosed AAV, or a patient who is suspected of undergoing relapse, a full assessment should be undertaken to establish disease activity and need for treatment. The established first-line treatment for newly diagnosed AAV is high-dose GCs combined with IV pulse CYC (7), which have been used for several decades (63). NICE recommends that RTX can be used in place of CYC when the person has contraindications or intolerance to CYC, there are potential fertility issues, the person has uroepithelial malignancy, AAV has remained active or progressed despite a course of CYC lasting 3 to 6 months, or a further CYC would exceed the maximum cumulative CYC dose (25 g, equivalent to 2

induction courses) (8). Regarding the latter stipulation, following considerations regarding the clinical and cost-effectiveness of RTX reported from trial evidence (64), NHS England will fund RTX treatment following a single relapse of AAV in a person who has received CYC (61). The licensed RTX dosing protocol is 375 mg/m^2/week for 4 weeks; however, 1 g repeated after 2 weeks is considered equally effective (8).

As discussed, whether CYC of RTX immunosuppressants are prescribed, they require adjunctive use of high-dose GCs. Usually, a daily dose of oral prednisolone is prescribed, at a dose of 1 mg/kg (up to a maximum of 60 mg). This dose is rapidly reduced to 15 mg prednisolone at 12 weeks and then typically further tapered over longer time frames (7). Longer courses of GCs are associated with increased toxicity and an increased risk of infection; however, such courses may also be associated with fewer relapses. Other immunosuppressant treatment options for active AAV include MTX (up to 25 to 30 mg/wk) or MMF (up to 3 g/d), which may be used in the presence of relatively mild disease activity when the person is not at risk of suffering organ damage, as assessed by the BVAS. In addition, AZA or MTX can be used to switch from CYC and be subsequently tapered. For people undergoing a severe relapse that is organ or life threatening, plasma exchange (PLEX) may be a last-line option.

Maintenance treatment

Once the induction period has been completed and patients are in remission, BSR/BHPR guidelines recommend maintenance therapy for at least 24 months (7). Administration of low-dose GCs, as well as AZA or MTX if CYC was used for remission induction, or a continuation of RTX if used for remission induction is recommended. MMF or leflunomide may be used as alternatives for intolerance to or lack of efficacy of AZA or MTX (7).

Patients in continual remission for at least 1 year on maintenance therapy should be considered for tapering of GC treatment, as per the BSR/BHPR guidelines. Following GC withdrawal, other immunosuppressive therapy may be withdrawn after 6 months (7).

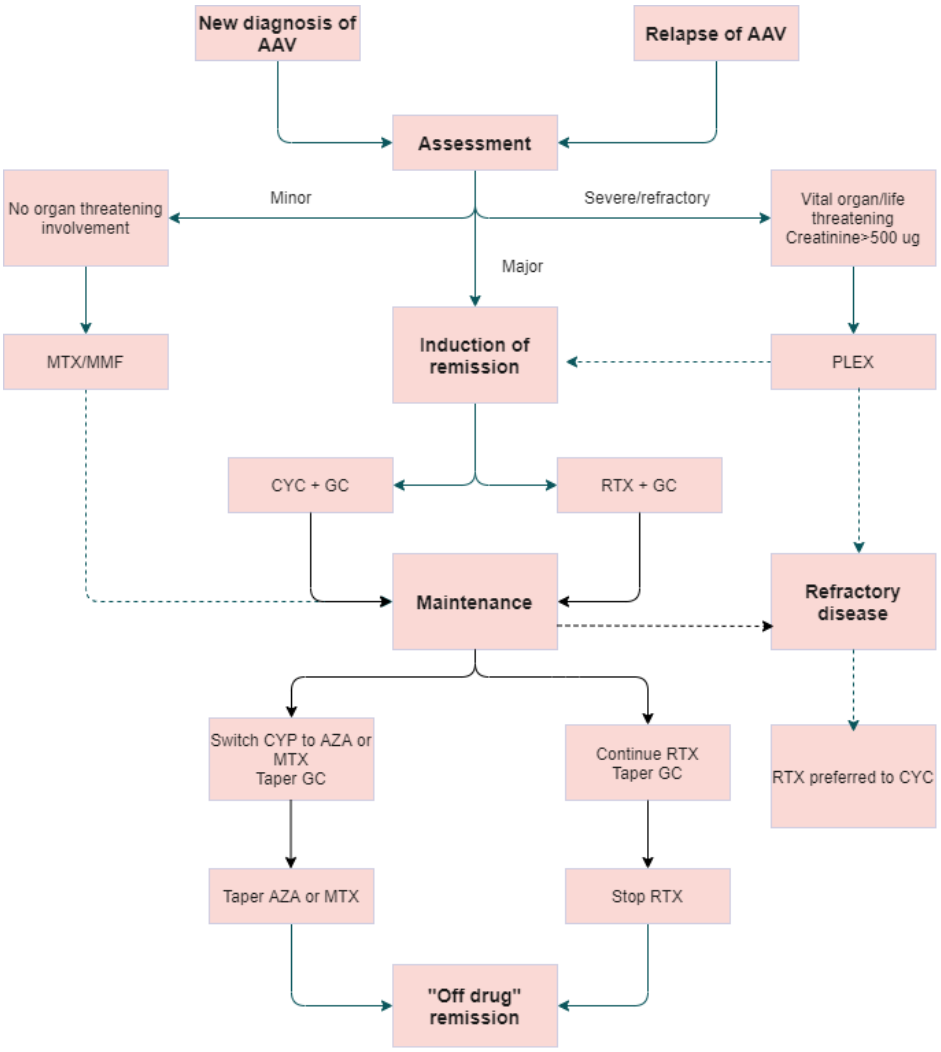
Management of relapse and refractory disease

Relapse occurs when AAV that has been previously well controlled has become active, with minor relapse defined as an increase of 1 or more new or worse minor items and no major BVAS items, and major relapse defined as an increase of 1 or more major BVAS items. For relapses that are considered ‘minor’ or non-organ threatening, BSR/BHPR recommend increasing the GC dosage and revaluating maintenance therapy for optimisation. Recommendations for patients experiencing a major relapse are broadly similar to those described for remission induction and include reintroduction of GCs plus CYC or RTX (7). In the RAVE trial, RTX was found to be superior to CYC for the treatment of relapsing disease (9).

AAV is considered refractory when progressive disease is unresponsive to current therapy (remission is not achieved). Management of refractory disease should be undertaken in close collaboration with specialised tertiary centres. RTX is considered more effective than other immunosuppressant drugs for treating refractory disease (7). In the evidence review group report published as part of the NICE technology appraisal of RTX, it is highlighted that possible treatments for refractory disease are wide-ranging, and may also include continuation of AZA (8).

The management pathways for the treatment of AAV are summarised in Figure 2 (adapted from BSR/BHPR guidelines) (7).

Figure 2. Current management pathway of AAV, adapted from BSR/BHPR guidelines



Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; AZA, azathioprine; CYC, cyclophosphamide; GC glucocorticoid; MMF mycophenolate mofetil; MTX, methotrexate; PLEX, plasma exchange; RTX, rituximab

B.1.3.7. Avacopan

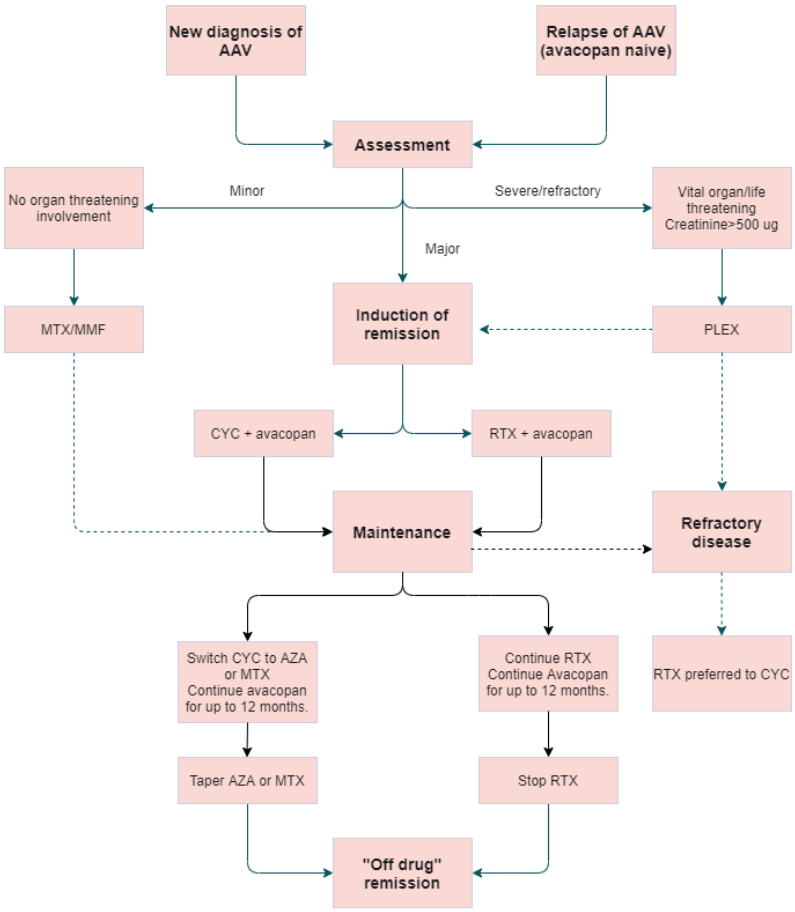
Avacopan is intended for use to induce and maintain remission in people with newly diagnosed AAV or people with AAV who are undergoing a significant relapse. It is to be used concomitantly with immunosuppressant drugs, CYC or RTX, and it reduces or replaces the need for adjunctive GC. The recommended dose is 30 mg twice per day, with doses to be taken orally approximately 12 hours apart. Once remission is achieved, avacopan treatment can be continued during the maintenance phase. In the ADVOCATE trial, avacopan was associated with significant reductions in GC use and related AEs (for up to 1 year), as well as significantly higher numbers of patients

achieving sustained remission and reduced relapse rates, compared with patients in the tapered GC arm at 52 weeks (65).

MTX and MMF are recommended as alternatives to CYC/AZA or RTX for remission induction in patients with localised disease at low risk of suffering organ damage. These patients were not studied in ADVOCATE and so they are not relevant comparators for avacopan. In practice, however, such immunosuppressants might be combined with avacopan in line with current pathways.

The BSR/BHPR management pathways for the treatment of AAV, with the additional availability of avacopan, are summarised in Figure 3 (7).

Figure 3. Current management pathway of AAV (adapted from BSR/BHPR guidelines) incorporating avacopan



Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; AZA, azathioprine; CYC, cyclophosphamide; DMARD, disease-modifying antirheumatic drug; GC glucocorticoid; MMF mycophenolate mofetil; MTX, methotrexate; PLEX, plasma exchange; RTX, rituximab

B 1.3.9. Unmet need

AAV is a rare, potentially fatal, remitting-relapsing, autoimmune condition that has a substantial impact on patient morbidity, mortality, and QoL.

With the advent of CYC or RTX plus high-dose GC treatment, the mortality rate of AAV has decreased, but it remains higher than that of the general population (10, 66-69). Almost 3 times as many AAV patients die over a period of 5.2 years compared with the general population ($p<0.0001$) (10). Despite current SoC treatment, patients with GPA have an increased mortality risk in the first year of disease, compared with healthy controls, with mortality attributed to infection, vasculitis, renal disease (70), and the medications used (11). The MPA clinical subtype is associated with worse survival than the GPA subtype, clinical trials showed that 5-year survival rates were 87% and 69% for patients with GPA and MPA, respectively (10). Longer-term mortality is increased because of disease-related complications, development of cardiovascular (CV) disease, renal disease, and GC-related toxicity (10, 11).

The BSR/BHPR guidelines stress that AAV therapy is aimed at rapidly inducing remission and sustaining it, thereby preventing organ damage while also avoiding drug toxicity (7). Induction of remission in AAV patients can take 4 weeks with RTX and up to 6 months with CYC (8). Although it is possible for most AAV patients to achieve remission with therapy, the majority of patients experience 1 or more relapses within 5 years of successful remission induction (9), and relapses can be fatal (71). Approximately 10-30% of patients do not respond to traditional immunosuppressive agents and pursue a refractory course (72). A number of factors, including specific treatment regimens, have been associated, albeit inconsistently, with high relapse rates (73-75). Although evidence suggests that longer courses of GCs are associated with fewer relapses (76, 77), their role for prevention of relapse remains unclear. For this reason, patients need to be regularly monitored to promptly diagnose and treat a possible recurrence of AAV.

The medications commonly used to treat vasculitis, including GCs and immunosuppressive drugs, carry substantial risk for toxicity, including malignancy,

infections, and other related side effects (78). High doses of GCs remain a mainstay of therapy for most types of vasculitis but are commonly associated with a wide range of potentially debilitating side effects (79, 80), with acute treatment-associated toxicity thought to cause approximately 60% of deaths (81). The odds of high levels of organ damage have been estimated to increase by 1.26 for every 12 months of GC use (p=0.022), and nearly half of patients on GCs have ≥5 items of damage recorded on the Vasculitis Damage Index (VDI) at long-term follow-up (82). In current management pathways, the risk of GC-mediated morbidity is likely to increase with each occurrence of relapse. In addition, a wide variation in the doses given, a long duration of use, and the need to gradually reduce dosage as treatment ends make them complex for clinicians to prescribe and for patients to comply accurately with treatment.

A number of studies have also suggested that the use of immunosuppressive agents can result in an impaired humoral response to vaccines (83). For instance, the use of RTX can result in an ineffective vaccination response to the coronavirus disease 2019 vaccine (84-86).

There is, therefore, a clear need for novel and effective treatments to replace current options that rapidly induce remission, reduce the rate of relapses (i.e., induce durable remission), and reduce the rate of GC-related toxicity. An avacopan-based regimen reduces, and in some cases eliminates, the need for GC therapy, thereby greatly benefiting patients through the reduction of GC-mediated AEs and complications. Furthermore, avacopan significantly improves the rate of sustained remission and reduces relapse compared with current SoC. CYC and RTX are also associated with significant AEs, including malignancy, infertility, urinary bladder complications and early menopause with CYC and increased risk of infections and hypogammaglobulinaemia with RTX. Improving the rate of sustained remission reduces the requirement for further induction therapy with CYC or RTX. Therefore, avacopan is likely to provide longer-term benefits in this patient group.

B.1.4 Equality considerations

The use of avacopan in AAV is not likely to raise any equality issues.

B.2 Clinical effectiveness

Summary
Three randomised controlled trials have investigated the efficacy and safety of avacopan in MPA and GPA, including ADVOCATE, a pivotal Phase 3 trial, and 2 Phase 2 trials, CLEAR and CLASSIC

B.2.1 Identification and selection of relevant studies

Full details of the identification and selection of the relevant studies are provided in Appendix D.

B.2.1.1. Search strategy

A systematic literature review was conducted to identify all relevant clinical evidence from the published literature reporting the clinical efficacy, safety, and tolerability of avacopan in combination with CYC or RTX (with or without GCs) compared with relevant comparator therapies for adult patients with GPA or MPA.

The searches were designed to meet the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. Initial searches were performed on 4 June 2018 with subsequent updates on 16 June 2020 and 18 June 2021.

Full details of the searches are provided in Appendix D.

B.2.1.2. Study selection

Details of the methods of study selection are provided in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

In total, 3 studies investigating the efficacy and safety of avacopan in MPA and GPA were identified: 2 Phase 2 randomised controlled trials, CLEAR (NCT01363388) (4, 87) and CLASSIC (NCT02222155) (88, 89), and a pivotal Phase 3 randomised controlled trial, ADVOCATE (NCT02994927) (2, 65) (Table 4).

Table 4. Clinical effectiveness evidence

Study		ADVOCATE (NCT02994927) (2, 65)	CLEAR (NCT01363388) (4, 87)	CLASSIC (NCT02222155) (88, 89)
Study design		Phase 3, randomised, double-blind, double-dummy, active-controlled, multicentre international clinical study	Phase 2, randomised, double-blind, double-dummy, placebo-controlled clinical study	Phase 2, randomised, double-blind, double-dummy, placebo-controlled clinical study
Population		Adults with newly diagnosed or relapsing MPA or GPA		
Intervention(s)		Avacopan in combination with CYC (followed by AZA) or RTX (with/without GCs)	• Avacopan in combination with CYC or RTX without GCs • Avacopan in combination with CYC or RTX with two-thirds reduced starting dose of GCs	• Low-dose avacopan in combination with CYC or RTX (with or without GCs) • High-dose avacopan in combination with CYC or RTX (with or without GCs)
Comparator(s)		Prednisone in combination with CYC (followed by AZA) or RTX	Placebo in combination with CYC or RTX with full starting dose of GCs	Placebo in combination with CYC or RTX
Indicate if trial supports application for marketing authorisation	**Yes**	X	X	X
	No			
Indicate if the trial is used in the economic model	**Yes**	X		
	No		X	X
Rationale for use/non-use in the model		Pivotal Phase 3 study of avacopan	Treatment duration too short to inform model; dosing regimens not in line with anticipated license	Treatment duration too short to inform model; dosing regimens not in line with anticipated license
Reported outcomes specified in the decision problem		• Remission rate • Sustained remission	• Remission rate • Sustained remission	• Remission rate • Sustained remission

	• VDI
	• Change in renal function:
	  ○ eGFR
	  ○ UACR
	  ○ Urinary MCP-1: creatinine ratio
	• GC-induced toxicity and GC-related adverse effects
	• Adverse effects of treatment
	• HRQoL
		• VDI
		• Change in renal function:
		  ○ eGFR
		  ○ UACR
		  ○ Urinary MCP-1: creatinine ratio
		  ○ CRP
		• Adverse effects of treatment
		• HRQoL
			• VDI
			• Change in renal function:
			  ○ eGFR
			  ○ UACR
			  ○ Urinary MCP-1: creatinine ratio
			  ○ CRP
			• Adverse effects of treatment
			• HRQoL

All other reported outcomes	• PD markers in plasma and urine • PK profile of avacopan	• Changes in ANCA (anti-PR3 and anti-MPO) • PD markers in plasma and urine • PK profile of avacopan	• Changes in ANCA (anti-PR3 and anti-MPO) • PD markers in plasma and urine • PK profile of avacopan
Abbreviations: ANCA, anti-neutrophil cytoplasmic autoantibody; AZA, azathioprine; CRP, C-reactive protein; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; GC, glucocorticoid; HRQoL, health-related quality of life; MCP-1, monocyte chemoattractant protein-1; MPO, myeloperoxidase; PD, pharmacodynamics; PK, pharmacokinetics; PR3, proteinase 3; RTX, rituximab; UACR, urinary albumin-to-creatinine ratio; VDI, Vasculitis Damage Index			

Treatment duration in the CLEAR and CLASSIC studies was too short to inform the economic model and the dosing regimens were not in line with anticipated license. Both studies present supportive data of avacopan efficacy and safety in AAV and are presented in sections B.2.3 to B2.6.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

ADVOCATE

ADVOCATE (NCT02994927) was a Phase 3 randomised, double-blind, double-dummy, active-controlled, multicentre international clinical study (see Table 5 for trial methodology summary). Patients were randomised in a 1:1 ratio to either of 2 study treatment groups (2, 65):

1. Avacopan 30 mg twice daily plus CYC (followed by AZA) or RTX plus prednisone-matching placebo
2. Tapering oral regimen of prednisone plus CYC (followed by AZA) or RTX plus avacopan-matching placebo

Avacopan (30 mg twice daily) or matching placebo was given for 52 weeks, with 8 weeks of follow-up. Prednisone or a matched placebo was given on a tapering schedule for 20 weeks (60 mg per day tapered to discontinuation by week 21) (2, 65).

CLEAR

CLEAR (NCT01363388) was a Phase 2 randomised, double-blind, double-dummy, placebo-controlled, clinical study (see Table 6 for trial methodology summary) (4, 87).

In step 1 (12 subjects) and step 2 (14 subjects) of the study, subjects were stratified to either of 2 strata (either newly diagnosed or relapsed AAV with renal involvement) and then randomised to avacopan or placebo (in a 2:1 ratio). For step 1 of the study, a two-thirds reduced starting dose of oral GCs was given to subjects randomised to avacopan (prednisone 20 mg per day [15 mg prednisone per day if body weight <55 kg]) and a full starting dose of oral GCs (prednisone 60 mg per day [45 mg prednisone per day if body weight <55 kg]) to subjects randomised to placebo. In step 2 of the study, oral GCs were not given to subjects randomised to avacopan, but a full starting dose of oral GCs (prednisone 60 mg per day [45 mg prednisone per day if body weight <55 kg]) was given to subjects randomised to placebo) (4, 87).

Step 2 was opened for enrolment if both of the following criteria were met (4, 87):

- Not more than 1 suspected unexpected serious adverse reaction most likely related to avacopan, as assessed by the data monitoring committee, was observed in subjects receiving avacopan in step 1
- Disease activity of AAV with renal involvement was controlled in most subjects (>50%) receiving avacopan in step 1, without the need for rescue GC therapy, as assessed by the data monitoring committee

All subjects in steps 1 and 2 of the study received intravenous (IV) CYC (15 mg/kg every 2 weeks [from days 1 through 29], on day 57, and every 4 weeks [from days 85 through 169, at the discretion of the principal investigator]), which is part of standard therapy for AAV. If necessary, rescue GCs were given to subjects with worsening disease (4, 87).

Step 3 was opened for enrolment if both of the following criteria were met (4, 87):

- Not more than 1 suspected unexpected serious adverse reaction most likely related to avacopan, as assessed by the data monitoring committee, was observed in subjects receiving avacopan in step 2
- AAV disease activity was controlled in most subjects (>50%) receiving avacopan in step 2, without the need for rescue GC therapy

In step 3, 41 subjects were stratified prior to randomisation based on the following 3 factors: newly diagnosed or relapsed AAV, MPO or PR3 ANCA positivity, and CYC or RTX use (4, 87).

Following stratification, subjects were randomised 1:1:1 to 1 of 3 groups (4, 87):

1. Avacopan plus CYC or RTX plus no oral GCs
2. Placebo plus CYC or RTX plus a full starting dose of oral GCs
3. Avacopan plus CYC or RTX plus a two-thirds reduced starting dose of oral GCs

In step 3, subjects in the CYC stratum received IV CYC (15 mg/kg on days 1, 15, 29, 57, and 85) as part of SoC treatment and oral AZA (to a target dose of 2 mg/kg/d, starting on day 99). Subjects in the RTX stratum received 375 mg/m^2 RTX IV once weekly for 4 weeks. If necessary, rescue GCs were given to subjects with worsening disease. The avacopan/placebo treatment period for all 3 steps of the study was 12 weeks, followed by a 12-week follow-up period (4).

CLASSIC

CLASSIC (NCT02222155) was a Phase 2 randomised, double-blind, placebo-controlled clinical study (see Table 7 for trial methodology summary) (88, 89).

Subjects were planned to be stratified based on the following factors: newly diagnosed or relapsed AAV, MPO or PR3 ANCA positivity, and CYC or RTX SoC treatment. Following stratification, subjects were randomised 1:1:1 to 1 of 3 groups (88):

1. Avacopan 10 mg twice daily plus CYC or RTX plus GCs
2. Avacopan 30 mg twice daily plus CYC or RTX plus GCs
3. Placebo twice daily plus CYC or RTX plus GCs

If necessary, rescue GCs were given to subjects with worsening disease.

All subjects received prednisone 60 mg orally per day starting on day 1 with a tapered dose, per protocol-specified schedule. Subjects in the CYC stratum received IV CYC (15 mg/kg on days 1, 15, 29, 57, and 85) as part of SoC treatment and oral AZA (to a target dose of 2 mg/kg/d, starting on day 99). Subjects in the RTX stratum received 375 mg/m^2 RTX IV once weekly for 4 weeks starting on day 1. No oral AZA was given to subjects receiving RTX (88).

Twice-daily dosing of avacopan or placebo continued for 12 weeks (88).

Table 5. Summary of trial methodology, ADVOCATE

Trial number	NCT02994927
Location	North America, Europe, Australia, New Zealand, and Japan
Trial design	Phase 3, randomised, double-blind, double-dummy, active-controlled, multicentre international clinical study
Eligibility criteria for participants	Inclusion criteria 1. Clinical diagnosis of GPA or MPA, consistent with Chapel Hill Consensus Conference definitions 2. Aged at least 18 years, with newly diagnosed or relapsed AAV for which treatment with CYC or RTX was needed; where approved, adolescents (12 to 17 years old) may have been enrolled. Female subjects of childbearing potential may have participated if adequate contraception was used during the study, for at least 6 months after the last CYC dose (if receiving CYC), and for at least 12 months after the last RTX dose (if receiving RTX). Male subjects with partners of childbearing potential may have participated in the study if they had a vasectomy at least 6 months prior to randomisation or if adequate contraception was used during the study, for at least 6 months after the last CYC dose (if receiving CYC), and for at least 12 months after the last RTX dose (if receiving RTX). Adequate contraception was defined as resulting in a failure rate of less than 1% per year (combined oestrogen and progestogen [oral, intravaginal, or transdermal], progestogen-only hormonal contraception [oral, injectable, or implantable], intra-uterine device, intra-uterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner, or absolute sexual abstinence [in line with the preferred and usual lifestyle of the subject]). For subjects who received mycophenolate instead of AZA, a second form of birth control must have been used if the first form of birth control was hormonal contraception. Sperm donation for at least 6 months after the last CYC dose (if receiving CYC), and for at least 12 months after the last RTX dose (if receiving RTX), must not have been performed 3. Tested positive for anti-PR3 or anti-MPO (current or historic) antibodies 4. Had at least 1 major item, or at least 3 minor items, or at least the 2 renal items of proteinuria and haematuria, in the BVAS; care must have been taken to ensure that the renal items were due to vasculitis activity and not other factors such as menses or CYC-related cystitis. If a subject had “other” items not specified in the BVAS, these needed to be discussed with the medical monitor before enrolment 5. Had an eGFR ≥15 mL/min/1.73 m^2 (using the MDRD method for adults, and modified Schwartz equation for adolescents)

	6. Willing and able to give written informed consent and to comply with the requirements of the study protocol; written informed consent should have been obtained from the legal guardian in accordance with regional laws or regulations for subjects aged 12 to 17 years 7. Judged by the investigator to be fit for the study, based on medical history, physical examination (including ECG), and clinical laboratory assessments. Subjects with clinical laboratory values that were outside normal limits (other than those specified in the exclusion criteria) and/or with other abnormal clinical findings that were judged by the Investigator not to compromise subject participation in the study may have been entered into the study <u>Exclusion criteria</u> 1. Was pregnant or breastfeeding 2. Had experienced alveolar haemorrhage requiring invasive pulmonary ventilation support anticipated to last beyond the screening period of the study 3. Had any other known multi-system autoimmune disease, including EGPA (Churg-Strauss), systemic lupus erythematosus, immunoglobulin A vasculitis (Henoch-Schönlein), rheumatoid vasculitis, Sjögren's syndrome, anti-glomerular basement membrane disease, or cryoglobulinaemic vasculitis 4. Required dialysis or plasma exchange within 12 weeks prior to screening 5. Had a kidney transplant 6. Received CYC within 12 weeks prior to screening; if on AZA, mycophenolate, or methotrexate at the time of screening, these drugs must have been withdrawn prior to receiving the CYC or RTX dose on day 1 7. Received IV GCs, >3000 mg methylprednisolone equivalent, within 4 weeks prior to screening 8. Had been taking an oral daily dose of a GC of more than 10 mg prednisone equivalent for more than 6 weeks continuously prior to the screening visit 9. Received RTX or other B-cell antibody within 52 weeks of screening or 26 weeks provided B cell reconstitution has occurred (i.e., CD19 count >0.01x10^9/L); received anti-TNF treatment, abatacept, alemtuzumab, intravenous immunoglobulin, belimumab, tocilizumab, or eculizumab within 12 weeks prior to screening; immunosuppressive drugs not listed here must have been discussed with the medical monitor 10. Was currently taking a strong inducer of the cytochrome P450 3A4 enzyme, such as carbamazepine, phenobarbital, phenytoin, rifampin, or St John’s wort 11. Had any of the following within 12 weeks prior to screening: symptomatic congestive heart failure requiring prescription medication, unstable angina (unless successfully treated with stent or bypass surgery), clinically significant cardiac arrhythmia, myocardial infarction, or stroke

	12. Had a history or presence of any form of cancer within the 5 years prior to screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or carcinoma in situ such as cervical or breast carcinoma in situ that had been excised or resected completely and was without evidence of local recurrence or metastasis 13. Had evidence of tuberculosis based on IGRA assay, PPD skin test, or chest radiography (X-rays or CT scan) done at screening or within 6 weeks prior to screening 14. Had an HBV, HCV, or HIV screening test showing evidence of active or chronic viral infection at screening or within 6 weeks prior to screening 15. Received a live vaccine within 4 weeks prior to screening 16. Had a white blood cell count less than 3500/μL, or neutrophil count less than 1500/μL, or lymphocyte count less than 500/μL before start of dosing 17. Had evidence of hepatic disease: AST, ALT, ALP, or bilirubin >3 times the upper limit of normal before start of dosing 18. Had a clinically significant abnormal ECG during screening (e.g., QT interval corrected by Fridericia greater than 450 msec) 19. Had a known hypersensitivity to avacopan or inactive ingredients of the avacopan capsules (including gelatin, polyethylene glycol, or Cremophor), CYC or its metabolites (for subjects scheduled to receive CYC), or known type I hypersensitivity or anaphylactic reactions to murine proteins, Chinese hamster ovary cell proteins, or to any component of RTX (for subjects scheduled to receive RTX), or any contraindications or hypersensitivity to the use of AZA, CYC, mycophenolate, or prednisone, or excipients, where applicable, as per the local prescribing information. For subjects who received AZA, concomitant use with allopurinol was contraindicated 20. For subjects scheduled to receive CYC treatment, urinary outflow obstruction, had an active infection (especially varicella zoster infection), or platelet count <50,000/μL before start of dosing 21. Had participated in any clinical study of an investigational product within 30 days prior to screening or within 5 half-lives after taking the last dose 22. Had participated previously in an avacopan study 23. Had a history or presence of any medical condition or disease which, in the opinion of the investigator, may have placed the subject at unacceptable risk for study participation
Settings and locations where the data were collected	143 study centres in North America, Europe, Australia, New Zealand, and Japan, including 31 centres in the UK and 3 in the Republic of Ireland.

Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	Patients were randomised in a 1:1 ratio to either of 2 study treatment groups: • 30 mg twice daily avacopan plus CYC (followed by AZA) or RTX plus prednisone-matching placebo (N=166) • tapering oral regimen of prednisone plus CYC (followed by AZA) or RTX plus avacopan-matching placebo (N=165) Avacopan (30 mg twice daily) or matching placebo was given for 52 weeks, with 8 weeks of follow-up. Prednisone or a matched placebo was given on a tapering schedule for 20 weeks (60 mg per day tapered to discontinuation by week 21).
Primary outcomes (including scoring methods and timings of assessments)	The primary outcomes were the following: 1. Remission, defined as achieving a BVAS of 0 and not taking GCs for AAV within 4 weeks prior to week 26 2. Sustained remission, defined as remission at week 26 and remission at week 52, without having a relapse between week 26 and week 52. Remission at week 52 was defined as having a BVAS of 0 and not taking GCs for AAV for 4 weeks prior to week 52 A relapse was defined as worsening of disease, after having previously achieved remission (BVAS=0), that involved any of the following: • 1 or more major item in the BVAS • 3 or more minor items in the BVAS • 1 or 2 minor items in the BVAS recorded at 2 consecutive study visits
Other outcomes used in the economic model/specified in the scope	The secondary outcomes were the following: 1. Rapidity of response, based on BVAS of 0 at week 4 (regardless of GC use) 2. GC-induced toxicity, assessed using GTI 3. Changes in parameters of renal disease in subjects with active renal disease at baseline, including:

<table>
<tr><td></td><td colspan="2">

eGFR
UACR
urinary MCP-1:creatinine ratio

4. Changes in cumulative organ damage based on VDI)
5. HRQoL changes, assessed using SF-36v2 and EQ-5D-5L
6. Incidence of AEs
</td></tr>
<tr><td>Pre-planned subgroups</td><td>
<u>Subgroups</u>

Subjects with renal disease at baseline (based on BVAS renal component)
Subjects without active renal disease at baseline
Subjects with GPA
Subjects with MPA
IV RTX
IV CYC
Oral CYC
Anti-PR3 ANCA
Anti-MPO ANCA
Newly diagnosed AAV
Relapsed AAV

</td><td>
<u>Covariates</u>

Sex (male, female)
BMI (<30 kg/m^2, ≥30 kg/m^2)
Age at diagnosis of AAV (≤50 years, >50 years)
Duration of AAV (<1 year, ≥1 year)
Subject's age (12-17 years, 18-50 years, 51-64 years, 65-74 years, ≥75 years old), race (Asian, black/African American, white/Caucasian, other), and ethnicity (Hispanic, non-Hispanic, unknown/not reported)
Geographic distribution (North America, Europe, and rest of world except Japan, Europe, Japan)
Baseline BVAS (<15, ≥15)
Baseline VDI (0, >0)
Baseline eGFR (<30 mL/min/1.73 m^2, 30-59 mL/min/1.73 m^2, >59 mL/min/1.73 m^2)

</td></tr>
</table>

		• Baseline haematuria (<10 RBCs/hpf, ≥10 RBCs/hpf) • Baseline UACR (<10 mg/g, 10-300 mg/g, >300 mg/g creatinine) • Baseline urinary MCP-1:creatinine ratio (<median of all subjects in study, ≥median of all subjects in study)

Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; AE, adverse event; ANCA, anti-neutrophil cytoplasmic autoantibody; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; AZA, azathioprine; BMI, body mass index; BVAS, Birmingham Vasculitis Activity Score; CD19, cluster of differentiation 19; CT, computed tomography; CYC, cyclophosphamide; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EGPA, eosinophilic granulomatosis with polyangiitis; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; GTI, Glucocorticoid Toxicity Index; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; hpf, high-power field; HRQoL, health-related quality of life; IGRA, interferon gamma release assay; IV, intravenous; MCP-1, monocyte chemoattractant protein-1; MDRD, Modification of Diet in Renal Disease; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PPD, purified protein derivative; PR3, proteinase 3; RBC, red blood cell; RTX, rituximab; SF-36v2, 36-Item Short Form Health Survey version 2; TNF, tumour necrosis factor; UACR, urinary albumin-to-creatinine ratio; VDI, Vasculitis Damage Index

Table 6. Summary of trial methodology, CLEAR

Trial number (acronym)	NCT01363388
Location	Austria, Belgium, Czech Republic, Hungary, France, Germany, Ireland, The Netherlands, Poland, Sweden, United Kingdom
Trial design	Phase 2, randomised, double-blind, double-dummy, placebo-controlled clinical study
Eligibility criteria for participants	Inclusion criteria 1. Clinical diagnosis of GPA, MPA, or renal-limited vasculitis, consistent with Chapel Hill Consensus Conference definitions 2. Male and female subjects aged at least 18 years with new (typically within 4 weeks prior to screening) or relapsed AAV for which treatment with CYC or RTX would be required. Female subjects of childbearing potential could have participated if adequate contraception was used during the study, for at least 6 months after the last CYC dose (if receiving CYC), and for at least 12 months after the last RTX dose (if receiving RTX). Male subjects with partners of childbearing potential could have participated if they had a vasectomy at least 6 months prior to randomisation or if adequate

	contraception was used during the study, for at least 6 months after the last CYC dose (if receiving CYC), and for at least 12 months after the last RTX dose (if receiving RTX). Adequate contraception was defined as 1 highly effective method plus 1 effective method; highly effective methods included hormonal contraceptives (e.g., combined oral contraceptives, patch, vaginal ring, injectables, implants, intrauterine device or intrauterine system, vasectomy, tubal ligation); effective methods included barrier methods of contraception (e.g., male condom, female condom, cervical cap, diaphragm, contraceptive sponge plus a spermicide) 3. Positive indirect immunofluorescence test for P-ANCA or C-ANCA, or positive ELISA test for anti-PR3 or anti-MPO, at screening. If only the indirect immunofluorescence 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. Have at least 1 "major" item, or at least 3 non-major items, or at least 2 renal items on the BVAS version 3 5. eGFR ≥20 mL/min/1.73 m^2 (MDRD) 6. Willing and able to give written informed consent and to comply with the requirements of the study protocol 7. Judged to be otherwise healthy by the investigator, based on medical history, physical examination (including ECG), and clinical laboratory assessments. Subjects with clinical laboratory values that were outside of normal limits (other than those specified in the exclusion criteria) and/or with other abnormal clinical findings that were judged by the investigator not to be of clinical significance may have been entered into the study <u>Exclusion criteria</u> 1. Severe disease as determined by rapidly progressive glomerulonephritis such that commencement of renal replacement therapy could be anticipated within 7 days, or alveolar haemorrhage 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]) 2. Any other multi-system autoimmune disease, including EGPA, systemic lupus erythematosus, immunoglobulin vasculitis, rheumatoid vasculitis, Sjögren's disease, anti-glomerular basement membrane disease, or cryoglobulinemia 3. Medical history of coagulopathy or bleeding disorder

	4. Received CYC within 12 weeks prior to screening; if subject was on AZA, mycophenolate mofetil, or methotrexate at the time of screening, these drugs must have been withdrawn prior to the subject receiving the CYC or RTX dose on day 1 5. Received IV corticosteroids, >3,000 mg methylprednisolone equivalent, within 12 weeks prior to screening 6. 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 corticosteroids at the time of screening, the non–study-supplied corticosteroids were stopped when the subject started taking the study supplied 60 mg prednisone dose on day 1 7. Received RTX or other B-cell antibody within 52 weeks of screening or 26 weeks provided B-cell reconstitution had occurred (i.e., CD19 count >0.01×10^9/L); received anti-TNF treatment, abatacept, alemtuzumab, IV immunoglobulin, belimumab, tocilizumab, or plasma exchange within 12 weeks prior to screening 8. Symptomatic congestive heart failure requiring prescription medication; clinically evident peripheral oedema of cardiac origin; poorly controlled hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg); history of unstable angina, myocardial infarction, or stroke within 6 months prior to screening 9. History or presence of any form of cancer within the 5 years prior to screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or cervical carcinoma in situ or breast carcinoma in situ that had been excised or resected completely and was without evidence of local recurrence or metastasis 10. Evidence of tuberculosis based on chest X-rays performed during screening as part of the BVAS assessment 11. Positive HBV, HCV, or HIV viral screening test 12. Any infection requiring antibiotic treatment within 4 weeks prior to screening (except for prophylactic treatment for *Pneumocystis carinii* pneumonia or treatment for suspected infection that instead turned out to be a consequence of AAV [e.g., pneumonitis]) 13. Received a live vaccine within 4 weeks prior to screening 14. White blood cell count <4,000/μL, or neutrophil count <2,000/μL, or lymphocyte count <1,000/μL 15. Haemoglobin <9 g/dL (or 5.56 mmol/L) at screening 16. Evidence of hepatic disease; AST, ALT, ALP, or bilirubin >3× the upper limit of normal

	17. Prothrombin time or partial thromboplastin time higher than the normal reference limit 18. Clinically significant abnormal ECG during screening (e.g., QTcF >450 msec) 19. Participated in any clinical study of an investigational product within 30 days prior to screening or within 5 half-lives after taking the last dose 20. History or presence of any medical condition or disease which, in the opinion of the investigator, may have placed the subject at unacceptable risk for study participation
Settings and locations where the data were collected	60 sites in Austria, Belgium, Czech Republic, Hungary, France, Germany, Ireland, The Netherlands, Poland, Sweden, and the United Kingdom
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	Patients were randomised in a 1:1:1 ratio to 1 of 3 treatment groups: • Avacopan plus CYC or RTX plus no oral GCs (N=22) • Avacopan plus CYC or RTX plus a two-thirds reduced starting dose of oral GCs (N=22) • Placebo plus CYC or RTX plus a full starting dose of oral GCs (N=23) Subjects in the CYC stratum received IV CYC (15 mg/kg on days 1, 15, 29, 57, and 85) as part of SoC treatment and oral AZA (to a target dose of 2 mg/kg/d, starting on day 99. Subjects in the RTX stratum received 375 mg/m^2 RTX IV once weekly for 4 weeks. If necessary, rescue GCs were given to subjects with worsening disease. The avacopan/placebo treatment period was 84 days (12 weeks), followed by an 84-day (12 weeks) follow-up period. All subjects were to visit the study centre during the screening period, and on days 1, 2, 8, 15, 22, 29, 43, 57, 71, 85, 99, 113, 141, and 169.
Primary outcomes (including scoring methods and timings of assessments)	The primary outcome was the following: • Clinical response, defined as a decrease from baseline to week 12 in BVAS of at least 50%, with no worsening in any body system
Other outcomes used in the economic model/specified in the scope	The secondary outcomes were the following: • In subjects with haematuria and albuminuria at baseline, the proportion of subjects achieving renal response at day 85. Renal response was defined as an improvement in the following parameters of renal vasculitis: o An increase from baseline to day 85 in eGFR (MDRD serum creatinine equation) o A decrease from baseline to day 85 in haematuria (central laboratory microscopic count of urinary RBCs)

	○ A decrease from baseline to day 85 in albuminuria (first morning UACR) • 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/hpf • Percent change from baseline to day 85 in BVAS • Change and percent change from baseline to day 85 in eGFR; • In subjects with baseline haematuria >5 RBCs/hpf, the proportion of subjects and time to first achieving urinary RBC count ≤5/hpf at any time during the 84-day treatment period • In subjects with baseline haematuria ≥30 RBCs/hpf, the proportion of subjects and time to first achieving urinary RBC count <30/hpf at any time during the 84-day treatment period • In subjects with haematuria at baseline, the percent change from baseline to day 85 in urinary RBC count • In subjects with albuminuria at baseline, the percent change from baseline to day 85 in UACR • Percent change from baseline to day 85 in urinary MCP-1:creatinine ratio • Proportion of subjects requiring rescue IV or oral GC treatment • Change from baseline to day 85 in the VDI • Change from baseline to day 85 in HRQoL, as measured by the SF-36 v2 and EQ-5D-5L • Total cumulative study-supplied prednisone dose and duration of dosing during the 84-day treatment period • Total cumulative systemic GC dose (any use) and duration of dosing during the 84-day treatment period • Total cumulative CYC or RTX dose and duration of dosing during the 84-day treatment period • Percent change from baseline in hsCRP • Percent change from baseline in ANCA (anti-PR3 and anti-MPO) at day 85 • Proportion of subjects becoming ANCA-negative at day 85 • Change and percent change from baseline in plasma and urine biomarkers • PK/PD endpoints
Pre-planned subgroups	• Subjects with renal disease at baseline (defined as subjects with BVAS items scored in the renal organ system)

	• Subjects without renal disease at baseline (defined as subjects with no BVAS items scored in the renal organ system) • Subjects who received CYC background treatment • Subjects who received RTX background treatment • Subjects with newly diagnosed disease • Subjects with relapsed disease • Subjects with MPO+ disease • Subjects with PR3+ disease • Subjects with GPA • Subjects with MPA

Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; ANCA, anti-neutrophil cytoplasmic autoantibody; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; AZA, azathioprine; BVAS, Birmingham Vasculitis Activity Score; C-ANCA, cytoplasmic anti-neutrophil cytoplasmic autoantibody; CYC, cyclophosphamide; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EGPA, eosinophilic granulomatosis with polyangiitis; ELISA, enzyme-linked immunosorbent assay; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; hsCRP, high-sensitivity C-reactive protein; IV, intravenous; MCP-1, monocyte chemoattractant protein-1; MDRD, Modification of Diet in Renal Disease; MPA, microscopic polyangiitis; MPO, myeloperoxidase; P-ANCA, perinuclear anti-neutrophil cytoplasmic autoantibody; PD, pharmacodynamics; PK, pharmacokinetics; PR3, proteinase 3; QTcF, Fridericia's correction formula; RBC, red blood cell; RTX, rituximab; SF-36v2, 36-Item Short Form Health Survey version 2; TNF, tumour necrosis factor; UACR, urinary albumin-to-creatinine ratio; VDI, Vasculitis Damage Index

Table 7. Summary of trial methodology, CLASSIC

Trial number	NCT02222155
Location	United States and Canada
Trial design	Phase 2, randomised, double-blind, double-dummy, placebo-controlled clinical study
Eligibility criteria for participants	Inclusion criteria 1. Clinical diagnosis of GPA, MPA, or renal-limited vasculitis, consistent with Chapel Hill Consensus Conference definitions 2. Male and female subjects aged at least 18 years with new (typically within 4 weeks prior to screening) or relapsed AAV for which treatment with CYC or RTX would be required. Female subjects of childbearing potential could have participated if adequate contraception was used during the study, for at least 6 months after the last CYC dose (if receiving CYC), and for at least 12 months after the last

	RTX dose (if receiving RTX). Male subjects with partners of childbearing potential could have participated if they had a vasectomy at least 6 months prior to randomisation or if adequate contraception was used during the study, for at least 6 months after the last CYC dose (if receiving CYC), and for at least 12 months after the last RTX dose (if receiving RTX). Adequate contraception was defined as 1 highly effective method plus 1 effective method; highly effective methods included hormonal contraceptives (e.g., combined oral contraceptives, patch, vaginal ring, injectables, implants, intrauterine device or intrauterine system, vasectomy, tubal ligation); effective methods included barrier methods of contraception (e.g., male condom, female condom, cervical cap, diaphragm, contraceptive sponge plus a spermicide) 3. Positive indirect immunofluorescence test for P-ANCA or C-ANCA, or positive ELISA test for anti-PR3 or anti-MPO at screening. If only the indirect immunofluorescence 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. Have at least 1 "major" item, or at least 3 non-major items, or at least 2 renal items on the BVAS version 3 5. eGFR ≥20 mL/min/1.73 m^2 (MDRD) 6. Willing and able to give written informed consent and to comply with the requirements of the study protocol 7. Judged to be otherwise healthy by the investigator, based on medical history, physical examination (including ECG), and clinical laboratory assessments. Subjects with clinical laboratory values that were outside of normal limits (other than those specified in the exclusion criteria) and/or with other abnormal clinical findings that were judged by the investigator not to be of clinical significance, may have been entered into the study <u>Exclusion criteria:</u> 1. Severe disease as determined by rapidly progressive glomerulonephritis such that commencement of renal replacement therapy could be anticipated within 7 days, or alveolar haemorrhage 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 mm Hg]) 2. Women who were pregnant or breastfeeding at study entry; women should not have breastfed during the study and, if receiving RTX, until drug levels were no longer detectable after study completion 3. Any other multi-system autoimmune disease, including EGPA, systemic lupus erythematosus, immunoglobulin vasculitis, rheumatoid vasculitis, Sjögren's disease, anti-glomerular basement membrane disease, or cryoglobulinemia

	4. Medical history of coagulopathy or bleeding disorder 5. Received CYC within 12 weeks prior to screening; if subject was on AZA, mycophenolate mofetil, or methotrexate at the time of screening, these drugs must have been withdrawn prior to the subject receiving the CYC or RTX dose on day 1 6. Received IV corticosteroids, >3,000 mg methylprednisolone equivalent, within 12 weeks prior to screening 7. 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 corticosteroids at the time of screening, the non–study-supplied corticosteroids were stopped when the subject started taking the study supplied 60 mg prednisone dose on day 1 8. Received RTX or other B-cell antibody within 52 weeks of screening or 26 weeks provided B-cell reconstitution had occurred (i.e., CD19 count >0.01×10^9/L); received anti-TNF treatment, abatacept, alemtuzumab, IV immunoglobulin, belimumab, tocilizumab, or plasma exchange within 12 weeks prior to screening 9. Symptomatic congestive heart failure requiring prescription medication; clinically evident peripheral oedema of cardiac origin; poorly controlled hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg); history of unstable angina, myocardial infarction, or stroke within 6 months prior to screening 10. History or presence of any form of cancer within the 5 years prior to screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or cervical carcinoma in situ or breast carcinoma in situ that had been excised or resected completely and was without evidence of local recurrence or metastasis 11. Evidence of tuberculosis based on chest X-rays performed during screening as part of the BVAS assessment 12. Positive HBV, HCV, or HIV viral screening test 13. Any infection requiring antibiotic treatment within 4 weeks prior to screening (except for prophylactic treatment for *Pneumocystis carinii* pneumonia or treatment for suspected infection that instead turned out to be a consequence of AAV [e.g., pneumonitis]) 14. Received a live vaccine within 4 weeks prior to screening 15. White blood cell count <4,000/μL, or neutrophil count <2,000/μL, or lymphocyte count <1,000/μL 16. Haemoglobin <9 g/dL (or 5.56 mmol/L) at screening 17. Evidence of hepatic disease; AST, ALT, ALP, or bilirubin >3×the upper limit of normal 18. Prothrombin time or partial thromboplastin time > normal reference limit 19. Clinically significant abnormal ECG during screening (e.g., QTcF >450 msec)

	20. Participated in any clinical study of an investigational product within 30 days prior to screening or within 5 half-lives after taking the last dose 21. Known hypersensitivity to avacopan or inactive ingredients of the avacopan capsules (including gelatin, polyethylene glycol, or Cremophor), CYC or its metabolites (for subjects scheduled to receive CYC), or known type I hypersensitivity or anaphylactic reactions to murine proteins, Chinese hamster ovary cell proteins, or to any component of RTX (for subjects scheduled to receive RTX) 22. Urinary outflow obstruction, active infection (especially varicella zoster infection), or platelet count <50,000/μL (for subjects scheduled to receive CYC treatment) 23. History or presence of any medical condition or disease which, in the opinion of the investigator, may have placed the subject at unacceptable risk for study participation
Settings and locations where the data were collected	47 sites in the United States and Canada
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	Patients were randomised in a 1:1:1 ratio to 1 of 3 study treatment groups: • Avacopan 10 mg twice daily plus CYC or RTX plus GCs (N=13) • Avacopan 30 mg twice daily plus CYC or RTX plus GCs (N=16) • Placebo twice daily plus CYC or RTX plus GCs (N=13) All subjects received prednisone 60 mg orally per day starting on day 1 with a tapered dose, per protocol-specified schedule. Subjects in the CYC stratum were to receive IV CYC (15 mg/kg on days 1, 15, 29, 57, and 85) as part of SoC treatment and oral AZA (to a target dose of 2 mg/kg/d, starting on day 99). Subjects in the RTX stratum received 375 mg/m^2 IV RTX once weekly for 4 weeks starting on day 1. No oral AZA was given to subjects receiving RTX. Twice-daily dosing of avacopan or placebo continued for 84 days (12 weeks).
Primary outcomes (including scoring methods and timings of assessments)	The primary outcome was the following: • 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 outcomes used in the economic model/specified in the scope	The secondary outcomes were the following: • In subjects with haematuria and albuminuria at baseline, the proportion of subjects achieving renal response at day 85. Renal response was defined as an improvement in the following parameters of renal vasculitis:

	○ An increase from baseline to day 85 in eGFR (MDRD serum creatinine equation) ○ A decrease from baseline to day 85 in haematuria (central laboratory microscopic count of urinary RBCs) ○ A decrease from baseline to day 85 in albuminuria (first morning UACR) • Proportion of subjects achieving disease remission at day 85 defined as BVAS of 0 • Proportion of subjects achieving early disease remission (BVAS of 0) at days 29 and 85 • Percent change from baseline to day 85 in BVAS • Change and percent change from baseline to day 85 in eGFR • In subjects with haematuria at baseline, the percent change from baseline to day 85 in urinary RBC count • In subjects with albuminuria at baseline, the percent change from baseline to day 85 in UACR • Percent change from baseline to day 85 in urinary MCP-1:creatinine ratio • Proportion of subjects requiring rescue glucocorticoid treatment • Change from baseline to day 85 in the VDI • Change from baseline to day 85 in HRQoL as measured by the SF-36v2 and EQ-5D • Total cumulative study-supplied prednisone dose and duration of dosing during the 84-day treatment period • Total cumulative systemic glucocorticoid dose (any use) and duration of dosing during the 84-day treatment period • Total cumulative CYC or RTX dose and duration of dosing during the 84-day treatment period • Percent change from baseline in hsCRP • Percent change from baseline in ANCA (anti-PR3 and anti-MPO) at day 85 • Proportion of subjects becoming ANCA negative at day 85 • Change and percent change from baseline in plasma and urine biomarkers All stated efficacy endpoints were assessed through the end of the follow-up period, day 169.
Pre-planned subgroups	• Subjects with renal disease at baseline (defined as subjects with BVAS items scored in the renal organ system)

	• Subjects without renal disease at baseline (defined as subjects with no BVAS items scored in the renal organ system) • Subjects receiving CYC background treatment • Subjects receiving RTX background treatment • Subjects with newly diagnosed disease • Subjects with relapsed disease • Subjects with MPO+ disease • Subjects with PR3+ disease • Subjects with GPA • Subjects with MPA

Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; ANCA, anti-neutrophil cytoplasmic autoantibody; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; AZA, azathioprine; BVAS, Birmingham Vasculitis Activity Score; C-ANCA, cytoplasmic anti-neutrophil cytoplasmic autoantibody; CD19, cluster of differentiation 19; CYC, cyclophosphamide; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EGPA, eosinophilic granulomatosis with polyangiitis; ELISA, enzyme-linked immunosorbent assay; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; IV, intravenous; MCP-1, monocyte chemoattractant protein-1; MDRD, Modification of Diet in Renal Disease; MPA, microscopic polyangiitis; MPO, myeloperoxidase; P-ANCA, perinuclear anti-neutrophil cytoplasmic autoantibody; PR3, proteinase 3; QTcF, Fridericia's correction formula; RBC, red blood cell; RTX, rituximab; SF-36v2, 36-Item Short Form Health Survey version 2; SoC, standard of care; TNF, tumour necrosis factor; UACR, urinary albumin-to-creatinine ratio; VDI, Vasculitis Damage Index

B.2.3.1 Baseline patient characteristics

ADVOCATE

In the ADVOCATE trial, a total of 166 patients were randomised to the avacopan group and 164 patients to the prednisone group (2, 65). The key baseline characteristics of participants are shown in Table 8.

The mean age of recruited subjects was 60.9 years, with the majority between the ages of 51 and 75 years (224 subjects [67.7%]); 3 subjects were aged 12 to 17 years. More male subjects than female subjects were randomised to treatment and most subjects were white and not Hispanic or Latino. Geographically, most subjects were enrolled at sites in Europe (70.1%). North America contributed 18.1% of subjects and Japan 6.3%. Germany (16.3%), the United States of America (14.2%), France (12.1%), and the United Kingdom (12.1%) were the highest enrolling countries (2, 65).

Most subjects enrolled in the study were newly diagnosed with AAV (69.4%) with a median duration of disease of approximately 0.2 months. The incidence of subjects with GPA was higher than those with MPA (54.8% vs 45.2%); most subjects were anti-MPO positive (57.0%), and most subjects were taking IV RTX as the SoC treatment. The most common organ systems affected by AAV were renal (81.2%); general (68.2%); ear, nose, and throat (43.6%); and chest (43.0%) (2, 65).

Table 8. Baseline characteristics of participants, ADVOCATE (2, 65)

Baseline characteristic	Avacopan	Prednisone
Number of patients, N	166	164
Mean age at screening ± SD, years	61.2±14.6	60.5±14.5
Male, n (%)	98 (59.0)	88 (53.7)
Race		
White, n (%)	138 (83.1)	140 (85.4)
Asian, n (%)	17 (10.2)	15 (9.1)
Black, n (%)	3 (1.8)	2 (1.2)
Other, n (%)	8 (4.8)	7 (4.3)
Mean BMI ± SD, kg/m^2	26.7±6.0	26.8±5.2
Newly diagnosed, n (%)	115 (69.3)	114 (69.5)

Median duration of ANCA-associated vasculitis, months (range)	0.23 (0-362.3)	0.25 (0-212.5)
ANCA status		
Anti-PR3 positive, n (%)	72 (43.4)	70 (42.7)
Anti-MPO positive, n (%)	94 (56.6)	94 (57.3)
Type of vasculitis		
GPA, n (%)	91 (54.8)	90 (54.9)
MPA, n (%)	75 (45.2)	74 (45.1)
Mean BVAS ± SD	16.3±5.9	16.2±5.7
Mean VDI ± SD	0.7±1.5	0.7±1.4
Immunosuppressant induction treatment		
Intravenous RTX, n (%)	107 (64.5)	107 (65.2)
Intravenous CYC, n (%)	51 (30.7)	51 (31.1)
Oral CYC, n (%)	8 (4.8)	6 (3.7)
Organ involvement		
Renal, n (%)	134 (80.7)	134 (81.7)
General, n (%)	111 (66.9)	114 (69.5)
Ear, nose, and throat, n (%)	75 (45.2)	69 (42.1)
Chest, n (%)	71 (42.8)	71 (43.3)
Nervous system, n (%)	38 (22.9)	31 (18.9)
Mucous membranes or eyes, n (%)	26 (15.7)	40 (24.4)
Cutaneous, n (%)	24 (14.5)	23 (14.0)
Cardiovascular, n (%)	6 (3.6)	3 (1.8)
Abdominal, n (%)	4 (2.4)	1 (0.6)
GC use during screening period		
Use of any GCs, n (%)	125 (75.3)	135 (82.3)
Intravenous use, n (%)	63 (38.0)	73 (44.5)
Oral use, n (%)	99 (59.6)	113 (68.9)
Total prednisone-equivalent dose ± SD, mg	654.0±744.4	727.8±787.8
Daily prednisone-equivalent dose ± SD, mg	46.7±53.2	52.0±56.3
Previous immunosuppressant use		
CYC, n (%)	4 (2.4)	2 (1.2)
RTX, n (%)	1 (0.6)	4 (2.4)

Abbreviations: ANCA, anti-neutrophil cytoplasmic autoantibody; BMI, body mass index; BVAS, Birmingham Vasculitis Activity Score; CYC, cyclophosphamide; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; N, number of subjects in the intention-to-treat population; PR3, proteinase 3; RTX, rituximab; SD, standard deviation; VDI, Vasculitis Damage Index

CLEAR

In the CLEAR trial, a total of 67 subject were randomised to 1 of 3 groups: the avacopan + 20 mg prednisone group (N=22), the avacopan + no prednisone group (N=22), and the placebo + 60 mg prednisone group (N=23) (4, 87). The key baseline characteristics of participants are shown in Table 9.

The mean age of subjects was 57.9 years (57.2 years for the 2 avacopan groups and 59.1 years for the placebo + 60 mg prednisone group). Overall, there were more male than female subjects (47 subjects [70.1%] vs 20 subjects [29.9%], respectively). All 67 subjects (100.0%) were white. The mean BMI was 26.3 kg/m^2. Most subjects (49 [73.1%]) had newly diagnosed AAV, and the median AAV duration at screening was 0.0 months. Most subjects were on CYC background treatment rather than RTX (54 subjects [80.6%] vs 13 subjects [19.4%], respectively). A total of 33 subjects (49.3%) had GPA and 28 subjects (41.8%) had MPA. A total of 35 subjects (52.2%) were anti-MPO positive and 29 subjects (43.3%) were anti-PR3 positive. The mean BVAS total score and mean VDI score were 13.7 and 0.9, respectively (4, 87).

Table 9. Baseline characteristics of participants, CLEAR (4, 87)

Baseline characteristic	Avacopan + 20 mg prednisone	Avacopan + no prednisone	Placebo + 60 mg prednisone
Number of patients, N	22	22	23
Mean age at screening ± SD, years	57.0±14.2	57.4±14.0	59.1±14.0
Male, n (%)	14 (63.6)	16 (72.7)	17 (73.9)
White, n (%)	22 (100.0)	22 (100.0)	23 (100.0)
Mean BMI ± SD, kg/m^2	24.9±4.0	26.5±4.7	27.3±7.1
Newly diagnosed, n (%)	15 (68)	16 (73)	18 (78)
Median duration of ANCA-associated vasculitis, months (range)	0.0 (0-61)	1.0 (0-108)	0.0 (0-162)
ANCA status			
Anti-PR3 positive, n (%)	10 (45)	8 (36)	11 (48)
Anti-MPO positive, n (%)	12 (55)	13 (59)	10 (43)
Both PR3- and MPO-positive	0 (0.0)	0 (0.0)	1 (4)
ANCA equivocal or negative	0 (0.0)	1 (5)	1 (4)
Type of vasculitis			

GPA, n (%)	11 (50)	12 (55)	10 (44)
MPA, n (%)	11 (50)	10 (45)	12 (52)
Renal-limited vasculitis	2 (9.1)	1 (4.5)	2 (8.7)
Unknown	0 (0.0)	0 (0.0)	1 (4.3)
Mean BVAS ± SD	14.3±6.0	13.8±6.4	13.2±5.8
Mean VDI ± SD	0.9±1.5	0.5±1.2	1.2±1.4
Mean eGFR ± SD, mL/min/1.73 m²	52.5±26.7	54.7±19.6	47.6±15.1
Mean UACR, mg/g	279 (24-2459)	283 (25-3051)	354 (28-5962)
Organ involvement			
Renal, n (%)	21 (95)	21 (95)	23 (100)
Rise in serum creatinine, n (%)	0 (0.0)	0 (0.0)	2 (9)
High serum creatinine, n (%)	11 (50)	6 (27)	15 (65)
Haematuria, n (%)	20 (91)	21 (95)	22 (96)
Proteinuria, n (%)	20 (91)	16 (73)	18 (78)
Hypertension, n (%)	5 (23)	2 (9)	3 (13)
Pulmonary involvement, n (%)	8 (36)	7 (32)	9 (39)
Constitutional signs or symptoms, n (%)	17 (77)	16 (73)	19 (83)
Cutaneous involvement, n (%)	1 (5)	4 (18)	4 (17)
Mucous membranes and eyes, n (%)	1 (5)	4 (18)	1 (4)
Ear, nose, and throat, n (%)	5 (23)	8 (36)	9 (39)
Cardiovascular involvement, n (%)	1 (5)	2 (9)	0 (0.0)
Neurologic involvement, n (%)	5 (23)	2 (9)	3 (13)
Prior GC use			
Use of any GCs, n (%)	14 (64)	11 (50)	11 (48)
Intravenous use, n (%)	9 (41)	5 (23)	5 (25)
Total prednisone-equivalent dose, mg	49	44	53
Prior immunosuppressant use			
Immunosuppressants, including AZA, MTX or mycophenolate mofetil, n (%)	4 (18)	3 (14)	2 (9)
CYC or RTX, n (%)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: ANCA, anti-neutrophil cytoplasmic autoantibody; AZA, azathioprine; BMI, body mass index; BVAS, Birmingham Vasculitis Activity Score; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; MTX, methotrexate; N, number of subjects in the intent-to-treat population; PR3, proteinase 3; RTX, rituximab; SD, standard deviation; UACR, urinary albumin-to-creatinine ratio; VDI, Vasculitis Damage Index

CLASSIC

In the CLASSIC trial, 42 subjects were randomised to 1 of 3 groups: the avacopan 10 mg + SoC group (N=13), the avacopan 30 mg + SoC group (N=16), and the placebo + SoC (N=13) (88, 89). The key baseline characteristics of participants are shown in Table 10.

The mean age of all subjects was 57.7 years (57.4 years for the 2 avacopan groups and 58.5 years for the placebo + SoC group). Overall, there were more female than male subjects (23 subjects [54.8%] vs 19 subjects (45.2%), respectively), and most subjects were white (38 subjects [90.5%]). The mean BMI was 30.2 kg/m^2. Most subjects (27 [64.3%]) had newly diagnosed AAV, and the median AAV disease duration at screening was 1.0 months (88, 89).

Most subjects were on RTX background treatment compared to CYC (39 subjects [92.9%] vs 3 subjects [7.1%], respectively). A total of 29 subjects (69.0%) had GPA, 11 subjects (26.2%) had MPA, and 2 subjects (4.8%) had renal-limited vasculitis. A total of 21 subjects (50.0%) were anti-MPO positive and 21 subjects (50.0%) were anti-PR3 positive. The mean BVAS and mean VDI score were 15.3 and 0.8, respectively (88, 89).

Table 10. Baseline characteristics of participants, CLASSIC (88, 89)

Baseline characteristic	Avacopan 10 mg + SoC	Avacopan 30 mg + SoC	Placebo + SoC
Number of patients, N	13	16	13
Mean age at screening ± SD, years	60.0±10.17	55.3±13.81	58.5±15.42
Male, n (%)	4 (30.8)	8 (61.5)	7 (43.8)
Race			
White, n (%)	11 (84.6)	14 (87.5)	13 (100)
Black, n (%)	2 (15.4)	1 (6.3)	0 (0.0)
Other, n (%)	0 (0.0)	1 (6.3)	0 (0.0)
Mean BMI ± SD, kg/m^2	27.6±8.91	31.5±7.59	31.0±12.51
Newly diagnosed, n (%)	10 (76.9)	9 (56.3)	8 (61.5)
Median duration of ANCA-associated vasculitis, months (range)	1.0 (0-347)	2.5 (0-170)	1.0 (0 -95)
ANCA status			

Anti-PR3 positive, n (%)	7 (53.8)	8 (50.0)	6 (46.2)
Anti-MPO positive, n (%)	6 (46.2)	8 (50.0)	7 (53.8)
Type of vasculitis			
GPA, n (%)	8 (61.5)	12 (75.0)	9 (69.2)
MPA, n (%)	4 (30.8)	4 (25.0)	3 (23.1)
Renal-limited vasculitis, n (%)	1 (7.7)	0 (0.0)	1 (7.7)
Mean BVAS ± SD	15.8±8.84	15.1±6.43	15.0±4.45
Mean VDI ± SD	0.8±2.49	0.6±1.15	1.2±1.77
Mean eGFR ± SD, mL/min/1.73 m^2	56.4±26.75	61.4±31.09	60.1±24.25
Mean UACR, mg/g	499 (103-3466)	464 (98-2693)	652 (163-7291)
Prior GC use			
Systemic GCs, n (%)	12 (92.3)	13 (81.3)	9 (69.2)
Prior immunosuppressant use			
CYC, n (%)	0 (0.0)	2 (12.5)	1 (7.7)
RTX, n (%)	13 (100.0)	14 (87.5)	12 (92.3)

Abbreviations: ANCA, anti-neutrophil cytoplasmic autoantibody; BMI, body mass index; BVAS, Birmingham Vasculitis Activity Score; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; N, number of subjects in the intention-to-treat population; PR3, proteinase 3; RTX, rituximab; SD, standard deviation; SoC, standard of care; UACR, urinary albumin-to-creatinine ratio; VDI, Vasculitis Damage Index

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

A summary of the statistical analyses used in the avacopan trials is presented in Table 11.

Table 11. Summary of statistical analyses

Trial	ADVOCATE (NCT02994927)	CLEAR (NCT01363388)	CLASSIC (NCT02222155)
Hypothesis objective	To evaluate the efficacy of avacopan to induce and sustain remission in subjects with active AAV, when used with CYC followed by AZA, or with RTX	To determine whether avacopan could replace oral GCs in the treatment of AAV without compromising efficacy	To determine the safety, tolerability, and efficacy of avacopan in subjects with MPA or GPA, on SoC CYC or RTX plus GC treatment
Statistical analysis	For the purposes of data analysis, the ITT population included all patients who had provided written informed consent and were randomised in the study. The safety population included all patients who were randomised and had received at least 1 dose of study drug. Data were summarised descriptively by treatment group. For continuous variables, numbers, means, medians, ranges, standard deviations, and standard error of means were calculated. Geometric means were calculated for UACR and urinary MCP-1:creatinine ratio, and other data that were not normally distributed. Frequency counts and percentages are	For the purposes of data analysis, the ITT population included all subjects who were randomised, had received at least 1 dose of study medication, and had at least 1 post-baseline, on-treatment BVAS assessment. The safety population included all subjects who were randomised and had received at least 1 dose of study medication. Data were summarised descriptively by treatment group, step of the study, and overall. For continuous variables, summary statistics included the sample size, mean, median, standard deviation, standard error of the mean, minimum, and maximum. Continuous variables with skewed distributions were log-transformed for analysis including UACR, urinary RBC count, urinary MCP-1:creatinine	The safety population included all subjects who were randomised and received at least 1 dose of study medication. The ITT population comprised all subjects who were randomised, received at least 1 dose of study medication and had at least 1 post-baseline, on-treatment BVAS assessment. The main efficacy analysis was in the ITT population. If deemed appropriate, sensitivity analyses also could have been performed on all randomised subjects and a per protocol population, excluding subjects with major protocol deviations. Data were summarised descriptively by treatment group and overall. For continuous variables, summary statistics included the sample size, mean, median, standard deviation,

	presented for categorical variables. The primary analysis was conducted when all randomised subjects completed at least the week 52 study visit. The database was locked on 20 November 2019 to conduct this analysis. The week 60 follow-up analysis results were subsequently summarised. The database lock date for the follow-up analysis was 27 January 2020. No inferential statistical analyses were conducted on the follow-up period data.	ratio, and hsCRP. Frequency counts and percentages were presented for categorical variables. All data were displayed in data listings. Data for subjects from steps 1, 2, and 3 treated with placebo were combined for summary and analyses purposes. Data were presented separately for the CYC and RTX strata.	standard error of the mean, minimum, and maximum. Continuous variables with skewed distributions were log-transformed for analysis including UACR, urinary RBC count, urinary MCP-1:creatinine ratio, and hsCRP. Frequency counts and percentages were presented for categorical variables.
Sample size, power calculation	A sample size of 150 patients per group (300 in total) was estimated to provide more than 90% power for the non-inferiority test. This sample size provides 90% power to detect approximately 18% superiority in the proportion of patients achieving clinical remission at week 26 if the control group remission rate is 60%. A sample size of 150 patients per group (300 in total) is estimated to provide 85% power to detect approximately 18% superiority if the control group	The planned study size was 60 patients. Assuming a control group BVAS response of 44% at day 85 and an avacopan group response of 86%, a sample size of 20 in each group provided ~90% power for the primary efficacy analysis.	The sample size was based on practical rather than statistical considerations, considering AAV is an orphan disease.

	sustained remission rate at week 52 is 45%.		
Data management, patient withdrawals	Investigators were to clearly distinguish between study drug treatment discontinuation and study withdrawal. Patients who discontinued study drug treatment or who initiated medication changes (including those prohibited by the protocol) were to be automatically withdrawn from the study, but all efforts were made to continue to follow the patients for all regularly scheduled visits. Patients were to be withdrawn from the study for only one of the following 2 reasons: 1. Patient withdrawal of consent to contribute additional outcome information 2. Loss to follow-up. In the event of early withdrawal from the study, the tests and evaluations listed for the early termination visit were to be performed, whenever possible.	In the event of withdrawal from the study prior to the day 85 visit, the tests and evaluations listed for study day 85 were to be carried out as part of the early termination visit, whenever possible. For subjects who withdrew after day 85, the day 169 study tests and evaluations were to be performed. In the event of treatment failure where rescue GC therapy was needed, the study medication (avacopan or placebo) and study-supplied prednisone were discontinued, and appropriate open-label SoC measures were taken. However, the subject was asked to remain in the study and complete all remaining study visits. If this was not possible, an attempt was made to complete all procedures scheduled for the day 85 visit (if the rescue event occurred prior to the day 85 visit) and day 169 (if the rescue event occurred after the day 85 visit).	In the event of withdrawal from the study prior to the day 85 visit, the tests and evaluations listed for study day 85 were to be carried out as part of the early termination visit, whenever possible. For subjects who withdrew after day 85, the day 169 study tests and evaluations were to be performed. In the event of treatment failure where rescue GC therapy was needed, the study medication (avacopan or placebo) and study-supplied prednisone were discontinued, and appropriate open-label SoC measures were taken. However, the subject was asked to remain in the study and complete all remaining study visits. If this was not possible, an attempt was made to complete all procedures scheduled for the day 85 visit (if the rescue event occurred prior to the day 85 visit) and day 169 (if the rescue event occurred after the day 85 visit).

Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; AZA, azathioprine; BVAS, Birmingham Vasculitis Activity Score; CYC, cyclophosphamide; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; hsCRP, high-sensitivity C-reactive protein; ITT, intention to treat; MCP-1, monocyte chemoattractant protein-1; MPA, microscopic polyangiitis; RBC, red blood cell; RTX, rituximab; SoC, standard of care; UACR, urinary albumin-to-creatinine ratio

B.2.4.1 Participant flow in the relevant randomised controlled trials

Details of the participant flow in the avacopan studies are shown in Appendix D1.3.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Quality assessment was conducted using the Risk of Bias 2 (ROB2) tool. Full details of the quality assessment are provided in Appendix D1.4.

B.2.6 Clinical effectiveness results of the relevant trials

Summary
• AAV is a rare, potentially fatal, remitting-relapsing, autoimmune condition impacting patients' QoL that has a substantial unmet need • An avacopan-based treatment regimen with its unique mode of action provides an effective and needed treatment option for the management of MPA and GPA over the current SoC, as demonstrated by reduction in relapses, statistically significant increase in sustained remission rates, sparing GC use, improvement of renal function, and improvement in patients' QoL

B.2.6.1 Remission

The effect of avacopan on inducing remission in AAV patients is summarised in Table 12.

In the ADVOCATE trial, a total of 120 of 166 subjects (72.3%) achieved remission (defined as achieving a BVAS of 0 at week 26; no administration of GCs for treatment of AAV within 4 weeks prior to week 26; no BVAS >0 during the 4 weeks prior to week 26) at week 26 in the avacopan group compared with 115 of 164 subjects (70.1%) in the prednisone group (estimated common difference, 3.4%; 95% CI, -6.0 to 12.8; p<0.001 for non-inferiority; p=0.24 for superiority] (2, 65).

In the CLEAR trial, clinical remission (i.e., BVAS of 0 at week 12 [post-hoc analysis]) was achieved in 10 of 22 subjects (45.5%) in the avacopan + low-dose prednisone group, 7 of 21 subjects (33.3%) in the avacopan + no prednisone group, and 8 of 20 subjects (40.0%) in the placebo + full-dose prednisone group (4, 87).

In the CLASSIC trial, clinical remission (i.e., BVAS of 0 at week 12) was achieved in 8 of 12 subjects (66.7%) in the avacopan 10 mg + SoC group, 7 of 15 subjects (46.7%) in the avacopan 30 mg + SoC group, and 7 of 13 subjects (53.8%) in the placebo + SoC group (88, 89).

Table 12. Effect of avacopan on remission

Trial	ADVOCATE (2, 65)		CLEAR (4, 87)			CLASSIC (88, 89)		
Treatment arm	**Avacopan-based regimen**	**Prednisone-based regimen**	**Avacopan + 20 mg prednisone**	**Avacopan + no prednisone**	**Placebo + 60 mg prednisone**	**Avacopan 10 mg + Soc**	**Avacopan 30 mg + SoC**	**Placebo + SoC**
Number of patients, N	166	164	22	21	20	12	15	13
Follow-up	26 weeks	26 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks
Remission								
n/N (%)	120/166 (72.3)	115/164 (70.1)	10/22 (45.5)	7/21 (33.3)	8/20 (40.0)	8/12 (66.7)	7/15 (46.7)	7/13 (53.8)
95% CI[a]	64.8 to 78.9	62.5 to 77.0	-	-	-	-	-	-
Estimate of common difference in %[b]	3.4		5.5	6.7	-	12.8	-7.2	-
Two-sided 95% CI for difference in %[c]	-6.0, 12.8		-19.6, 30.5	-31.4, 18.1	-	-19.09, 44.73	-38.26, 23.90	-
Non-inferior p value	<0.0001		0.0476	0.1875	-	-	-	-
Superior p value	0.2387		-	-	-	-	-	-

Abbreviations: CI, confidence interval; N, number of subjects in the intention-to-treat population; n, number of patients achieving remission; SoC, standard of care

[a]Clopper and Pearson exact CI

[b]Summary score estimate of the common difference in remission rates by using inverse-variance stratum weights

[c]Miettinen-Nurminen (score) confidence limits for the common difference in remission rates

B.2.6.2 Sustained remission

The effect of avacopan on inducing sustained remission in AAV patients is summarised in Table 13.

In the ADVOCATE trial, a total of 109 of 166 subjects (65.7%) achieved sustained disease remission at week 52 in the avacopan group compared with 90 of 164 subjects (54.9%) in the prednisone group (estimated common difference, 12.5%; 95% CI, 2.6 to 22.3; p<0.001 for non-inferiority; p=0.007 for superiority). The prespecified 20-percentage-point difference between groups was not exceeded in the CI for the between-group difference at 26 weeks or 52 weeks; therefore, the criteria for non-inferiority of avacopan were met, and superiority was met at week 52 (2, 65).

In the CLEAR trial, 3 of 22 subjects (13.6%) in the avacopan + low-dose prednisone group and 6 of 21 subjects (28.6%) in the avacopan + no prednisone group achieved remission at week 4 (based on BVAS of 0), which was sustained at week 12 (post-hoc analysis), compared with 1 of 20 subjects (5.0%) in the placebo + full-dose prednisone group (4, 87).

In the CLASSIC trial, 1 of 12 subjects (8.3%) in the avacopan 10 mg + SoC group, 3 of 15 subjects (20.0%) in the avacopan 30 mg + SoC group, and 2 of 13 subjects (15.4%) in the placebo + SoC group achieved remission (based on BVAS of 0) at week 4, which was sustained at week 12 (88, 89).

Table 13. Effect of avacopan on sustained remission

Trial	ADVOCATE (2, 65)		CLEAR (4, 87)			CLASSIC (88, 89)		
Treatment arm	Avacopan-based regimen	Prednisone-based regimen	Avacopan + 20 mg prednisone	Avacopan + no prednisone	Placebo + 60 mg prednisone	Avacopan 10 mg + Soc	Avacopan 30 mg + SoC	Placebo + SoC
Number of patients, N	166	164	22	21	20	12	15	13
Follow-up	52 weeks	52 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks
Sustained remission								
n/N (%)	109/166 (65.7)	90/164 (54.9)	3/22 (13.6)	6/21 (28.6)	1/20 (5.0)	1/12 (8.3)	3/15 (20.0)	2/13 (15.4)
95% CI[a]	57.9, 72.8	46.9, 62.6	-	-	-	-	-	-
Estimate of common difference in %[b]	12.5		8.6	23.6	-	7.1	4.6	-
Two-sided 95% CI for difference in %[c]	2.6, 22.3		-5.8, 23.1	5.5, 41.7	-	-28.10, 14.00	-19.04, 28.27	-
Non-inferior p value	<0.001		-	-	-	-	-	-
Superior p value	0.0066		-	-	-	-	-	-

Abbreviations: CI, confidence interval; N, number of subjects in the intention-to-treat population; n, number of subjects achieving sustained remission; SoC, standard of care
[a]Clopper and Pearson exact CI
[b]Summary score estimate of the common difference in remission rates by using inverse-variance stratum weights
[c]Miettinen-Nurminen (score) confidence limits for the common difference in remission rates

B.2.6.3 Early remission (BVAS of 0 at week 4)

The effect of avacopan on inducing early remission in AAV patients (i.e., BVAS=0 at week 4) is summarised in Table 14.

In the ADVOCATE trial, early remission was observed in 62.7% of subjects in the avacopan group and 68.9% of subjects in the prednisone group, which was not statistically different between treatment groups (2, 65).

In the CLASSIC trial, early remission was observed in 2 of 13 subjects in the placebo + SoC group, 1 of 12 subjects in the avacopan 10 mg + SoC group, and 5 of 15 subjects in the avacopan 30 mg + SoC group (88, 89).

Table 14. Effect of avacopan on early remission (BVAS of 0 at week 4)

Trial	**ADVOCATE (2, 65)**		**CLASSIC (88, 89)**		
Treatment arm	**Avacopan-based regimen**	**Prednisone-based regimen**	**Avacopan 10 mg + Soc**	**Avacopan 30 mg + SoC**	**Placebo + SoC**
Number of patients, N	166	164	12	15	13
Follow-up	4 weeks	4 weeks	4 weeks	4 weeks	4 weeks
BVAS=0 at week 4					
Mean ± SD at baseline	16.3±5.87	16.2±5.69	15.8±8.84	15.1±6.43	15.0±4.45
n/N (%)	104/166 (62.7)	113/164 (68.9)	1/12 (8.3)	5/15 (33.3)	2/13 (15.4)
95% CI[a]	54.8, 70.0	61.2, 75.9	-	-	-
Estimate of common difference in %[b]	-5.6		-	-	-
Two-sided 95% CI for difference in %[c]	-15.4, 4.2		-	-	-
Superior P-value	0.8695		-	-	-

Abbreviations: CI, confidence interval; N, number of subjects in the intention-to-treat population; n, number of patients achieving BVAS of 0 at week 4; SD, standard deviation; SoC, standard of care

[a]Clopper and Pearson exact CI

[b]Summary score estimate of the common difference in remission rates by using inverse-variance stratum weights

[c]Miettinen-Nurminen (score) confidence limits for the common difference in remission rates

B.2.6.4 Relapses

In the ADVOCATE trial, relapses after achieving remission at week 26 occurred in 14 subjects (12.2%) in the prednisone group compared with 9 subjects (7.5%) in the avacopan group (p=0.08) (Table 15) (2, 65).

Table 15. Effect of avacopan on relapses following previous remission (BVAS of 0) at week 26, ADVOCATE (2, 65)

Trial	**ADVOCATE**	
Treatment arm	**Avacopan-based regimen**	**Prednisone-based regimen**
Number of patients in the ITT population, N	166	164
Follow-up	52 weeks	52 weeks
Relapse after previous remission (BVAS=0) at week 26		
Number of patients achieving previous remission at week 26, N'	120	115
Patients experiencing a relapse following previous remission at week 26, n/N' (%)	9/120 (7.5)	14/115 (12.2)
95% CI[a]	3.5, 13.8	6.8, 19.6
Difference in %	-4.7	
Estimate common difference in %[b]	-6.0	
Two-sided 95% CI for difference in %[c]	-14.4, 2.4	
Superiority P-value	0.0810	

Abbreviations: CI, confidence interval; ITT, intention to treat; N, number of subjects in the intention-to-treat population; n, number of subjects relapsing following disease remission at week 26; N', number of subjects achieving disease remission (BVAS=0) at week 26
[a]Clopper and Pearson exact CI
[b]Summary score estimate of the common difference in remission rates by using inverse-variance stratum weights
[c]Miettinen-Nurminen (score) confidence limits for the common difference in remission rates

Exploratory analysis of relapses occurring at any time during the study after BVAS of 0 had been achieved showed a significantly lower rate of relapse in the avacopan group (10.1%) compared to the prednisone group (21.0%) (p=0.0091). A 54% significantly lower relative risk of relapse (hazard ratio [HR], 0.46; 95% CI, 0.25 to 0.84; p=0.0091) was observed in the avacopan group compared with the prednisone group (Table 16). Figure 4 shows the probability of remaining relapse free after

induction of remission among patients in the avacopan-regimen arm and those in the comparator arm.

Table 16. Exploratory analysis of rate of relapse after any time point when remission (BVAS=0) was achieved, ADVOCATE (2, 65)

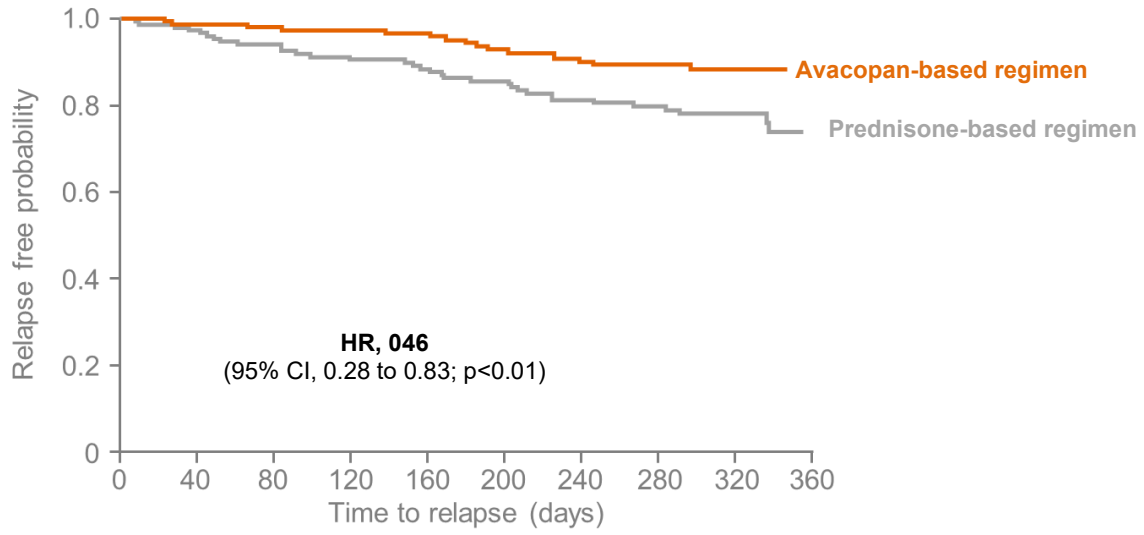
Trial	**ADVOCATE**	
Treatment arm	**Avacopan-based regimen**	**Prednisone-based regimen**
Number of patients in the ITT population, N	166	164
Number of patients who achieved BVAS=0, N'	158	157
Patients experiencing relapse after BVAS=0 was achieved, n/N' (%)[a]	16/158 (10.1)	22/157 (21.0)
Patients censored, n (%)	142 (89.9)	124 (79.0)
Treatment comparison vs SoC		
Hazard ratio	NA	0.461
95% CI for hazard ratio	NA	0.254 to 0.838
p value	NA	0.0091

Abbreviations: BVAS, Birmingham Vasculitis Activity Score; CI, confidence interval; ITT, intention to treat; N, number of subjects in the intention-to-treat population; n/N', number of subjects in the specified category/number of subjects who achieved BVAS=0 during the 52-week treatment period and is used as the denominator for percentage calculations; NA, not applicable; SoC, standard of care

[a]As assessed by the Adjudication Committee; based on the Investigators' assessment, a relapse was defined as worsening of disease, after previous achievement of a BVAS of 0 (on a scale from 0 to 63, with higher scores indicating greater disease activity), that involved 1 or more major items in the BVAS, three or more minor items in the BVAS, or 1 or 2 minor items in the BVAS recorded at 2 consecutive trial visits

Note: The median time to relapse was not estimable because of small number of relapsed subjects. Therefore, the Kaplan-Meier estimates were not calculated. The p values are from the log-rank test to compare the treatment groups.

Figure 4. Relapse-free probability following achievement of remission, ADVOCATE (65)

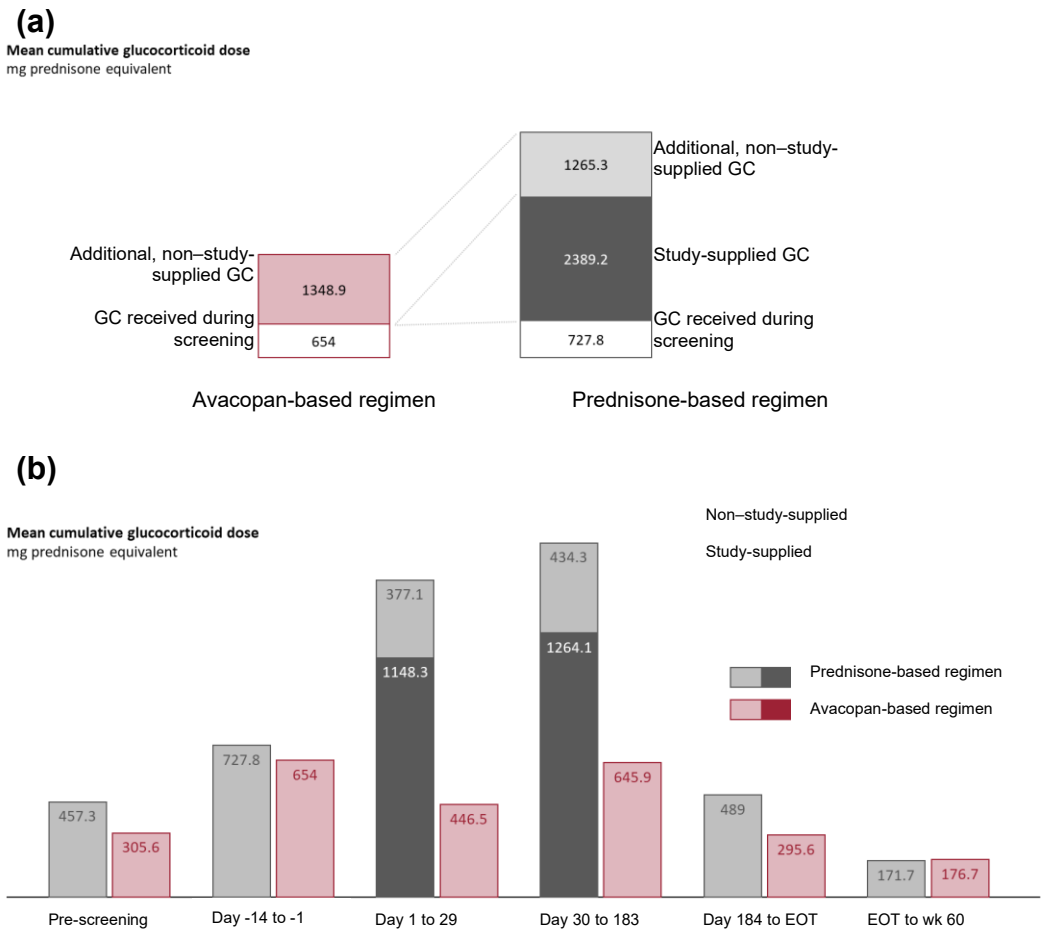


Abbreviations: CI, confidence interval; HR, hazard ratio
Relapse was defined as the absence of worsening disease, as measured by BVAS, with no involvement of major items in the BVAS, <3 minor items in the BVAS, and no minor items in the BVAS recorded at 2 consecutive trial visits

B.2.6.5 Glucocorticoid-induced toxicity

In the ADVOCATE trial, over 52 weeks, GC exposure was 63% lower in the avacopan-based regimen group, with a mean cumulative GC dose during the treatment period of 1,348.9 mg for an avacopan group versus 3,654.5 mg for prednisone group driven by study design (Figure 5). Sources of additional, non–study-supplied GCs in both groups were tapered in the first 4 weeks from pre-randomisation GC dosing, GC from co-administration with RTX (65% of all subjects) over first 4 weeks, and off-protocol GC use (for AAV relapse or no improvement in major BVAS item in the first 4 weeks) as prescribed by clinician. During the last 26 weeks of the treatment period, 39.0% of the prednisone group and 27.1% of the avacopan group received non-study supplied GCs. Thus, an additional 11.9% of patients in the avacopan arm were able to stop using GCs altogether during the ADVOCATE trial (2, 65).

Figure 5. Mean cumulative glucocorticoid dose over time in the ADVOCATE trial (ITT population): (a) overall and (b) by time period (65)



Abbreviations: EOT, end of treatment; GC, glucocorticoid; wk, week

In addition to recording the cumulative use of GCs over the course of the ADVOCATE trial, GC toxicity was assessed using the Glucocorticoid Toxicity Index (GTI) 2.0, a measure of side effects related to the use of GCs comprising the Cumulative Worsening Score (CWS) and the Aggregate Improvement Score (AIS) (90). The GTI-CWS captures cumulative GC toxicity regardless of whether it is permanent or transient. The GTI-CWS can only increase or remain the same over time; a lower score indicates lower GC toxicity. The GTI-AIS captures both worsening and improvement in glucocorticoid toxicity. New or worsening toxicities contribute a positive score and improvement in existing toxicities contributes a negative score; a lower score indicates lower GC toxicity (2).

In the ADVOCATE trial, the use of avacopan was associated with statistically less GC-induced toxicity relative to prednisone for both scores of the GTI (Table 17). The least-squares mean (LSM) for the GTI-CWS at week 26 was 39.7 in the avacopan group and 56.6 in the prednisone group, and the difference between groups was -16.8 points (95% CI, -25.6 to -8.0; p=0.0002). The LSM for the GTI-AIS at week 26 was 11.2 in the avacopan group and 23.4 in the prednisone group, and the difference between groups was -12.1 points (95% CI, -21.1 to -3.2; p=0.008) (2, 65).

Table 17. Effect of avacopan on glucocorticoid-induced toxicity, ADVOCATE (2, 65)

Trial	**ADVOCATE**			
Follow-up	**13 weeks**		**26 weeks**	
Treatment arm	**Avacopan-based regimen**	**Prednisone-based regimen**	**Avacopan-based regimen**	**Prednisone-based regimen**
Number of patients, N	166	164	166	164
GTI-CWS				
Mean ± SD at baseline	NA	NA	NA	NA
LSM ± SEM	25.7±3.40	36.6±3.41	39.7±3.43	56.6±3.45
p value	0.014		0.0002	
GTI-AIS				
Mean ± SD at baseline	NA	NA	NA	NA
LSM ± SEM	9.9±3.45	23.2±3.46	11.2±3.48	23.4±3.50
p value	0.003		0.008	

Abbreviations: AIS, Aggregate Improvement Score; CWS, Cumulative Worsening Score; GTI, Glucocorticoid Toxicity Index; ITT, intention-to-treat; LSM, least squares mean; N, number of subjects in the intention-to-treat population; NA, not applicable; SD, standard deviation; SEM, standard error of measurement

Less GC use was associated with lower increases in several factors, with the greatest benefits seen in BMI, glucose tolerance, lipids, steroid myopathy, skin AEs and complications, and infection components of the GTI-CWS and GTI-AIS. Scores for these outcomes were lower in the avacopan-based regimen group at weeks 13 and 26 (Table 18) (2, 65). In addition, the neuropsychiatric AEs and complications component of the GTI-CWS was also lower in the avacopan-based regimen group at weeks 13 and 26 (2, 65).

Table 18. GTI aggregate improvement score in individual components in ADVOCATE ITT population at week 13 and 26, and at last measure, in the avacopan- and prednisone-based regimen groups (2, 65)

	Avacopan-based regimen group		Prednisone-based regimen group	
Number of patients, N	166		164	
Mean ± SD GTI improvement in BMI				
Week 13	n=160	0.6±6.19	n=161	3.7±8.32
Week 26	n=154	1.1±7.70	n=153	3.3±8.72
Final GTI measure	n=163	1.0±7.48	n=162	3.2±8.62
Mean ± SD GTI improvement in glucose tolerance				
Week 13	n=160	-6.3±13.37	n=161	-1.3±15.47
Week 26	n=154	-5.3±16.30	n=153	-4.5±14.38
Final GTI measure	n=163	-5.2±16.02	n=162	-3.6±15.04
Mean ± SD GTI improvement in blood pressure				
Week 13	n=160	3.9±19.14	n=161	4.0±17.85
Week 26	n=154	4.5±20.45	n=153	4.7±19.24
Final GTI measure	n=163	4.1±20.50	n=162	4.8±19.26
Mean ± SD GTI improvement in lipids				
Week 13	n=160	4.2±7.89	n=161	6.7±8.20
Week 26	n=154	4.2±9.41	n=153	6.5±9.62
Final GTI measure	n=163	3.9±9.39	n=162	6.4±9.51
Mean ± SD GTI improvement in steroid myopathy				
Week 13	n=160	0.2±1.73	n=161	0.7±7.99
Week 26	n=154	0.2±1.44	n=153	0.6±8.64
Final GTI measure	n=163	0.3±1.56	n=162	0.6±8.40
Mean ± SD GTI improvement in skin AEs and complications				
Week 13	n=160	0.1±3.94	n=161	1.7±5.01
Week 26	n=154	-0.3±4.29	n=153	0.8±4.22
Final GTI measure	n=163	-0.3±4.22	n=162	1.1±4.99
Mean ± SD GTI improvement in neuropsychiatric AEs and complications				
Week 13	n=160	1.5±14.55	n=161	1.0±17.72
Week 26	n=154	-0.9±9.34	n=153	-0.7±16.72
Final GTI measure	n=163	-0.5±10.84	n=162	-1.0±16.99
Mean ± SD GTI improvement in infection				
Week 13	n=160	6.8±22.72	n=161	8.0±24.59
Week 26	n=154	8.5±25.09	n=153	13.3±31.34
Final GTI measure	n=163	9.2±26.18	n=162	13.1±31.23

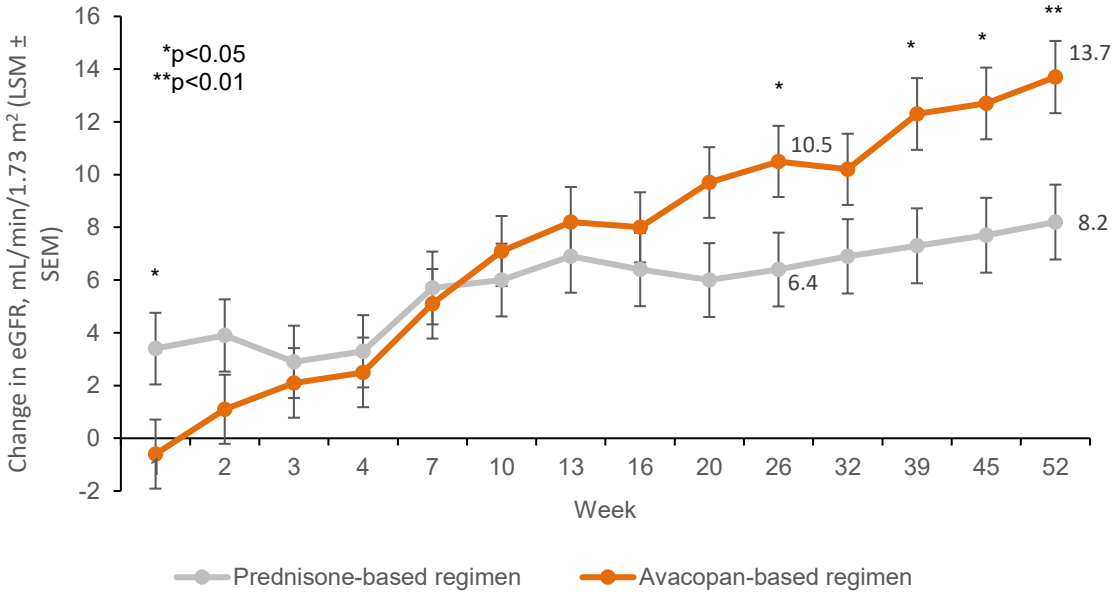
Abbreviations: AE, adverse event; GTI, Glucocorticoid Toxicity Index; ITT, intention-to-treat; N, number of subjects in the intention-to-treat population; n, number of subjects with GTI

B.2.6.6 Estimated glomerular filtration rate (eGFR)

The effect of avacopan on eGFR in subjects with renal disease at baseline is summarised in Table 19.

In the ADVOCATE trial, kidney function of subjects with renal disease at baseline, as measured by eGFR, was improved statistically and clinically significantly more in the avacopan group than the prednisone group. At week 26, the LSM increase in eGFR in the avacopan and prednisone groups was 5.8 and 2.9 mL/min/1.73 m^2 (p=0.046), respectively. At week 52, the LSM change from baseline in the eGFR was 7.3 mL/min/1.73 m^2 in the avacopan group and 4.1 mL/min/1.73 m^2 in the prednisone group, and the difference between groups was 3.2 mL/min/1.73 m^2 (95% CI, 0.3 to 6.1) (2, 65). Among patients with stage 4 kidney disease (i.e., baseline eGFR of <30 mL/min/1.73 m^2), the LSM change at week 26 was 10.5 and 6.4 mL/min/1.73 m^2 in the avacopan and prednisone groups, respectively; and at week 52 the LSM change was 13.7 mL/min/1.73 m^2 in the avacopan group and 8.2 mL/min/1.73 m^2 in the prednisone group, and the LSM difference between groups was 5.6 mL/min/1.73 m^2 (95% CI, 1.7 to 9.5, p=0.005) (Figure 6) (2, 65). The mean improvement of 13.7 mL/min/1.73 m^2 in the avacopan group equates to a transition from CKD stage 4 to CKD stage 3b over the 52 weeks of treatment. Table 20 summarises the change from baseline in eGFR during the ADVOCATE trial in subjects with renal disease at baseline, stratified by renal disease severity.

Figure 6. Change from baseline in eGFR during the ADVOCATE trial in subjects with renal disease at baseline (based on BVAS) and baseline eGFR <30 mL/min/1.73 m^2 (ITT population) (2, 65)



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

Table 19. Effect of avacopan on eGFR

Trial	ADVOCATE (2, 65)		CLEAR (4, 87)			CLASSIC (88, 89)		
Treatment arm	**Avacopan-based regimen**	**Prednisone-based regimen**	**Avacopan + 20 mg prednisone**	**Avacopan + no prednisone**	**Placebo + 60 mg prednisone**	**Avacopan 10 mg + Soc**	**Avacopan 30 mg + SoC**	**Placebo + SoC**
Population (N'/N)	119/134	125/134	21/22	19/21	20/20	8/12	10/15	9/13
Follow-up	52 weeks	52 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks
eGFR								
Mean + SD at baseline	44.6±27.67	45.6±27.27	52.50 ±26.70	54.76 ±20.12	47.20± 15.79	47.9±6.97	57.8±11.71	57.2±8.55
Mean ± SD following treatment	53.2±24.09	50.5±22.09	56.19 ±19.66	56.05 ±22.63	52.57 ±16.01	49.1±6.66	64.0±11.16	59.2±8.02
LSM ± SEM	7.3±1.05	4.1±1.03	NR	NR	NR	9.6±13.03	18.3±10.66	13.4±11.44
95% CI	5.2 to 9.4	2.1 to 6.1	NR	NR	NR	-17.09 to 36.37	-3.73 to 40.29	-10.21 to 36.96
p value	0.0294		0.8231	0.2332	NA	0.8132	0.7400	NA

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; LSM, least squares mean; N, number of subjects in the analysis population for the specified treatment group; N'/N, subjects with data at baseline and specified visit/number of subjects in the analysis population for the specified treatment group; NA, not applicable; NR, not reported; SD, standard deviation; SEM, standard error of measurement; SoC, standard of care

Table 20. Change from baseline in eGFR during the ADVOCATE trial in subjects with renal disease at baseline, stratified by renal disease severity (2, 65)

Treatment	N	Week 26			Week 52		
		N'	LSM change in eGFR	p value	N'	LSM change in eGFR	p value
Subjects with baseline eGFR <30 mL/min/1.73 m^2							
Prednisone-based regimen	48	42	6.4	0.0361	42	8.2	0.005
Avacopan-based regimen	52	46	10.5		45	13.7	
Subjects with baseline eGFR 30 to 59 mL/min/1.73 m^2							
Prednisone-based regimen	51	51	5.4	0.3535	50	7.8	0.2115
Avacopan-based regimen	46	44	7.3		43	10.5	
Subjects with baseline eGFR >59 mL/min/1.73 m^2							
Prednisone-based regimen	35	34	-6.0	0.3640	33	-7.5	0.6721
Avacopan-based regimen	33	31	-2.6		31	-5.9	

Abbreviations: eGFR, estimated glomerular filtration rate; LSM, least squares mean; N, number of subjects in the analysis population for the specified treatment group; N', number of subjects with data at baseline and the specified visit

In the CLEAR trial, following the 12-week treatment period, the mean eGFR, based on the MDRD formula using serum creatinine, in the avacopan + low-dose prednisone group was 56.2 mL/min/1.73 m^2 (mean increase from baseline: 6.0 [19.9%]); in the avacopan + no prednisone group, it was 56.1 mL/min/1.73 m^2 (mean increase from baseline: 0.8 [0.9%]). The mean eGFR in the placebo + full-dose prednisone was 52.8 mL/min/1.73 m^2 (mean increase from baseline: 5.6 [15.4%]). The mean eGFR was higher for the avacopan + no prednisone group and avacopan + low-dose prednisone group than the placebo + full-dose prednisone group for the entire 12-week treatment period (4, 87).

In the CLASSIC trial, in subjects with baseline renal disease, following the 12-week treatment period, the mean eGFR, based on the MDRD formula using serum

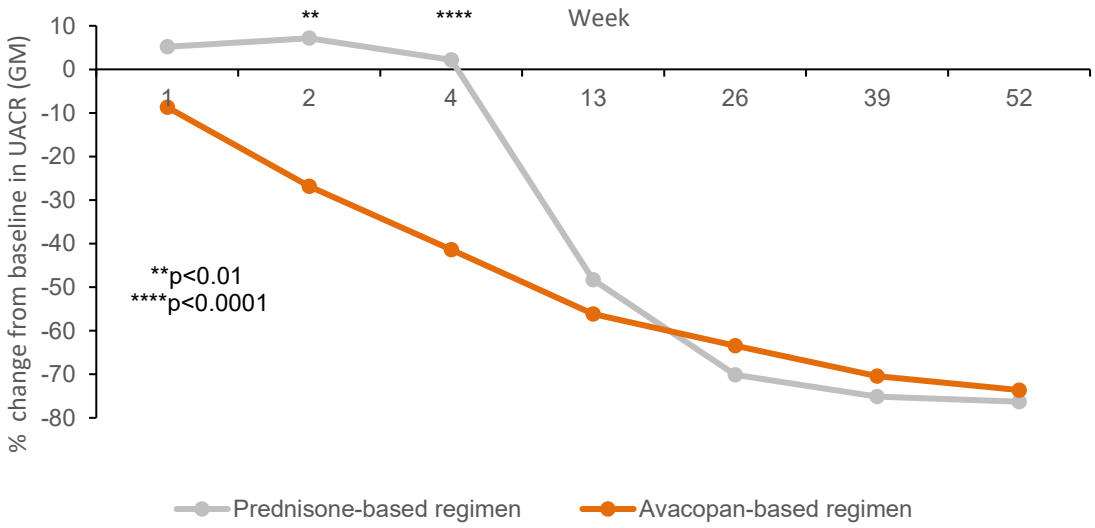
creatinine, in the avacopan 10 mg + SoC group was 49.1 mL/min/1.73 m^2 (mean increase from baseline: 1.3 [4.4%]); in the avacopan 30 mg + SoC group, it was 64.0 mL/min/1.73 m^2 (mean increase from baseline: 6.2 [15.4%]). The mean eGFR in the placebo + SoC group was 59.2 mL/min/1.73 m2 (mean increase from baseline: 2.0 [10.2%]) (88, 89).

B.2.6.7 Urinary albumin-to-creatinine ratio (UACR)

The effect of avacopan on UACR in subjects with renal disease at baseline is summarised in Table 21.

In the ADVOCATE trial, albuminuria in subjects with renal disease at baseline improved more rapidly in the avacopan group than the prednisone group. At week 4, there was a LSM change from baseline in UACR of -40% in the avacopan group compared with no change in the prednisone group (p<0.0001). The extent of overall improvement in UACR was similar between treatment groups at week 52 (-74% in the avacopan group and -77% in the prednisone group; not significantly different) (2, 65).

Figure 7. Percent change from baseline in UACR during the ADVOCATE trial in subjects with renal disease (based on BVAS) and albuminuria (UACR ≥10 mg/g creatinine) at baseline (ITT population) (2, 65)



Abbreviations: BVAS, Birmingham Vasculitis Activity Score; ITT, intent-to-treat; GM, geometric mean; UACR, urinary albumin-to-creatinine ratio

In the CLEAR trial, following the 12-week treatment period (day 85), there was a greater mean decrease in the first morning UACR in the avacopan + low-dose prednisone group (geometric mean ratio [GMR]: 0.44; mean decrease from baseline: 56.0%) and the avacopan + no prednisone group (GMR: 0.57; mean decrease from baseline: 43.0%) compared with the placebo + full-dose prednisone group (GMR: 0.79; mean decrease from baseline: 21.0%) (4, 87).

In the CLASSIC trial, following the 12-week treatment period (day 85), in subjects with albuminuria at baseline, UACR decreased from baseline in all 3 treatment groups. The geometric mean ration of UACR was 0.49 (mean decrease from baseline: 51%) in the avacopan 10 mg + SoC group, 0.32 (mean decrease from baseline: 68%) in the avacopan 30 mg + SoC group, and 0.27 (mean decrease from baseline: 73%) in the placebo + SoC group (88, 89).

Table 21. Effect of avacopan on UACR

Trial	ADVOCATE (2, 65)				CLEAR (4, 87)			CLASSIC (88, 89)		
Treatment arm	Avacopan-based regimen		Prednisone-based regimen		Avacopan + 20 mg prednisone	Avacopan + no prednisone	Placebo + 60 mg prednisone	Avacopan 10 mg + SoC	Avacopan 30 mg + SoC	Placebo + SoC
Population (N'/N)	109/125		114/128		20/22	18/21	20/20	12	15	13
Follow-up	4 weeks	52 weeks	4 weeks	52 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks
UACR										
GM at baseline	432.87		312.16		278.60	279.76	317.64	181.92	287.04	311.59
GM following treatment	254.95	285.31	310.36	276.28	126.96	158.41	252.09	88.18	98.95	85.01
GMR	0.59	0.26	1.02	0.24	0.438	0.569	0.794	0.485	0.317	0.273
GM % change	-41.37	-73.62	2.18	-76.29	NR	NR	NR	51	68	73
LSM ratio ± SEM	0.60± 1.136	1.12± 1.141	NA	NA	0.49	0.72	NA	1.597±1.699	1.123±1.575	NA
LSM ratio 95% CI	0.47 to 0.78	0.86 to 1.45	NA	NA	0.31 to 0.76	0.46 to 1.14	NA	0.532 to 4.792	0.438 to 2.880	NA
p value	<0.0001	0.3991	NA	NA	0.0016	0.1627	NA	0.3869	0.8006	NA

Abbreviations: CI, confidence interval; GM, geometric mean; GMR, geometric mean ratio; LSM, least squares mean; N'/N, subjects with data at baseline and specified visit/number of subjects in the analysis population for the specified treatment group; NA, not applicable; NR, not reported; SD, standard deviation; SEM, standard error of measurement; SoC, standard of care; UACR, urinary albumin-to-creatinine ratio

B.2.6.8 Urinary monocyte chemoattractant protein 1 (MCP-1):creatinine ratio

The effect of avacopan on urinary MCP1:creatinine ratio in patients with renal disease at baseline (based on BVAS) is summarised in Table 22.

In the ADVOCATE trial, urinary MCP-1 excretion in subjects with renal disease at baseline decreased more in the avacopan group than the prednisone group by week 13 (-59% vs -52%, respectively, p=0.0339). There was a similar decrease in the 2 treatment groups by week 52 (-73% in the avacopan group and -71% in the prednisone group; not significantly different) (2, 65).

In the CLEAR trial, the GMR (day 85/baseline) for the first morning urinary MCP-1:creatinine ratio in the avacopan + low-dose prednisone group was 0.30 (mean decrease from baseline: 70.0%), in the avacopan + no prednisone group was 0.50 (mean decrease from baseline: 50.0%), and in the placebo + full-dose prednisone group was 0.57 (mean decrease from baseline: 43.0%) (4, 87).

In the CLASSIC trial, following the 12-week treatment period (on day 85), the GMR (day 85/baseline) for the first morning urinary MCP-1:creatinine ratio was 0.50 (mean decrease from baseline: 50%) in the avacopan 10 mg + SoC group, 0.78 (mean decrease from baseline: 22%) in the avacopan 30 mg + SoC group, and 0.51 (mean decrease from baseline: 49%) in the placebo + SoC group (88, 89).

Table 22. Effect of avacopan on urinary MCP-1:creatinine ratio in subjects with renal disease at baseline (based on BVAS)

Trial	ADVOCATE (2, 65)		CLEAR (4, 87)			CLASSIC (88, 89)		
Treatment arm	Avacopan-based regimen	Prednisone-based regimen	Avacopan + 20 mg prednisone	Avacopan + no prednisone	Placebo + 60 mg prednisone	Avacopan 10 mg + Soc	Avacopan 30 mg + SoC	Placebo + SoC
Population (N'/N)	67/81	67/82	20/22	19/21	20/20	12	15	13
Follow-up	52 weeks	52 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks
Urinary MCP-1:creatinine ratio								
GM at baseline	983.84	947.76	1266.09	806.08	752.24	411.08	423.56	651.65
GM at follow-up	252.10	274.64	373.26	373.54	425.92	317.91	527.60	490.42
GMR	0.27	0.30	0.299	0.504	0.566	0.50	0.78	0.51
GM % change	-72.89	-70.10	NR	NR	NR	50	22	49
LSM ratio ± SEM	0.90±1.086	NA	0.55	0.93	NA	0.928±1.432	1.337±1.386	NA
LSM ratio 95% CI	0.77 to 1.06	NA	0.40 to 0.76	0.68 to 1.29	NA	0.445 to 1.935	0.685 to 2.609	NA
p value	0.2223		0.0004	0.6779	NA	0.8354	0.3815	NA

Abbreviations: CI, confidence interval; GM, geometric mean; GMR, geometric mean ratio; LSM, least squares mean; MCP-1, monocyte chemoattractant protein 1; N'/N, subjects with data at baseline and specified visit/number of subjects in the analysis population for the specified treatment group; NA, not applicable; NR, not reported; SEM, standard error of measurement; SoC, standard of care

B.2.6.9 Vasculitis Damage Index (VDI)

The effect of avacopan on VDI is summarised in Table 23.

In the ADVOCATE trial, both treatment groups showed a similar LSM increase from baseline to week 52 in VDI, as assessed by the adjudication committee (1.17 in the avacopan group and 1.15 in the prednisone group; not statistically different) (2, 65).

In the CLEAR trial, the mean VDI at week 12 was 1.2 (mean increase from baseline: 0.3 [37.5%]) in the avacopan + low-dose prednisone group, 0.8 (mean increase from baseline: 0.2 [45.0%]) in the avacopan + no prednisone group, and 1.8 (mean increase from baseline: 0.7 [41.1%]) in the placebo + full-dose prednisone group (4, 87).

In the CLASSIC trial, the mean VDI at week 12 was 1.00 (mean increase from baseline: 0.09) in the avacopan 10 mg + SoC group, 0.86 (mean increase from baseline: 0.14) in the avacopan 30 mg + SoC group was, and 1.46 (mean increase from baseline:0.31) in the placebo + SoC group (88, 89).

Table 23. Effect of avacopan on VDI

Trial	ADVOCATE (2, 65)		CLEAR (4, 87)			CLASSIC (88, 89)		
Treatment arm	**Avacopan-based regimen**	**Prednisone-based regimen**	**Avacopan + 20 mg prednisone**	**Avacopan + no prednisone**	**Placebo + 60 mg prednisone**	**Avacopan 10 mg + Soc**	**Avacopan 30 mg + SoC**	**Placebo + SoC**
Population (N'/N)	151/166	150/164	20/22	19/21	20/20	12	15	13
Follow-up	52 weeks	52 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks
VDI								
Mean + SD at baseline	0.66±1.544	0.72±1.393	0.9±1.46	0.5±1.21	1.2±1.35	0.83±2.588	0.67±1.175	1.15±1.772
Mean ± SD at follow-up	1.99±1.711	1.95±1.368	1.2±1.53	0.8±1.51	1.8±1.88	1.00±2.720	0.86±1.292	1.46±2.295
Mean % change	NR	NR	37.50	45.00	41.11	NR	NR	NR
LSM difference ± SEM	0.03 ± 0.118	NA	-0.32	-0.37	NA	-0.20 ±0.209	-0.15 ±0.199n	NA
LSM difference 95% CI	-0.20, 0.26	NA	-0.74, 0.10	-0.80, 0.06	NA	-0.625 to 0.228	-0.557 to 0.253	NA
LSM difference p value	0.7868	NA	NR	NR	NR	0.3492	0.4490	NA
p value for % change	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: CI, confidence interval; LSM, least squares mean; N'/N, subjects with data at baseline and specified visit/number of subjects in the analysis population for the specified treatment group; NA, not applicable; NR, not reported; SD, standard deviation; SEM, standard error of measurement; SoC, standard of care; UACR, urinary albumin-to-creatinine ratio; VDI, Vasculitis Damage Index

B.2.7 Subgroup analysis

B.2.7.1 Sustained disease remission

In the ADVOCATE trial, treatment with an avacopan-based regimen rather than SoC resulted significantly in a greater proportion of patients achieving sustained disease remission. In subgroups of interest, with the greatest differences seen in patients with relapsed AAV, patients receiving RTX, patients with MPA, and patients with MPO+ AAV. However, it is important to note limitations that subgroup analyses present in a clinical trial, including the small sample size which increases the likelihood of false positive results. Furthermore, baseline immunosuppressive therapy (CYC or RTX) was selected by the investigator which may introduce bias in these subgroup analyses (2, 65). Outcomes for these subgroups are briefly summarised below; results for additional subgroups are reported in Table 24 and illustrated in

Figure 8.

In the relapsing disease subgroup, 86.3% of patients receiving an avacopan-based regimen and 78.0% of patients receiving a prednisone-based regimen were in remission at week 26. However, by week 52, 76.5% of avacopan-based regimen patients were in sustained remission versus 48.0% of prednisone-based regimen patients, indicating that treatment with an avacopan-based regimen results in fewer disease relapses than SoC (2, 65).

With all the limitations of the subgroup analyses, greater efficacy was also seen in the RTX treatment subgroup, in which sustained remission was achieved at week 52 by 71.0% and 56.1% of the patients receiving avacopan-based and prednisone-based regimen groups, respectively ($p<0.0001$). At the same time point, 70.2% of anti-MPO+ patients treated with an avacopan-based regimen were in sustained remission versus 53.2% of that subgroup treated with prednisone-based regimen control group (2, 65).

In the GPA subgroup, 71.4% of patients treated with an avacopan-based regimen and 72.2% of patients treated with a prednisone-based regimen had achieved

remission by week 26. At week 52, rates of sustained remission had decreased to 61.5% and 57.8%, respectively. Rates of remission at week 26 were comparable in the MPA cohort, with 73.3% of prednisone-treated patients and 67.6% of avacopan-treated patients in remission at this time point. However, at week 52, the proportion of patients in sustained remission had fallen to 51.4% among patients treated with a prednisone-based versus 70.7% of those treated with an avacopan-based regimen (2, 65).

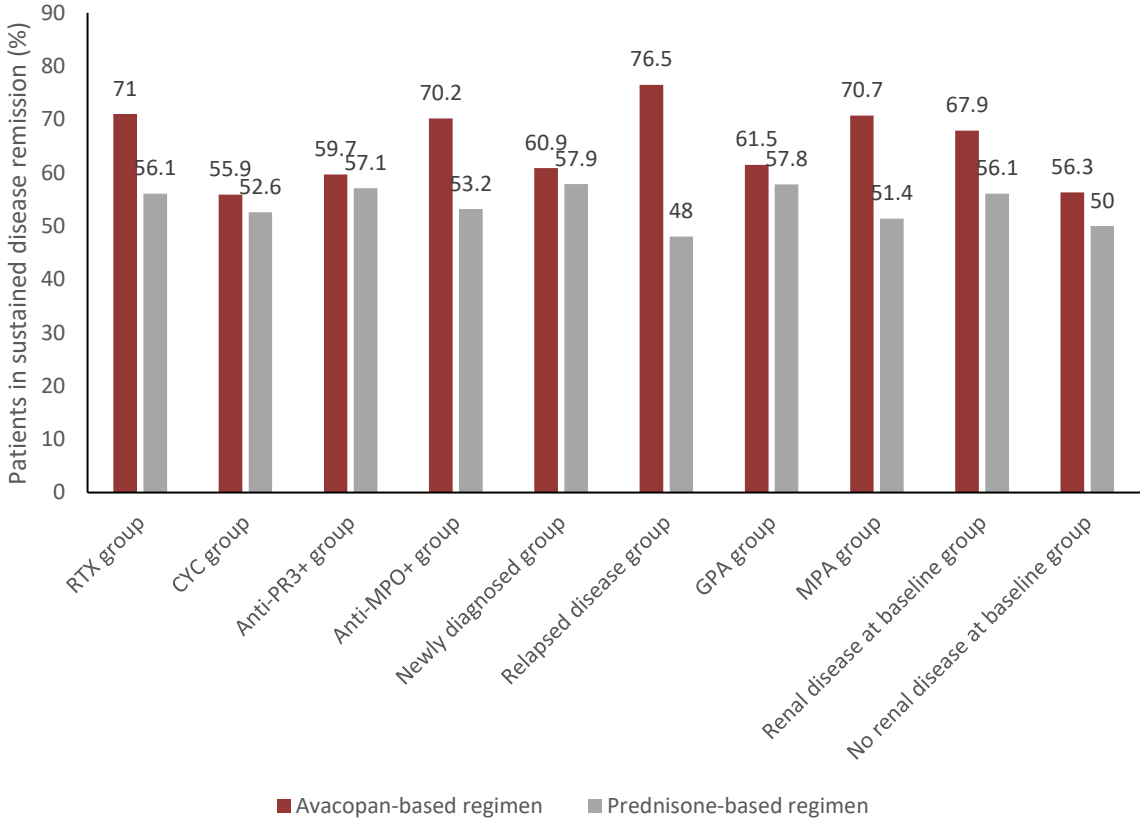
Table 24. Proportion of patients in sustained remission in ITT population at week 26 and week 52 stratified by subgroup (2, 65)

	Avacopan-based regimen (N=166)		**Prednisone-based regimen (N=164)**	
Patient subgroup	**Number of patients in the ITT population**	**Number of patients with sustained remission data at this time point (%)**	**Number of patients in the ITT population**	**Number of patients with sustained remission data at this time point (%)**
Patients receiving RTX (IV)				
Week 26	107	83 (77.6)	107	81 (75.7)
Week 52		76 (71.0)		60 (56.1)
Patients receiving CYC (oral/IV)				
Week 26	59	37 (62.7)	57	34 (59.6)
Week 52		33 (55.9)		30 (52.6)
Anti-PR3+ AAV patients				
Week 26	72	51(70.8)	70	50 (71.4)
Week 52		43 (59.7)		40 (57.1)
Anti-MPO+ AAV patients				
Week 26	94	69 (73.4)	94	65 (69.1)
Week 52		66 (70.2)		50 (53.2)
Newly diagnosed patients				
Week 26	115	76 (66.1)	114	76 (66.7)
Week 52		70 (60.9)		66 (57.9)
Patients with relapsing disease				
Week 26	51	44 (86.3)	50	39 (78.0)
Week 52		39 (76.5)		24 (48.0)

Patients with GPA				
Week 26	91	65 (71.4)	90	65 (72.2)
Week 52		56 (61.5)		52 (57.8)
Patients with MPA				
Week 26	75	55 (73.3)	74	50 (67.6)
Week 52		53 (70.7)		38 (51.4)
Patients with renal disease at baseline				
Week 52	134	91 (67.9)	132	74 (56.1)
Patients without renal disease at baseline				
Week 52	32	18 (56.3)	32	16 (50)

Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; CYC, cyclophosphamide; ITT, intention-to-treat; IV, intravenous; MPA, microscopic polyangiitis; MPO, myeloperoxidase; RTX, rituximab

Figure 8. Sustained remission at week 52 in subgroups, ADVOCATE (2, 65)



Abbreviations: CYC, cyclophosphamide; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; RTX, rituximab

B.2.8 Meta-analysis

No meta-analyses were carried out.

B.2.9 Indirect and mixed treatment comparisons

The ADVOCATE trial protocol specified maintenance treatment with AZA after week 26 for patients who have received CYC induction treatment only. In practice, patients who have achieved remission with avacopan in combination with RTX may continue with RTX maintenance therapy in line with clinical guidelines in AAV. Given that maintenance treatment with avacopan in combination with RTX has not been tested in an RCT, an indirect treatment comparison (ITC) is not possible in this case. Furthermore, the treatment effect of RTX maintenance will cancel out if it is assumed to apply to both the avacopan and SoC arms. The adjusted hazard ratio for relapse is, therefore, not expected to be substantially different to the one observed in the ADVOCATE trial.

The feasibility of conducting an anchored ITC between avacopan and fixed dose RTX maintenance treatment in patients with AAV entering remission following RTX induction treatment was assessed. The feasibility assessment was conducted comparing the ADVOCATE trial to the identified comparator trials listed in Table 25 based on study design, treatment, and outcomes. Three relevant RCTs for RTX maintenance were identified: RITAZAREM (91), MAINRITSAN (76) and MAINRITSAN 2 (92).

Of the three comparator trials, MAINRITSAN 2 could be ruled out immediately for an anchored comparison based on study design, since both arms of the study received RTX maintenance treatment and therefore could not be included in an anchored comparison. The feasibility assessment also found that the main barrier to an anchored comparison between ADVOCATE and RITAZAREM is the difference in maintenance treatments received in the control arms. That is, patients in the control arm of RITAZAREM received RTX induction treatment followed by AZA but there were no patients treated with RTX induction followed by AZA in the ADVOCATE study. In addition, given the use of only RTX for induction therapy in the RITAZAREM trial, an ITC against ADVOCATE would be limited to RTX-induced

patients in ADVOCATE which would impact the sample size and reduce the power to detect differences in efficacy between treatments.

A further key barrier across MAINRTISAN and RITAZAREM comparisons is the fact patients in the ADVOCATE study were not randomised at the point of entering remission; they have been randomised prior to induction treatment. In an anchored comparison this may result in imbalance in patient characteristics between study arms.

In conclusion, an indirect comparison between avacopan and fixed dose RTX maintenance treatment was not feasible due to the issues highlighted above and the conduct on any anchored indirect comparison would likely produce highly uncertain and biased results.

Table 25. Details of the RCTs included in the ITC feasibility assessment

Study	Design	RTX maintenance dosing (fixed/flexible)	Maintenance interventions	Outcomes
ADVOCATE	Randomised, double-blind, double-dummy, active-controlled clinical study	Fixed	• avacopan (+ AZA/MMF in some patients) • prednisone (+ AZA/MMF in some patients)	Proportion maintaining remission, GC toxicity, AEs, VDI damage severity, changes in renal disease parameters, time to relapse[3]
MAINRITSAN	Randomised, controlled, national, multicentre, prospective trial	Fixed	• RTX + prednisone • AZA + prednisone	Proportion relapsing, relapse-free survival, AEs, CD19+ B-cell counts
MAINRITSAN 2	Open label, multicentre, randomised controlled trial	Fixed + Flexible	• RTX + prednisone	Proportion relapsing, VDI damage severity, AEs, CD19+ B-cell counts, GC duration, relapse-free survival
RITZAREM	International, multicentre, open label, randomised controlled trial	Fixed	• RTX + prednisone • AZA/MTX/MMF + prednisone	Relapse-free survival, AEs, cumulative GC exposure, CDA damage score, proportion maintaining remission

Abbreviations: AE, adverse event; AZA, azathioprine; CDA, combined damage assessment; GC, glucocorticoid; MMF, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab; VDI, vasculitis damage index

B.2.10 Adverse reactions

Summary
The avacopan-based regimen has a favourable risk-benefit profile in patients with AAV

B.2.10.1 Incidence of treatment-emergent adverse events (TEAEs)

In the ADVOCATE trial, the patient incidence of treatment-emergent adverse events (TEAEs) was comparable between the avacopan-based regimen and prednisone-based regimen groups (98.8% vs 98.2%, respectively). However, the number of TEAEs reported was 20% lower in the avacopan group compared with the prednisone group (1779 vs 2139, respectively, Table 26) (2, 65).

All TEAEs reported by ≥5% of patients occurred at a higher patient incidence in the prednisone-based regimen group compared with the avacopan-based regimen group, or at a similar incidence in both treatment groups (Table 27). In both treatment groups, the majority of TEAEs were moderate in severity (49.4% and 41.5% in the avacopan- and prednisone-based regimen groups, respectively), and approximately a quarter of patients in both treatment groups experienced severe TEAEs (Table 26) (2, 65).

Table 26. Overview of patient incidence of TEAEs in the ADVOCATE study (safety population) (2, 65)

	Avacopan-based regimen (N=166)	Prednisone-based regimen (N=164)
All TEAEs		
TEAEs, n	1779	2139
Patient incidence of TEAEs, n (%)	164 (98.8)	161 (98.2)
Maximum severity of TEAE, n (%)		
Mild	33 (19.9)	34 (20.7)
Moderate	82 (49.4)	68 (41.5)
Severe	39 (23.5)	41 (25.0)
Life-threatening	8 (4.8)	14 (8.5)
Death	2 (1.2)	4 (2.4)
Patient incidence of discontinuation due to AEs, n (%)	27 (16.3)	28 (17.1)

Serious TEAEs		
Number of serious TEAEs	116	166
Patient incident of serious TEAEs, n (%)	70 (42.2)	74 (45.1)
Patients with any serious infection, n (%)	22 (13.3)	25 (15.2)
Deaths due to infection, n (%)	1 (0.6)	2 (1.2)
Patients with any serious hepatic system AE, n (%)	9 (5.4)	6 (3.7)
GC-related AEs		
Patients with any AE potentially related to GCs[a], n (%)	110 (66.3)	132 (80.5)

Abbreviations: AE, adverse event; GC, glucocorticoid; N, number of subjects randomised to treatment group in the safety population; n, number of subjects in specified category; TEAE, treatment-emergent adverse event (serious or non-serious events starting on or after the date/time of first dose of study medication)

[a]Investigators blinded assessment

Table 27. Summary of TEAEs by preferred term observed in ≥5% in either treatment group of ADVOCATE (2, 65)

Preferred Term	Avacopan-based regimen (N=166)		Prednisone-based regimen (N=164)	
	Subjects, n (%)	Events, n	Subjects, n (%)	Events, n
Any TEAE	164 (98.8)	1,779	161 (98.2)	2,139
Nausea	39 (23.5)	54	34 (20.7)	46
Oedema peripheral	35 (21.1)	39	40 (24.4)	56
Headache	34 (20.5)	43	23 (14.0)	30
Arthralgia	31 (18.7)	42	36 (22.0)	48
Hypertension	30 (18.1)	36	29 (17.7)	31
Anti-neutrophil cytoplasmic antibody positive vasculitis	26 (15.7)	30	34 (20.7)	46
Cough	26 (15.7)	31	26 (15.9)	29
Diarrhoea	25 (15.1)	33	24 (14.6)	31
Nasopharyngitis	25 (15.1)	38	30 (18.3)	46
Vomiting	25 (15.1)	29	21 (12.8)	27
Upper respiratory tract infection	24 (14.5)	28	24 (14.6)	33
Rash	19 (11.4)	26	13 (7.9)	17
Muscle spasms	18 (10.8)	23	37 (22.6)	47
Fatigue	17 (10.2)	19	15 (9.1)	15

Back pain	16 (9.6)	16	22 (13.4)	22
Myalgia	16 (9.6)	17	22 (13.4)	25
Pyrexia	15 (9.0)	18	19 (11.6)	25
Epistaxis	14 (8.4)	21	21 (12.8)	30
Anaemia	13 (7.8)	13	18 (11.0)	19
Insomnia	13 (7.8)	13	25 (15.2)	27
Pain in extremity	13 (7.8)	13	13 (7.9)	13
Hypercholesterolaemia	12 (7.2)	13	20 (12.2)	21
Leukopenia	12 (7.2)	15	14 (8.5)	20
Urinary tract infection	12 (7.2)	19	23 (14.0)	33
Abdominal pain upper	11 (6.6)	12	10 (6.1)	13
Constipation	11 (6.6)	11	11 (6.7)	11
Dizziness	11 (6.6)	14	10 (6.1)	10
Pneumonia	11 (6.6)	12	11 (6.7)	11
Blood creatinine increased	10 (6.0)	10	8 (4.9)	10
Pruritus	10 (6.0)	15	10 (6.1)	11
Sinusitis	10 (6.0)	10	12 (7.3)	12
Paraesthesia	9 (5.4)	10	7 (4.3)	8
Dyspnoea	8 (4.8)	11	11 (6.7)	14
Alopecia	7 (4.2)	7	12 (7.3)	12
Increased tendency to bruise	7 (4.2)	7	10 (6.1)	11
Lymphopenia	6 (3.6)	7	18 (11.0)	27
Oropharyngeal pain	6 (3.6)	7	12 (7.3)	12
Bronchitis	5 (3.0)	7	10 (6.1)	11
Dyspepsia	5 (3.0)	6	10 (6.1)	12
Cushingoid	3 (1.8)	3	9 (5.5)	9
Tremor	1 (1.2)	2	10 (6.1)	11
Weight increased	1 (0.6)	1	17 (10.4)	19

Abbreviations: N, number of subjects randomised to treatment group in the safety population; n, number of subjects in specified category; TEAE, treatment-emergent adverse event

Note: An AE was considered treatment-emergent if the start date/time of the event was on or after the date/time of first dose of study medication. AEs were coded using Medical Dictionary for Regulatory Activities (version 19.1).

Overall, there were more serious adverse events (SAEs) among patients in the prednisone-based regimen group compared with patients in the avacopan-based regimen group (166 events in 74 subjects [45.1%] vs 116 events in 70 subjects [42.2%], respectively), although discontinuation due to AEs was similar between patients in the avacopan-based and prednisone-based regimen groups (16.3% vs 17.1%, respectively). Fewer patients experienced life-threatening TEAEs in the avacopan-based regimen group compared with the prednisone-based regimen group (4.8% vs 8.5%, respectively). Four (2.4%) patients in the prednisone group died compared with 2 (1.2%) patients in the avacopan group (the first due to disease worsening and the second due to broncho-pneumonia) (2, 65). Table 28 presents SAEs reported in the 2 treatment groups of the ADVOCATE trial.

Table 28. Serious adverse events reported in the ADVOCATE trial (2, 65)

	Prednisone-based regimen (N=164)		**Avacopan-based regimen (N=166)**	
	Subjects n (%)	Events n	Subjects n (%)	Events n
AAV	20 (12.2)	25	12 (7.2)	12
Pneumonia	6 (3.7)	6	8 (4.8)	9
GPA	1 (0.6)	1	5 (3.0)	5
Acute kidney injury	1 (0.6)	2	3 (1.8)	3
Urinary tract infection	2 (1.2)	2	3 (1.8)	3
Angina pectoris	0 (0.0)	0	2 (1.2)	2
Cardiac failure	0 (0.0)	0	2 (1.2)	2
Device-related infection	0 (0.0)	0	2 (1.2)	2
Drug hypersensitivity	2 (1.2)	3	2 (1.2)	2
Hepatic enzyme increased	3 (1.8)	3	2 (1.2)	2
Hepatic function abnormal	0 (0.0)	0	2 (1.2)	2
Hyperglycaemia	1 (0.6)	1	2 (1.2)	2
Influenza	1 (0.6)	1	2 (1.2)	2
Pyrexia	3 (1.8)	3	2 (1.2)	3
Acute myocardial infarction	2 (1.2)	2	1 (0.6)	1
Agranulocytosis	2 (1.2)	2	1 (0.6)	1
Blood creatinine increased	2 (1.2)	2	1 (0.6)	1
Lymphopenia	3 (1.8)	3	1 (0.6)	1
Pulmonary alveolar haemorrhage	2 (1.2)	2	1 (0.6)	1
Anaemia	2 (1.2)	2	0 (0.0)	0
Dehydration	2 (1.2)	2	0 (0.0)	0

Diarrhoea	3 (1.8)	3	0 (0.0)	0
Epistaxis	2 (1.2)	2	0 (0.0)	0
Glomerulonephritis	2 (1.2)	2	0 (0.0)	0
Herpes zoster	2 (1.2)	2	0 (0.0)	0
Infectious pleural effusion	2 (1.2)	2	0 (0.0)	0
Large intestinal polyp	2 (1.2)	2	0 (0.0)	0
Microscopic polyangiitis	2 (1.2)	2	0 (0.0)	0
Mononeuropathy multiplex	2 (1.2)	2	0 (0.0)	0
Neutropenia	2 (1.2)	2	0 (0.0)	0
Pneumonia bacterial	2 (1.2)	2	0 (0.0)	0
Prostate cancer	2 (1.2)	2	0 (0.0)	0
Pulmonary embolism	3 (1.8)	3	0 (0.0)	0
Respiratory syncytial virus infection	2 (1.2)	2	0 (0.0)	0
Thrombocytopenia	2 (1.2)	2	0 (0.0)	0
Vomiting	2 (1.2)	2	0 (0.0)	0

The incidence of SAEs in most system organ classes was higher among patients in the prednisone group compared with the avacopan group. The most common SAE system organ class among patients in both treatment groups was infections and infestations (15.2% and 13.3% in the prednisone- and avacopan-based regimen groups, respectively), with patient incidence of infections and infestations lower in the avacopan-based regimen group compared with the prednisone-based group. Furthermore, there was a lower proportion of patients with any TEAEs of infection, serious TEAEs of infection, serious opportunistic infections, life-threatening TEAEs of infection, and infections resulting in death in the avacopan-based group compared with the prednisone-based group (2, 65). Data on infections are presented in Table 29.

Table 29. Summary of subject incidence of treatment-emergent infections by system organ class and preferred term (safety population) (2, 65)

Category	**Avacopan-based regimen (N=166), n (%)**	**Prednisone-based regimen (N=164), n (%)**
Any treatment-emergent infection	113 (68.1)	124 (75.6)
Any serious treatment-emergent infection	22 (13.3)	25 (15.2)
Any severe treatment-emergent infection	12 (7.2)	10 (6.1)

Any treatment-emergent infection leading to study withdrawal	4 (2.4)	5 (3.0)
Any treatment-emergent life-threatening infection	1 (0.6)	2 (1.2)
Any treatment-emergent infection leading to death	1 (0.6)	2 (1.2)
Most common TEAEs of infection (≥3% in any treatment group)		
Nasopharyngitis	25 (15.1)	30 (18.3)
Upper respiratory tract infection	24 (14.5)	24 (14.6)
Urinary tract infection	12 (7.2)	23 (14.0)
Pneumonia	11 (6.6)	11 (6.7)
Sinusitis	10 (6.0)	12 (7.3)
Bronchitis	5 (3.0)	10 (6.1)
Gastroenteritis	5 (3.0)	1 (0.6)
Lower respiratory tract infection	5 (3.0)	8 (4.9)
Rhinitis	5 (3.0)	2 (1.2)
Herpes zoster	4 (2.4)	6 (3.7)
Influenza	4 (2.4)	8 (4.9)
Oral candidiasis	4 (2.4)	7 (4.3)
Oral herpes	4 (2.4)	6 (3.7)
Viral upper respiratory tract infection	4 (2.4)	5 (3.0)
Viral infection	2 (1.2)	5 (3.0)
Most common serious TEAEs of infection [≥1% (2 subjects) in any treatment group]		
Pneumonia	8 (4.8)	6 (3.7)
Urinary tract infection	3 (1.8)	2 (1.2)
Device related infection	2 (1.2)	0 (0)
Influenza	2 (1.2)	1 (0.6)
Herpes zoster	0 (0)	2 (1.2)
Infectious pleural effusion	0 (0)	2 (1.2)
Pneumonia bacterial	0 (0)	2 (1.2)
Respiratory syncytial virus infection	0 (0)	2 (1.2)
Abbreviations: N, number of subjects randomised to treatment group in the safety population; n, number of subjects in specified category; TEAEs, treatment-emergent adverse events		

In support of the efficacy results, there was a numerically lower number of events indicating a worsening of vasculitis (anti-neutrophil cytoplasmic antibody positive vasculitis) among patients in the avacopan-based group (30 events in 26 subjects, 15.7%) compared with patients in the prednisone-based group (46 events in 34 subjects, 20.7%) (2, 65).

The SAE profile in the Phase 2 studies was generally consistent with the ADVOCATE study (4, 87-89). Because both the CLEAR and CLASSIC trials had a 12-week treatment duration, safety data from these trials were integrated. Details of this pooled, phase 2 safety population can be found in Table 30.

Table 30. Summary of TEAEs during CLEAR and CLASSIC trials (combined)

Demographic variable statistic/Category	Avacopan-based regimen (N=73), n (%)	Prednisone-based regimen (N=36), n (%)
Participants reporting at least 1 TEAE	69 (94.5)	34 (94.4)
Maximum severity of TEAE		
Mild	21 (28.8)	15 (41.7)
Moderate	34 (46.6)	15 (41.7)
Severe	12 (16.4)	4 (11.1)
Life-threatening	2 (2.7)	0 (0.0)
Death	0 (0.0)	0 (0.0)
SAE	24 (32.9)	8 (22.2)
TEAEs leading to discontinuation of study medications	8 (11.0)	4 (11.1)

Abbreviations: N, total number of subjects; n, number of subjects in specified category; SAE, serious adverse event; TEAE, treatment-emergent adverse event

B.2.10.2 Incidence of glucocorticoid-related adverse events

In the ADVOCATE trial, the incidence of GC-related AEs was reduced with an avacopan-based regimen compared with prednisone-based regimen. In the ADVOCATE study, treatment with the avacopan-based regimen was associated with a significantly lower number of potentially GC-related AEs (based on European Alliance of Associations of Rheumatology criteria) compared with the prednisone arm (66% vs 81% of patients, respectively) (Table 31). A statistically significant difference was found in the endocrine/metabolic (12% vs 28%) and dermatological (7% vs 16%) systems ($p<0.05$). Metabolic effects included diabetes, Cushingoid signs (facial swelling and weight gain), and adrenal insufficiency (2, 65). These findings reinforced results from the Phase 2 CLEAR trial, which also showed a

higher number of potentially GC-related AEs in patients receiving SoC compared with an avacopan-based regimen (4, 87).

Table 31. Adverse events potentially related to glucocorticoid use in the ADVOCATE study (2, 65)

	Avacopan-based regimen (N=166), n (%)	Prednisone-based regimen (N=164), n (%)	Difference (%)	Difference, 95% CI
Any adverse event	110 (66.3%)	132 (80.5%)	-14.2[a]	-23.7 to -3.8
Cardiovascular	72 (43.4%)	85 (51.8%)	-8.5	-19.2 to 2.6
Dermatological	14 (8.4%)	28 (17.1%)	-8.6[a]	-16.2 to -1.0
Endocrine/metabolic	23 (13.9%)	48 (29.3%)	-15.4[a]	-24.3 to -6.0
Gastrointestinal	3 (1.8%)	4 (2.4%)	-0.6	-4.6 to 3.1
Infectious	22 (13.3%)	25 (15.2%)	-2.0	-9.9 to 5.7
Musculoskeletal	19 (11.4%)	21 (12.8%)	-1.4	-8.7 to 5.9
Ophthalmological	7 (4.2%)	12 (7.3%)	-3.1	-8.7 to 2.1
Psychological	27 (16.3%)	39 (23.8%)	-7.5	-16.5 to 1.3

Abbreviations: CI, confidence interval; N, number of subjects randomised to treatment group in the safety population; n, number of subjects in specified category

[a]$p<0.05$

B.2.10.3 Incidence of adverse events related to background treatment

In the ADVOCATE trial, the incidence of AEs was generally higher in patients with background treatment with CYC compared with those treated with RTX in both the avacopan- and prednisone-based regimen groups (Table 32). In the prednisone group, there was no difference in overall non-serious TEAEs between patients treated with CYC compared with RTX (98.2% vs 98.1%, respectively). Prednisone + CYC was generally associated with higher incidence of AEs compared with prednisone + RTX except for psychiatric disorders, eye disorders, cardiac disorders, ear and labyrinth disorders, endocrine disorders, and hepatobiliary disorders. In the avacopan-based regimen group, there was no difference in overall non-serious TEAEs between patients treated with CYC compared with RTX (98.3% vs 96.3%, respectively). The largest difference in incidence of AEs between CYC-treated and

RTX-treated patients in the avacopan-based regimen group was observed in gastrointestinal disorders (72.9% CYC vs 50.5% RTX) (2, 65).

Table 32. Summary of treatment-emergent non-serious AEs by system organ class and preferred term by background therapy with RTX or CYC, ADVOCATE (safety population) (2, 65)

	Avacopan + CYC (N=59), n (%)	Avacopan + RTX (N=166), n (%)	Prednisone + CYC (N=57), n (%)	Prednisone + RTX (N=107), n (%)
Any treatment-emergent non-serious AE	58 (98.3)	103 (96.3)	56 (98.2)	105 (98.1)
Infections and infestations	42 (71.2)	62 (57.9)	45 (78.9)	75 (70.1)
Gastrointestinal disorders	43 (72.9)	54 (50.5)	39 (68.4)	43 (40.2)
Musculoskeletal and connective tissue disorders	36 (61.0)	56 (52.3)	34 (59.6)	59 (55.1)
General disorders and administration site conditions	24 (40.7)	50 (46.7)	32 (56.1)	51 (47.7)
Skin and subcutaneous tissue disorders	28 (47.5)	44 (41.1)	30 (52.6)	55 (51.4)
Nervous system disorders	23 (39.0)	48 (44.9)	31 (54.4)	41 (38.3)
Respiratory, thoracic, and mediastinal disorders	9 (15.3)	17 (15.9)	23 (22.8)	13 (12.1)
Investigations	24 (40.7)	40 (37.4)	32 (56.1)	33 (30.8)
Metabolism and nutrition disorders	25 (42.4)	30 (28.0)	22 (38.6)	39 (36.4)
Blood and lymphatic system	24 (40.7)	20 (18.7)	30 (52.6)	20 (18.7)
Vascular disorders	13 (22.0)	29 (27.1)	17 (29.8)	28 (26.2)
Injury, poisoning and procedural complications	17 (28.8)	16 (15.0)	21 (36.8)	25 (23.4)
Psychiatric disorders	10 (16.9)	22 (20.6)	14 (24.6)	28 (26.2)
Eye disorders	8 (13.6)	17 (15.9)	12 (21.1)	30 (28.0)
Renal or urinary disorders	11 (18.6)	13 (12.1)	10 (17.5)	14 (13.1)
Cardiac disorders	12 (20.3)	11 (10.3)	6 (10.5)	12 (11.2)
Ear and labyrinth disorders	3 (5.1)	17 (15.9)	3 (5.3)	13 (12.1)
Immune system disorders	8 (13.6)	12 (11.2)	10 (17.5)	17 (15.9)
Reproductive system, and breast disorders	3 (5.1)	5 (4.7)	3 (5.3)	2 (1.9)
Endocrine disorders	1 (1.7)	4 (3.7)	6 (10.5)	15 (14.0)
Hepatobiliary disorders	2 (3.4)	3 (2.8)	0 (0.0)	3 (2.8)

Neoplasms benign, malignant, and unspecified	0 (0.0)	4 (3.7)	7 (12.3)	5 (4.7)
Abbreviations: AE, adverse event; CYC, cyclophosphamide; RTX, rituximab				

B.2.11 Ongoing studies

There are no ongoing studies of avacopan in AAV.

B.2.12 Innovation

An avacopan-based regimen has a unique and targeted approach that, at week 52, appeared to be superior in controlling active GPA and MPA compared with current GC-based regimens. It is also associated with reductions in relapses and improvements in kidney function among patients with prior renal involvement, without the considerable complications of long-term GC therapy. The clinical benefits, together with improved QoL, a simpler dosing regimen than GCs, and cost-savings for the health system including reduced frequency and duration of hospitalisation, offer prescribers, patients, and payers a significant advance in the treatment of GPA and MPA.

Avacopan selectively targets a single component of the complement cascade, C5a, that plays a key role in the inflammatory amplification process in GPA and MPA driven by C5a-neutrophil interactions. This unique mechanism of action enables avacopan, as part of a combination therapy, to control MPA and GPA as effectively as current treatments but keeps a greater number of patients in remission than standard treatments. An avacopan-based regimen protects the kidney and other organs from the damage caused by AAV, potentially reducing the need for treatments such as dialysis and decreasing patient mortality and suffering. Unlike other complement system modifying agents, avacopan does not inhibit the formation of membrane attack complex, a major advantage with regards to vulnerability for major infections. No vaccinations are required prior application of avacopan.

Due to lack of new therapies, GCs have been a foundation of AAV management, but their use is associated with several issues. Most important, the treatment-related AEs and complications associated with prolonged and high-dose GC treatment can increase susceptibility to infections and cause serious metabolic side effects and

complications. In addition, a wide variation in the doses given, a long duration of use, and the need to gradually reduce dosage as treatment ends make them complex for clinicians to prescribe and for patients to adhere to treatment accurately. An avacopan-based regimen reduces, and in some cases eliminates, the need for GC therapy, greatly benefiting patients by positively affecting QoL while also providing a simpler fixed-dosing regimen.

B.2.13 Interpretation of clinical effectiveness and safety evidence

AAV is a rare, potentially fatal, remitting-relapsing, autoimmune condition that has a substantial impact on patients' QoL. It can damage vital organs, including the kidneys, often resulting in end-stage renal disease (ESRD) (62). Controlling AAV by inducing and sustaining disease remission are essential for good prognosis. However, incident GPA and MPA patients often experience a complex pathway of diagnosis, referral and management that delays effective treatment (93).

Although current standard induction therapies such as CYC-AZA or RTX result in remission in many patients, remission rates are still variable and fewer than a third of AAV patients remain in relapse-free remission for more than a decade (9, 94). Patients who achieve remission remain at high risk of relapse and require long-term GC treatment (95), which further increases the risk for treatment-related AEs and complications, including malignancy, infections, metabolic side effects, and cumulative organ damage (78, 96). The majority of patients experience 1 or more relapses within 5 years of successful remission induction (9), and relapses can be fatal (71). Furthermore, ~10% to 30% of patients do not respond to traditional immunosuppressive agents and pursue a refractory course (72). Longer-term mortality is increased because of disease-related complications, development of cardiovascular disease, renal disease, and GC-related toxicity (10, 11).

Avacopan, an orally administered C5a receptor inhibitor, provides potential clinical benefit as a GC-sparing agent that can induce sustainable remission in AAV. In the ADVOCATE clinical study, patients receiving an avacopan-based regimen experienced remission rates similar to those of patients receiving prednisone on a tapering schedule at 26 weeks; however, at 52 weeks, sustained remission was

higher in the avacopan group than the prednisone group (65.7% vs 54.9%, respectively; p=0.007). In addition, treatment with avacopan-based regimen was associated with a 54% lower risk of relapse following remission achieved at any point during the study (HR: 0.46; 95% CI, 0.25 to 0.84; p=0.0091] compared with the prednisone group (2, 65).

An avacopan-based regimen may also improve renal function, including eGFR, albuminuria, and MCP-1:creatinine ratio improvements, in patients with renal disease at baseline, thus significantly reducing the risk of developing end-stage renal disease. The effects of avacopan on kidney function were consistent across all 3 clinical studies (4, 65, 88).

Furthermore, the assessments of HRQoL in the 3 trials investigating the use of avacopan in AAV found that the addition of avacopan to SoC led to broad improvements in various aspects of well-being, including bodily pain, vitality, mental health, physical functioning, and emotional role (4, 65, 88). Such QoL improvements have not been reported with the use of other interventions.

In addition to its clinical efficacy benefits, an avacopan-based regimen has an acceptable safety profile. The number of SAEs in avacopan-treated groups across the 3 trials was lower than in SoC groups (4, 65, 88). The use of an avacopan-based regimen is associated with a reduced need for GC treatment in AAV patients. In the ADVOCATE trial, over 52 weeks of treatment, GC exposure in the avacopan-based regimen group was 63% lower with the mean cumulative GC dose during the treatment period (1,348.9 mg for an avacopan-based regimen versus 3,654.5 mg for SoC). Treatment with avacopan was also associated with lower GC AEs and complications, including lower infection rates and serious infection rates, compared with SoC (65).

B.3 Cost-effectiveness

B.3.1 Published cost-effectiveness studies

A literature review using systematic methodology was undertaken to identify and summarise the best available cost-effectiveness evidence for avacopan and relevant comparator therapies for the treatment of AAV. The original search was undertaken in June 2018, with updated searches undertaken in June 2020 and June 2021. These searches identified 2 studies, 1 of which was a fully published peer-reviewed article (97) and the other a conference abstract (98). An additional 2 HTAs, published by NICE (8) and the Scottish Medicines Consortium (SMC) (99), were identified through hand searching. Full details of the methodology of the searches and quality assessment of the identified studies are presented in Appendix G. A summary of the findings of the studies is reported in Table 33.

Table 33. Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Intervention and comparator(s)	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Montante (97) France Fully published journal article	2019	Direct CUA based on patient level data from MAINRITSAN trial (n=112) (76)	I: RTX (in combination with IV CYC and GCs) C: AZA (in combination with IV CYC and GCs)	Patients with GPA, MPA, or renal-limited AAV at the beginning of their remission phase achieved (maintenance phase) Aged 18 to 75 years	I: mean ± SD, 1.522±0.104 C: mean ± SD, 1.438±0.209	I: mean ± SD, €10,217±11,036 C: mean ± SD, €13,387±7,399	€92,700 at 12 months €37,782 at 28 months
Harland (98) United Kingdom Conference abstract	2014	Markov model (complete remission, non-remission, uncontrolled disease, and death health states)	I: RTX in combination with GCs C: CYC (in combination with GCs)	Patients with severe GPA and MPA NR	I: 0.306 (incremental QALY) C: NR	I: £3,700 (incremental cost) C: NR	£12,100
NICE TA308 (8) United Kingdom	2014	Markov model (non-remission, complete remission, uncontrolled	I: RTX in combination with GCs	Patients with severe, active GPA and MPA Equivalent characteristics	I: Manufacturer's original analysis: 8.18 Manufacturer's revised base-case	I: Manufacturer's original analysis: £100,874 Manufacturer's revised base-case	Manufacturer's original analysis: £10,898 Manufacturer's revised base-

Study	Year	Summary of model	Intervention and comparator(s)	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
HTA		disease, and death; lifetime time horizon; 6-month cycle with a half cycle correction)	C: CYC (in combination with GCs)	to the RAVE study (64) 52 years.	analysis after ERG comments: 8.19 C: Manufacturer's original analysis: 8.02 Manufacturer's revised base-case analysis after ERG comments: 8.03	analysis after ERG comments: £97,210 C: Manufacturer's original analysis: £99,087 Manufacturer's revised base-case analysis after ERG comments: £95,819	case analysis after ERG comments: £8544 NICE Committee's ICER based on ERG analysis: £12,075
SMC 894/13 (99) United Kingdom HTA	2013	Markov model (non-remission, complete remission, uncontrolled disease, and death; lifetime time horizon)	I: RTX in combination with GCs C: CYC (in combination with GCs)	Patients with severe, active GPA and MPA. Equivalent characteristics to the RAVE study (64). NR	I: 0.1628 (incremental QALY) C: NR	£1,391 (incremental cost)	£8,544

Abbreviations: AAV, anti-neutrophil cytoplasmic antibody–associated vasculitis; AZA, azathioprine C, comparator; CUA, cost-utility analysis; CYC, cyclophosphamide; ERG, Evidence Review Group; GC, glucocorticoids; GPA. granulomatosis with polyangiitis; HTA, health technology assessment; I, intervention; ICER, incremental cost-effectiveness ratio; IV, intravenous; MPA, microscopic polyangiitis; NICE, National Institute for Health and Care Excellence; NR, not reported; QALY, quality-adjusted life year; RTX, rituximab; SMC, Scottish Medicines Consortium

B.3.2 Economic analysis

An economic evaluation was conducted to assess the cost-effectiveness of avacopan in the treatment of adult patients with AAV. Avacopan is used in combination with CYC or RTX for the induction of sustained remission and prevention of relapses.

A de novo economic model was developed in the absence of previously published cost-effectiveness models of avacopan for the treatment of AAV. The model includes the key elements of the disease pathway in AAV, including remission and relapse of AAV, end-stage renal disease, and complications of glucocorticoid treatment.

B.3.2.1 Patient population

The population in the economic evaluation included people with newly diagnosed or relapsed AAV. The starting age of the cohort in the model is 60 years. This reflects the population defined in the final scope for the NICE technology appraisal of avacopan, the avacopan summary of product characteristics (SmPC), and the ADVOCATE Phase 3 trial (65).

B.3.2.2 Model perspective

The perspective for this analysis is that of the NHS and Personal and Social Services in England and Wales in line with the NICE reference case. All costs are reported in pounds sterling, reflecting the 2020 cost year.

B.3.2.3 Time horizon and discount rate

The base-case analysis uses a lifetime horizon, given that AAV is a serious, life-threatening disease that requires lifetime treatment. A lifetime horizon thus captures all relevant costs and outcomes associated with treatment of AAV and its long-term complications. Shorter time horizons were explored using scenario analyses. Future costs and outcomes were discounted at a rate of 3.5% per annum as per NICE guidance. Alternative discount rates were explored using scenario analyses.

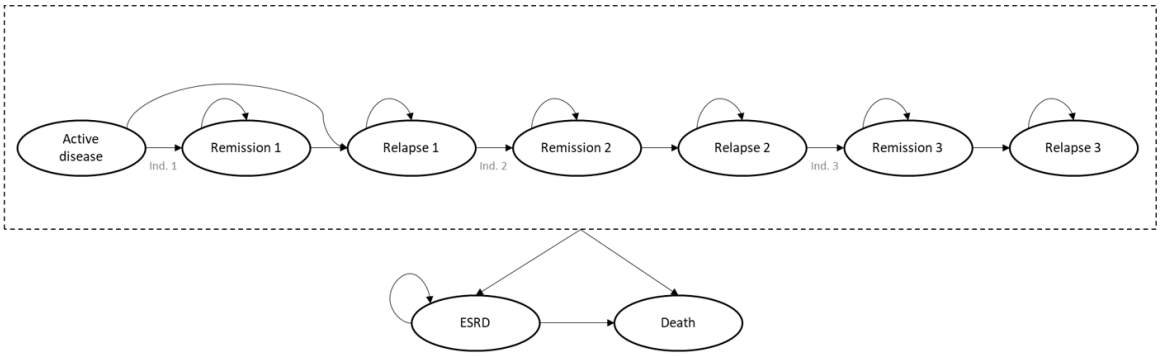
B.3.2.4 Cycle length

Patients transitioned between model health states once per 28-day cycle. The short length of the model cycle was motivated by the posology of induction and maintenance treatments in AAV and the rapid progression of the disease. A half-cycle correction was applied to the model to account for transitions in the middle of a model cycle.

B.3.2.5 Model structure

The cost-effectiveness analysis employs a Markov model consisting of 9 core health states: active disease, 3 remission health states, 3 relapse health states, ESRD, and death. The model structure reflects the clinical pathway in AAV, which is characterised by induction phases to treat relapsed AAV and maintenance treatment phases aimed at preventing further relapses. ESRD was included as a separate health state as a severe complication of renal relapse. In addition, complications of GC treatment have been included as separate events in the model based on the incidence of AEs observed in the ADVOCATE trial.

Figure 9. Economic model structure



The sequential modelling of remission and relapse is similar to the method employed in the NICE technology appraisal of RTX in AAV (TA308) (8). Patients with newly diagnosed or relapsed AAV enter the model in the active disease health states, where they receive induction treatment with avacopan in combination with CYC or RTX, or CYC or RTX in combination with GCs. If remission is achieved, patients transition to the remission 1 health state, where they receive maintenance treatment.

If remission is not achieved, or if patients relapse after reaching the remission health states, they are treated with an additional course of CYC/RTX in combination with GCs to induce remission in the relapse 1 health state. Patients continue cycling through remission and relapse health states until death, ESRD, or reaching the relapse 3 health state. Relapse 3 reflects refractory disease, and patients remain in this health state without further induction treatment until progression to ESRD or death.

In any given model cycle, patients can develop ESRD. Once reaching the ESRD health state, patients remain until death. The model assumes that patients cannot recover from ESRD and do not receive additional treatment for induction or maintenance of remission. Patients in the ESRD health state receive chronic renal replacement therapy until death or undergo a renal transplant.

B.3.2.6 Health state definitions

Active disease was defined as patients with a Birmingham Vasculitis score (BVAS) greater than 0. Remission in the model was defined in accordance with the protocol for the ADVOCATE trial as patients achieving a BVAS of 0 and no glucocorticoid treatment within 4 weeks of the end of the 6-month induction period in the study (65). Relapse was defined as worsening of the disease, after having previously achieved remission, that involved any of the following:

- One or more major items in the BVAS, or
- Three or more minor items in the BVAS, or
- One of 2 minor items in the BVAS recorded at 2 consecutive study visits

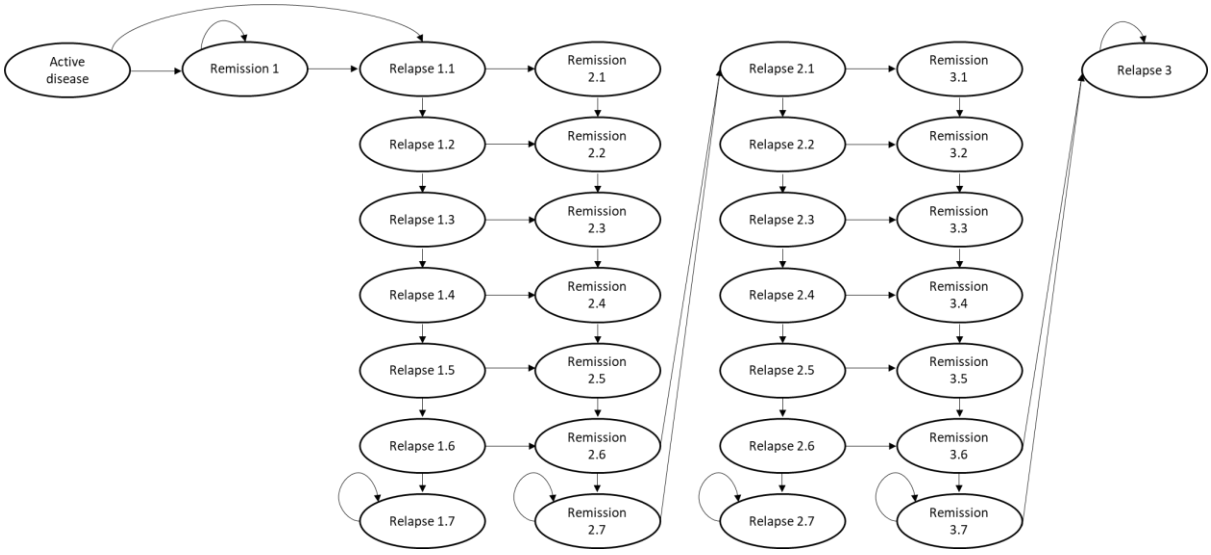
ESRD was defined as GFR/eGFR <15mL/min and a chronic need for renal replacement therapy.

AEs of induction therapy were included as separate events in the model. In the base-case, the model included severe AEs reported in the ADVOCATE trial. As a scenario analysis, incidence of AEs of glucocorticoid therapy were included based on data from the Clinical Practice Research Datalink (CPRD).

B.3.2.7 Programming of health states and tunnel states

The length of an induction treatment course in AAV is 6 months, per ADVOCATE protocol, which was simplified to six 28-day cycles in the model. Each model cycle during induction and maintenance treatment includes different treatments and dosages; therefore, it was necessary to track when patients enter and exit the remission and relapse health states using tunnel states as shown in Figure 10 below. Please note that the ESRD and death states, as well as AEs, were omitted from the figure for simplicity and clarity.

Figure 10. Diagram of Markov health states and tunnel states



Relapse 1 and relapse 2 health states each have 7 tunnel states reflecting the 6 model cycles of induction therapy, in addition to a seventh tunnel state for patients who do not reach remission and therefore remain in the relapse state until they develop ESRD or die. Patients do not receive further induction treatment courses once they reach the relapse 3 health state and the use of tunnel states was therefore not necessary for this health state.

Patients transition from active disease to remission 1 in the first 6 model cycles but continue receiving induction therapy. Patients in remission 1 receive maintenance therapy starting from model cycle 7. The model cycles allow appropriate tracking of patients through the first induction course without the need for tunnel states. However, patients can relapse and enter the subsequent relapse health states at any

point from model cycle 7 onwards. Thus, it was necessary to track patients using tunnel states in remission 2 and remission 3. The first 5 tunnel states are for the second to sixth model cycles of the induction period (patients in remission continue induction therapy until cycle 6). From the sixth tunnel state (seventh cycle since start of re-induction therapy), patients receive maintenance therapy for 24 months per clinical guidelines (7, 12). A one-off cost of maintenance therapy is applied to patients in the sixth tunnel state.

B.3.2.8 Intervention technology and comparators

The chosen intervention and comparators in the model reflect the decision problem and scope of the NICE technology appraisal. As a first-in-class, highly selective antagonist of C5aR1, avacopan inhibits the complement cascade marker C5a, which plays a key role in the inflammatory amplification process in GPA and MPA, driven by C5a-neutrophil interactions. This unique mechanism of action enables avacopan, as part of a combination therapy, to control MPA and GPA as effectively as current treatments but keeps a greater number of patients in remission than standard treatments. An avacopan-based regimen protects the kidney and other organs from the damage caused by AAV, potentially reducing the need for treatments such as dialysis and decreasing patient mortality and suffering. The posology of avacopan in the model reflected the avacopan SmPC and the ADVOCATE trial protocol, which specified 30 mg (3 capsules of 10 mg each) twice a day for 52 weeks.

In line with the protocol for ADVOCATE trial, the intervention arm in the model included induction treatment with avacopan in combination with CYC or RTX. The comparator arm included induction with RTX or CYC in combination with GCs. This is in line with clinical guidelines that recommend CYC or RTX with GCs as the first-line therapy for the induction of remission in AAV (7, 12). RTX was assumed to be administered intravenously weekly for 4 weeks with a dose of 375 mg/m^2 body surface area. IV CYC 15 mg/kg of body weight was assumed to be administered on days 1, 15, 29, 49, 70, and 91 in line with the dosage schedule specified in the ADVOCATE protocol. In the comparator arm, patients were additionally treated with prednisolone for 20 weeks with dosage tapered to 60 mg/d.

Once the induction period has been completed and patients are in remission, clinical guidelines recommend maintenance therapy for 24 months (equivalent to 26 cycles in our model). In line with the ADVOCATE study protocol and clinical guidelines, patients in remission who were induced with CYC receive AZA 2 mg/kg/d maintenance therapy for 26 model cycles. Patients induced with RTX were also assumed to be maintained on AZA for 26 cycles. This deviates from the ADVOCATE study protocol, which did not prespecify any maintenance treatment for RTX-induced patients. However, in the NICE technology appraisal of RTX in AAV, the absence of maintenance therapy for patients induced with RTX was considered to be unlikely by the clinical advisors to the evidence review group (ERG) (100). It was more clinically valid to assume that patients would receive some form of maintenance therapy, and the model assumed AZA as the maintenance treatment of choice as recommended by the ERG. After the induction phase, patients induced with avacopan in combination with CYC or RTX were assumed to receive maintenance treatment with avacopan in combination with AZA for 7 model cycles followed by AZA alone for the remainder of the 26-cycle maintenance period.

The model assumed that all patients receive AZA after achieving sustained remission by week 26. This is a deviation from the ADVOCATE protocol, which assumed that only patients induced with CYC received AZA maintenance, and RTX-induced patients received either active or placebo avacopan treatment in the maintenance phase. The absence of maintenance treatment is not a clinically plausible scenario, and the cost of AZA was added to all patients in remission, whilst assuming that the effectiveness of AZA maintenance is not significantly different from placebo. This may have overestimated the treatment effect of avacopan in the model. The hazard ratio for relapse was tested in scenario analyses to gauge the impact of this assumption on the ICER.

The BSR/BHPR guidelines specify RTX maintenance treatment for patients achieving remission after RTX induction (7), which is not reflected in the ADVOCATE trial protocol or the model base case. An anchored ITC between avacopan against RTX maintenance was not deemed to be feasible, and an unanchored indirect comparison is likely to be highly uncertain and prone to bias, as described in Section

B.2.9. Therefore, the cost-effectiveness model was not adjusted based on a comparison between avacopan and RTX maintenance.

Given that patients who achieve remission after avacopan induction treatment in combination with RTX are likely to continue RTX treatment in the maintenance phase, a comparison of avacopan in combination with RTX vs. RTX maintenance alone is a more clinically valid scenario. As described in Section B2.9, the impact of this scenario cannot be tested in an ITC due to an absence of published data on the effectiveness of avacopan in combination with RTX for the maintenance of remission in AAV. Furthermore, the addition of RTX maintenance to both the avacopan and comparator arms of the model is unlikely to have a substantial impact on the cost-effectiveness analysis results, given that the treatment effect and cost of RTX maintenance will cancel out in the incremental analysis. For these reasons, RTX maintenance was not included in the cost-effectiveness model.

B.3.2.9 Treatment discontinuation rules

The duration of treatment with avacopan in the model was assumed to be 52 weeks (13 model cycles), which is in line with the ADVOCATE trial protocol and the avacopan SmPC. Discontinuation of treatment was only assumed in case of transition to ESRD (consistent with the SmPC) or death. RTX induction therapy was limited to 4 weeks, in line with NICE guidance (100). CYC induction was assumed for 13 weeks, per clinical guidelines (62). In the model base case, patients induced with CYC or RTX received glucocorticoid treatment for 5 model cycles (20 weeks), per ADVOCATE trial protocol.

B.3.3 Clinical parameters and variables

B.3.3.1 Relapse

The movement between model states during the induction phase (first 6 cycles) is based on the ADVOCATE trial results at week 26 (65). To avoid unnecessary complexity, we do not differentiate between the active disease state and relapse state before 26 weeks. Therefore, relapses are not modelled explicitly until cycle 7 onwards. The probability of relapse can vary between the intervention and

comparator and change over time according to the natural history of the disease or waning treatment effect.

Comparator (CYC/RTX + GC)

In the first 26 weeks (7 cycles) after a treatment course with CYC or RTX, the per-cycle probability of relapse was calculated based on the proportions of patients in remission at weeks 26 and 52 from ADVOCATE.

Based on the CPRD study (101), the probability of moving from remission to relapse [redacted]. In the absence of long-term data for CYC or RTX, the relapse probability for these treatments was assumed to be [redacted]. The transition probability from remission to relapse after 2 years in remission is assumed to be [redacted], based on data from the CPRD study.

Intervention (AVA + CYC/RTX)

The probability of relapse following treatment courses with avacopan in the first 26 weeks (7 cycles) after treatment used a hazard ratio derived from the remission rates at 26 and 52 weeks for both treatment arms. This hazard ratio was then used to adjust the probability of relapse 26 to 52 weeks after treatment with CYC or RTX described above.

The hazard ratio for the rate of relapse with avacopan between week 52 and 60 is derived from extension study data reported in the ADVOCATE clinical study report (2). This hazard ratio is used to derive transition probabilities that are applied in cycles 14 and 15. Beyond this point, it is conservatively assumed that the treatment effect of avacopan decreases at a constant rate over time for 3 months and that there is no residual benefit and the probability of relapse beyond month 15 is equal to that following treatment with CYC or RTX, based on advice from clinical experts in the UK. Scenario analyses are used to explore alternative assumptions regarding the duration of residual treatment benefit of avacopan.

B.3.3.2 Remission

The per-cycle probability of transitioning from active disease/relapse states to remission was derived based on the proportions of patients in remission at week 26 and from ADVOCATE (65). These proportions were used to obtain the 28-day transition probabilities for induction with avacopan or with either CYC or RTX, assuming a constant hazard over the 26 weeks. These transition probabilities were assumed to apply to transitions from both the active disease state and the relapsed states to remission, for both the intervention and comparator. The probability of remission for RTX and CYC are considered equal, based on non-inferiority of RTX in the RAVE clinical trial (64).

B.3.3.3 End-stage renal disease

ESRD linked to disease activity has a major impact on survival, QoL, and healthcare cost in AAV patients. The model includes 2 options for data sources to inform transition into the ESRD health state: literature and CPRD. With both sources, 3 transition probabilities were applied, corresponding to active disease or relapse, remission, and refractory disease. In addition, the probability of relapse was adjusted to reflect renal outcomes in AAV based on eGFR data from the ADVOCATE trial, the association between eGFR and the probability of ESRD reported in the literature, and assumptions supported by clinical experts.

Base-case: ESRD informed by observational data and adjusted for future changes in eGFR

Based on a study by Robson et al. (82), the risk of ESRD is substantially higher in the first 6 months following disease onset than in subsequent years. The transition probability in the first 6 months after diagnosis in the Robson et al. study was used as the basis for the transition probability into the ESRD state from active disease or relapse, whereas the 4-week transition probability from remission to ESRD was based on long-term data from up to 7 years of follow-up (82). It was assumed that the probability of ESRD in refractory disease is equal to that of relapse, based on clinical expert opinion.

Relapse in AAV is associated with worsening renal outcomes (2) and a 9-fold increase in the risk of ESRD (102). The model includes an adjustment for current and future eGFR to simulate the increasing risk of ESRD with subsequent relapses. The adjustment is applied in the following steps:

- The probability of ESRD in active disease is adjusted based on the improvement in eGFR in the avacopan and comparator arms of the ADVOCATE trial observed between weeks 0 and 26 (5.8 mL/min and 2.9 mL/min, respectively). The probability of ESRD in remission is adjusted based on the improvement in eGFR observed between weeks 0 and 52 in the ADVOCATE trial (7.3 mL/min and 4.1 mL/min, respectively). The hazard rate, and subsequently the probability of ESRD, was adjusted based on a study by Gercik et al., which reported a hazard ratio for ESRD per mL/min change in eGFR from baseline (103). It was assumed that renal function, and probability of ESRD, for patients in sustained remission is no different between patients previously induced with avacopan or GC SoC.

- Each subsequent relapse was associated with a 10-mL/min decrease in eGFR. This was a conservative assumption supported by clinical experts, who suggested that a relapse may be associated with a decrease of up to 20 mL/min. The hazard rate of ESRD was adjusted with each subsequent relapse based on the assumed 10-mL/min drop and the corresponding hazard ratio estimated from the Gercik et al. study (103).

The adjustments based on changes in eGFR were applied sequentially with each relapse and course of induction in the model. For a hypothetical scenario of a patient treated with avacopan, their eGFR improves by 5.8 points, resulting in a reduction in the risk of ESRD by 45.7% [(c) in the table below], resulting in a 4-week ESRD probability of 0.0055. If they achieve remission within the first 26 weeks of treatment, their eGFR improvement rises from 5.8 to 7.3 units, resulting in a probability of ESRD of 0.0047. If they remain in sustained remission beyond week 26, their probability of ESRD reduces further to 0.0006. If they experience a relapse after achieving remission, their eGFR drops by 10 points due to the renal impact of AAV

and recovers by 2.9 points due to re-induction treatment with GC SoC. This results in a probability of ESRD of 0.0116. If they are brought back into remission with GC SoC, their probability of ESRD reduces to 0.0088 and 0.0011. The probability of ESRD in all health states increases with each subsequent relapse, which reflects worsening renal function over time due to AAV, until it reaches a maximum value of 0.033 in refractory disease after three inductions, which is the worst outcome in the model for patients who remain alive and ESRD-free.

Table 34. Calculation of eGFR-adjusted ESRD transition probabilities

Parameter	Avacopan arm	GC SoC arm	Description and sources
Baseline unadjusted probability of ESRD in active disease or relapse (a)	0.0101		Based on 6.4% of patients with ESRD at 6 months in Robson et al. (82)
Baseline unadjusted probability of ESRD in remission (b)	0.0009		Based on the proportion of patients developing ESRD between 6 months and 7 years in Robson et al. (13.9%-6.4%=7.5%)
eGFR recovery at induction (in eGFR points)	5.8	2.9	ADVOCATE trial
eGFR recovery at remission (in eGFR points)	7.3	4.1	ADVOCATE trial
Decrease in eGFR with each relapse (in eGFR points)	10		Clinical expert opinion
Hazard ratio for ESRD per eGFR unit decrease	0.90		Gercik et al. (103)
Adjustment of ESRD risk, induction (c)	0.543	0.737	Calculated based on hazard ratio per eGFR unit decrease and eGFR recovery: e.g. 0.90^5.8 = 0.543
Adjustment of ESRD risk, remission (d)	0.463	0.649	Calculated based on hazard ratio per eGFR unit decrease and eGFR recovery: e.g. 0.90^7.3 = 0.463
Adjustment in ESRD risk, per relapse (e)	2.87		Calculated based on hazard ratio per eGFR unit decrease and eGFR drop: 1/(0.90^10) = 2.87
ESRD probability, active disease	0.0055	0.0075	(a) adjusted based on eGFR effect in (c)
ESRD probability, first relapse	0.0116	0.0158	(a) adjusted based on eGFR effect in (c) and (e)

ESRD probability, second relapse	0.0244	0.0330	a) adjusted based on eGFR effect in (c) and (e)
ESRD probability, refractory disease after first relapse	0.0158	0.0158	Equal to probability of ESRD in relapse based on clinical expert opinion
ESRD probability, refractory disease after second relapse	0.0330	0.0330	Equal to probability of ESRD in relapse based on clinical expert opinion
ESRD probability, first remission, cycles 1-6	0.0047	0.0066	(a) adjusted based on eGFR effect in (d)
ESRD probability, second remission, cycles 1-6	0.0088	0.0123	(a) adjusted based on eGFR effect in (d) and (e)
ESRD probability, third remission, cycles 1-6	0.0163	0.0227	(a) adjusted based on eGFR effect in (d) and (e)
ESRD probability, first remission, cycles 7+	0.0006	0.0006	(b) adjusted based on eGFR effect in SoC arm in (d)
ESRD probability, second remission, cycles 7+	0.0011	0.0011	(b) adjusted based on eGFR effect in SoC arm in (d) and (e)
ESRD probability, third remission, cycles 7+	0.0020	0.0020	(b) adjusted based on eGFR effect in SoC arm in (d) and (e)

Scenario: rates from CPRD stratified by dose

The probability of ESRD was additionally obtained from CPRD, which informed a scenario analysis. ESRD was defined in CPRD using diagnosis codes or presence of 3 dialysis codes within a 6-month period. In the CPRD study, rates of ESRD onset were stratified based on GC dosage ("high dose": patients with a GC dose >10 mg/d; "low dose": patients with a GC dose >0 mg/d and <10 mg/d; and "no GC": patients with 0 mg/d recorded). Hazard rates obtained from CPRD were converted to transition probabilities in the model. GC dosage is used strictly as a proxy for AAV activity, rather than assuming a direct relationship between GC dose and ESRD. Therefore, it is assumed that avacopan prevents ESRD through sustained remission and a reduced rate of relapse. The high-dose GC rate is assumed to be a proxy for the rate corresponding to active disease with the highest renal impact of AAV activity. This rate is applied to the first 6 cycles in health states with active disease or relapse requiring induction treatment. The high-dose rate was also applied to patients with refractory disease (who are assumed to have the same level of AAV activity as relapsing patients). The no-GC rate applies to patients in long-term

remission (cycle 7 and onward in first remission and cycle 6 onward in subsequent periods of remission).

Table 35. ESRD transition probabilities based on CPRD study

Health state	Rate per 1000 patient-years	Probability
Active disease, relapse, and refractory disease	[redacted]	[redacted]
Remission	[redacted]	[redacted]

B.3.3.4 Mortality

Probability of death from AAV

Background mortality in the model was derived from the 2015 to 2017 National Life Tables for England (104). To account for the increased mortality rate in the AAV patient population and patients with ESRD compared with the general population mortality, a relative risk was applied to the mortality rates in the life tables for England. The relative risk was derived from Wallace et al. (105), who investigated mortality trends in patients diagnosed with GPA between 1992 and 2013 using the Health Improvement Network (THIN) database in the United Kingdom. They demonstrated that mortality in the first year following a diagnosis of GPA was higher than in subsequent years. It was assumed that the relative risk of death compared with the general population was 6.31 in the first year and 2.51 in subsequent years after diagnosis of AAV. Mortality rates in the active disease, remission, and relapse health states were assumed to be equal, based on Jayne et al. (106). The relative risk for mortality for patients with ESRD was derived from a study by Choi et al. (107), which compared patients with ESRD against the general population in South Korea.

Probability of death from treatment-related infections

Treatment with immunosuppressants in AAV is associated with a significantly increased risk of infections (7, 108). Around half of all deaths in the first year following AAV diagnosis are caused by infections (10, 11). To reflect the reduced burden of infection-related deaths through the GC-sparing capacity of avacopan, the

HR for mortality from literature was adjusted in the first year for avacopan. The adjustment was carried out using the following method:

$$HR_{adj} = \left[\left(\frac{HR_{yr1}}{HR_{yr2+}} - 1\right) \cdot (1 - \alpha \cdot \beta) + 1\right] \cdot HR_{yr2+}$$

HR_{adj} = Adjusted HR of death in first year in AAV

HR_{yr1} = HR of death in first year in AAV from CPRD or literature

HR_{yr2+} = HR of death in subsequent years in AAV from CPRD or literature

α = Proportion of deaths attributed to GC

β = Proportion of infections avoided using avacopan

The value for α is set to 0.5, based on Little et al., who observed that half of deaths in the first year in AAV are attributed to infections (11). The rate of death in the first year can thus be adjusted by changing the value for parameter β. If we assume that all infections are prevented by avoiding GCs (β is set to 1), the equation reduces to $HR_{adj} = HR_{yr2+}$; that is, all excess infection-related deaths in first year are avoided and the rate equals the HR applied in subsequent years of treatment. If we assume that no infections can be avoided by using avacopan (β is set to 0), the equation reduces to $HR_{adj} = HR_{yr1}$; in other words, the probability of death with avacopan is equal to GC-based treatments.

The value for β was obtained from the ADVOCATE trial, which reported an incidence of serious infection-related AEs of 1.8% in the AVA+CYC/RTX arm and 6.7% in the CYC/RTX+GC arm. The relative reduction in the incidence was (6.7%-1.8%)/6.7%=73.1%. The annual mortality in the first year was adjusted using a weighted average based on the number of cycles with high- and low-dose GC in comparator arms.

B.3.3.5 Treatment-related adverse events

GC therapies are associated with numerous side effects and the toxicity increases with daily and cumulative dose (82, 109). Several AEs are considered in the model,

including infections, CV disease, bone disease, and ocular disease, to reflect potential additional benefits of treatment with avacopan, given its potential GC-sparing properties. Rates of AEs are taken either from the ADVOCATE trial or from the CPRD study.

Adverse events from the ADVOCATE trial

Rates of SAEs were obtained from the avacopan and standard care arms of the ADVOCATE trial. The list of AEs with associated probabilities and unit costs is reported in Table 36.

Table 36. Serious adverse event rates from the ADVOCATE trial

Adverse event	GC SoC	Avacopan	Unit cost	Source
AAV	12.2%	7.2%	£911.17	NHS Reference Costs 2019-20: HRG DZ29G-K
Pneumonia	3.7%	4.8%	£1,214.31	NHS Reference Costs 2019-20: HRG DZ22K-Q
GPA	0.6%	3.0%	£911.17	NHS Reference Costs 2019-20: HRG DZ29G-K
Acute kidney injury	0.6%	1.8%	£1,961.20	NHS Reference Costs 2019-20: HRG LA07H-P
Urinary tract infection	1.2%	1.8%	£1,724.59	NHS Reference Costs 2019-20: HRG LA04H-S
Angina pectoris	0.0%	1.2%	£776.43	NHS Reference Costs 2019-20: HRG EB13A-D
Cardiac failure	0.0%	1.2%	£2,061.06	NHS Reference Costs 2019-20: HRG EB03A-E
Device-related infection	0.0%	1.2%	£1,319.95	NHS Reference Costs 2019-20[a]
Drug hypersensitivity	1.2%	1.2%	£0.00	No additional cost assumed
Hepatic enzyme increased	1.8%	1.2%	£169.11	NHS Reference Costs 2019-20; hepatology outpatient visit, consultant led: service code 306
Hepatic function abnormal	0.0%	1.2%	£169.11	NHS Reference Costs 2019-20; hepatology outpatient visit, consultant led: service code 306
Hyperglycaemia	0.6%	1.2%	£1,169.76	NHS Reference Costs 2019-20: HRG KB02G-K
Influenza	0.6%	1.2%	£1,214.31	NHS Reference Costs 2019-20: HRG DZ22K-Q
Pyrexia	1.8%	1.2%	£0.00	No additional cost assumed
Acute myocardial infarction	1.2%	0.6%	£1,596.39	NHS Reference Costs 2019-20: HRG EB10A-E

Agranulocytosis	1.2%	0.6%	£1,694.30	NHS Reference Costs 2019-20: HRG SA35A-E
Blood creatinine increased	1.2%	0.6%	£175.63	NHS Reference Costs 2019-20; nephrology outpatient visit, consultant led: service code 361
Lymphopenia	1.8%	0.6%	£0.00	No additional cost assumed
Pulmonary alveolar haemorrhage	1.2%	0.6%	£911.17	NHS Reference Costs 2019-20: HRG DZ29G-K
Anaemia	1.2%	0.0%	£672.11	NHS Reference Costs 2019-20: HRG SA04G-L
Dehydration	1.2%	0.0%	£0.00	No additional cost assumed
Diarrhoea	1.8%	0.0%	£797.26	NHS Reference Costs 2019-20; HRG FD01J: Gastrointestinal Infections without Interventions, with CC Score 0-1
Epistaxis	1.2%	0.0%	£452.00	NHS Reference Costs 2019-20: HRG CA12Z, CA13A
Herpes zoster	1.2%	0.0%	£1,479.28	NHS Reference Costs 2019-20: HRG JD07A-K
Infectious pleural effusion	1.2%	0.0%	£1,812.57	NHS Reference Costs 2019-20: HRG DZ16H-R
Large intestinal polyp	1.2%	0.0%	£705.87	NHS Reference Costs 2019-20; HRG FE30Z: Therapeutic colonoscopy, 19 years and over
Microscopic polyangiitis	1.2%	0.0%	£911.17	NHS Reference Costs 2019-20: HRG DZ29G-K
Mononeuropathy multiplex	1.2%	0.0%	£0.00	No additional cost assumed
Neutropenia	1.2%	0.0%	£760.00	NHS Reference Costs 2013-14; HRG WA04Z: Acute Febrile Illness with LOS 4 days or less; uplifted to 2020 prices using the NHS inflation index
Pneumonia bacterial	1.2%	0.0%	£1,214.31	NHS Reference Costs 2019-20: HRG DZ22K-Q
Prostate cancer	1.2%	0.0%	£0.00	Long-term AE - not captured in short-term AE cost
Pulmonary embolism	1.8%	0.0%	£1,498.57	NHS Reference Costs 2019-20: HRG DZ09J-Q
Respiratory syncytial virus infection	1.2%	0.0%	£1,214.31	NHS Reference Costs 2019-20: HRG DZ22K-Q
Thrombocytopenia	1.2%	0.0%	£770.92	NHS Reference Costs 2019-20: HRG SA12G-K
Vomiting	1.2%	0.0%	£1,366.10	NHS Reference Costs 2019/20: HRG FD01A-J

Abbreviations: AAV, anti-neutrophil cytoplasmic antibody–associated vasculitis; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; HRG, Healthcare Resource Group; NHS, National Health Service; SoC, standard of care

[a] Weighted average of HRG cost by type of infection based on CPRD: respiratory tract infection (n=456), gastrointestinal infection (n=75), skin/wound infection (n=80), urinary tract infection (n=79)

Adverse events from CPRD

An alternative source for the probability of treatment-related AEs is the CPRD database. Rates of infections, CV, bone, and ocular disease were derived from observational data in the United Kingdom. AE rates were stratified based on GC dose, recognising the increased risk of events with exposure to GCs. Hazard rates were derived for patients who were not treated with GCs (0 mg/d) and for patients treated with low- and high-dose GC, using a threshold of 30 mg/d to define high dose. Adverse event rates and associated transition probabilities from CPRD are presented in

Table 37. In the GC SoC arm, for each induction course, the following AE transition probabilities were applied, depending on the number of 28-day model cycles from the start of induction treatment. These probabilities were consistent with the GC dose protocol in the GC SoC arm of the ADVOCATE trial:

- The high-dose transition probability was applied in the first cycle
- The low-GC dose transition probability was applied in cycles 2 to 5
- The no-GC transition probability was applied in the sixth cycle

Once patients receive maintenance or refractory disease treatment (remission 1 from cycle 7 onward; remission 2.6, 2.7, 3.6, 3.7; relapse 1.7, 2.7, 3), they are applied the no-GC transition probability. In the avacopan arm, the no-GC TP is applied in the active disease and remission 1 health state. Therefore, if patients are re-inducted with CYC or RTX in combination with GC, the AE transition probabilities are applied as detailed above for the CYC and RTX arms.

Table 37. GC-related infection rates and probabilities from CPRD

Adverse event rate per 1000 person-years	Infections	CV events	Bone disease	Ocular disease
High-dose GC (>30 mg/d)	[redacted]	[redacted]	[redacted]	[redacted]
Low-dose GC (<30 mg/d)	[redacted]	[redacted]	[redacted]	[redacted]
No GC (0 mg/d)	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event transition probabilities				
High-dose GC (>30 mg/d)	[redacted]	[redacted]	[redacted]	[redacted]
Low-dose GC (<30 mg/d)	[redacted]	[redacted]	[redacted]	[redacted]
No GC (0 mg/d)	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: CV, cardiovascular; GC, glucocorticoid				

B.3.3.6 Refractory disease and long-term GC use

Patients who do not achieve remission after 2 or more courses of induction are considered to have refractory disease, which is characterised by continuing AAV activity with long-term AZA treatment. However, as observed in the CPRD study in routine clinical practice, patients are likely to receive GC for a long period of time (up to a year for some patients). To reflect this, a scenario is implemented in the model to allow for long-term GC use in patients with refractory disease. A constant probability of discontinuation per cycle of [redacted] was applied based on a [redacted] from CPRD data. This scenario increases the probability of GC-related AE and cost of treatment assuming a GC dose of 10 mg/d.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

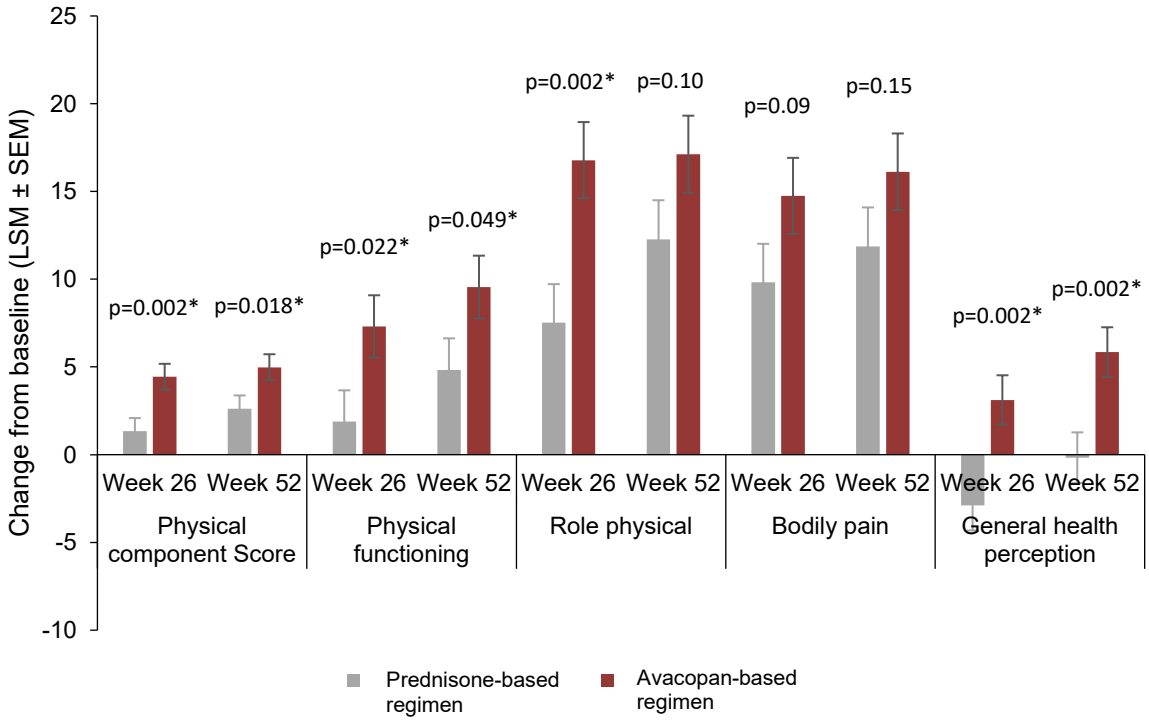
The phase 3 ADVOCATE trial collected data using the SF-36 and EQ-5D-5L (index and visual analogue scale [VAS]) methods of HRQoL measurement (65). These outcomes were measured at baseline and at follow-up at 4, 10, 16, 26, 39, 52, and 60 weeks. Key HRQoL outcome data were considered to be at 26 and 52 weeks, to coincide with the primary outcome measurement. The EQ-5D-5L index data were mapped to inform the utilities in the de novo model (Section B.3.4.5).

SF-36 measurement

The SF-36v2 is a multi-purpose, short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores, as well as psychometrically based physical and mental health summary measures and a preference-based health utility index (110).

Using the SF-36v2 measurement, treatment with an avacopan-based regimen was associated with a significant improvement in patients' physical component score (PCS). At week 26, the mean PCS was 4.445 in the avacopan group compared with 1.344 in the SoC group (p=0.002). At week 52, the PCS values were 4.980 and 2.626 respectively (p=0.018, Figure 11). Specifically, avacopan was associated with significantly improved scores for the domains of physical functioning, role physical, and general health perception (which is regarded as particularly important in AAV), compared with SoC at weeks 26 and 52.

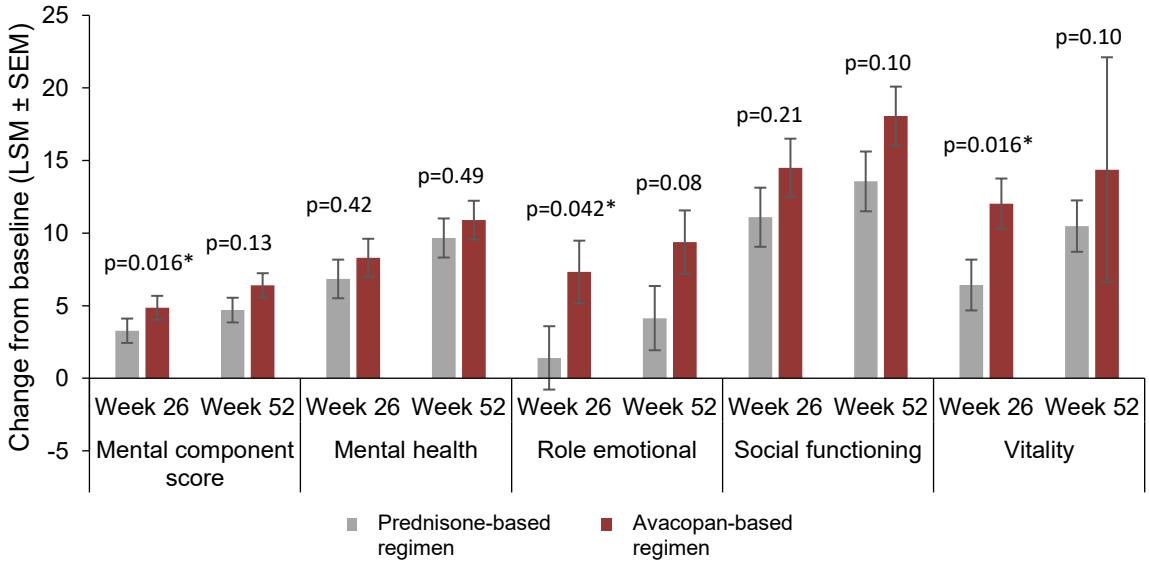
Figure 11. SF-36 v2.0 change from baseline (least-squares mean [LSM] ± standard error of the mean [SEM]) for physical component score and other physical aspects during the ADVOCATE study period in the ITT population (2, 65)



Patients on the avacopan-based regimen also scored higher than patients on SoC in the mental component score (MCS) overall at week 26 (p=0.16), although not at week 52. There was an improvement in the role emotional domain at week 26 (p=0.042), although not at week 52. The vitality domain showed a similar result at week 26 (p=0.016), with the numerically superior score at 52 weeks not being significant (Figure 12) (65).

The ADVOCATE data are consistent with those from the CLEAR trial, which also reported a significant improvement in HRQoL compared with SOC, with physical functioning and mental health statistically superior as early as 4 weeks after starting an avacopan-based regimen, as measured by the SF-36v2 (4).

Figure 12. SF-36 v2 change from baseline (least-squares mean [LSM] ± standard error of the mean [SEM]) for mental component score and other mental domains during the ADVOCATE study period in the intent-to-treat population (2, 65)

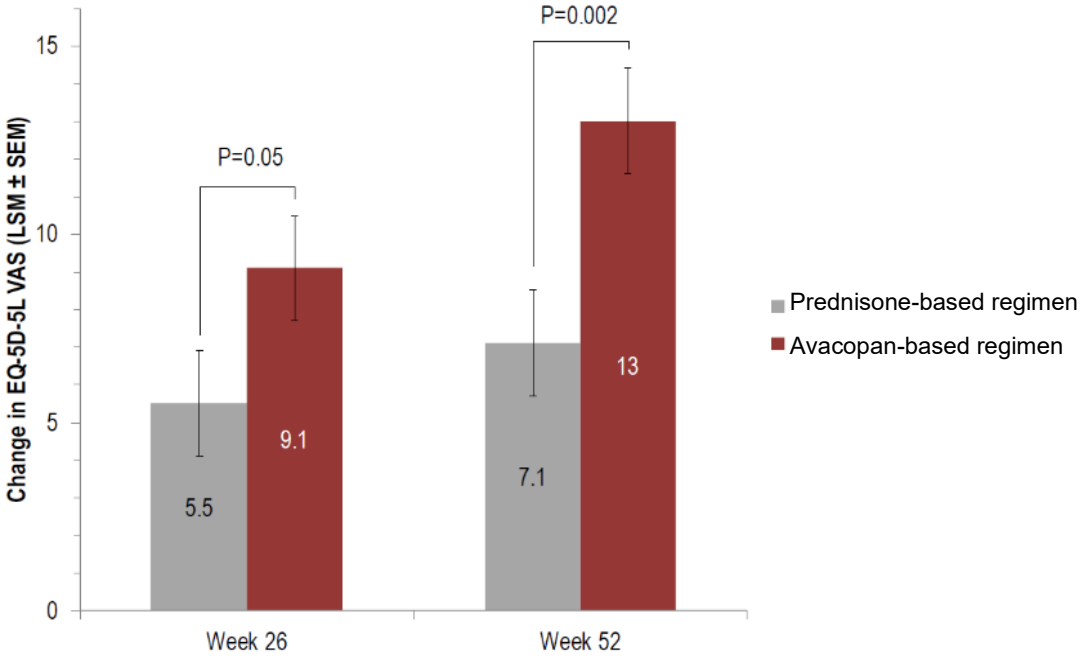


EQ-5D measurement

The EQ-5D-5L is a standardised instrument for use as a measure of health outcome that includes a descriptive system consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) set at 5 levels of severity. It is used alongside an EQ-5D visual analogue scale (111).

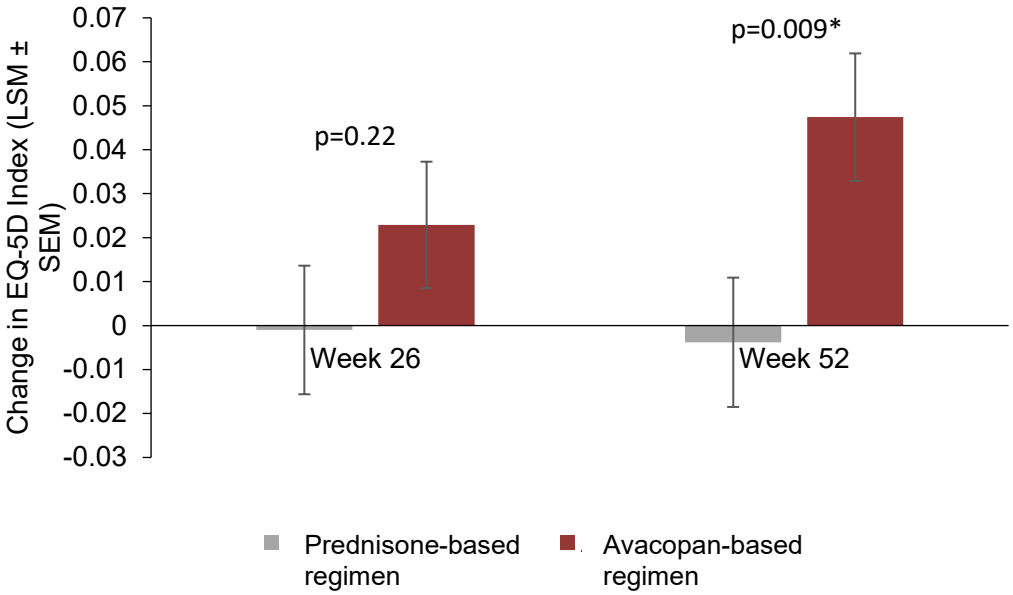
The ADVOCATE trial reported treatment with an avacopan-based regimen resulted in a significantly higher EQ-5D VAS score at week 52 compared with the SoC group. Using the method of least squares, the mean change from baseline in the avacopan-based regimen group was 9.1 compared with 5.5 at 26 weeks (p=0.05), and 13.0 compared with 7.1 (p=0.002) at 52 weeks (Figure 13) (65).

Figure 13. EQ-5D health scale visual analogue score (VAS) change from baseline (least-squares mean [LSM] ± standard error of the mean [SEM]) during the ADVOCATE study period in the intent-to-treat population (2, 65)



Patients in the avacopan-based regimen group experienced increases from baseline in their EQ-5D index score compared with decreases in those receiving SoC. Avacopan patients had a numerically higher EQ-5D index score at week 26 (p=0.05), with a significantly higher difference in EQ-5D at 52 weeks (0.0474 vs -0.0038; p=0.009), compared with the SoC group (Figure 14).

Figure 14. EQ-5D health scale index score change from baseline (least-squares mean [LSM] ± standard error of the mean [SEM]) during the ADVOCATE study period in the intent-to-treat population (2, 65)



B.3.4.2 Mapping

As stated in the previous section, cross-walk mapping (112) was used in the base-case to provide a value set for the EQ-5D-5L. A scenario analysis was performed in which the EQ-5D-5L value set for England is used.

B.3.4.3 Health-related quality-of-life studies

A literature review was conducted to identify relevant studies reporting HRQoL and utility data in patients with AAV. Further details of the review are provided in Appendix H.

Five studies were identified that reported HRQoL outcomes relevant to the decision problem. These included 2 HTAs on RTX (8, 99), a cross-sectional study (113), and 2 RCTs (4, 65).

Utility values

Two studies included in the HRQoL review reported utility values in AAV patients. These were the NICE (8) and SMC (99) HTAs of the use of RTX in combination with

GCs for treating AAV. These were secondary analyses and did not report primary empirical data relevant to the decision problem.

The population in both submissions were patients with severe, active GPA and MPA. The health-related utility values used within both submissions were derived from SF-36 data collected at baseline and at 6 months in the RAVE trial (64) using a previously published mapping algorithm (114). SF-36 scores were converted from the non-remission and remission health states to the EQ-5D in a post hoc analysis and adjusted for age. Disutility adjustments were applied for adverse events. The model calculated utility values for 3 disease states: uncontrolled disease, remission, and non-remission.

A summary of the utility values used by these studies is reported in Table 38.

Table 38. Characteristics of utility studies included in the review

		Study (year)	
		NICE TA308 (2014)	**SMC ID 894/13 (2013)**
Country		United Kingdom	United Kingdom
Patient population		Adult patients with severe, active GPA and MPA	Adult patients with severe, active GPA and MPA
Intervention comparator		RTX (in combination with GCs) CYC (in combination with GCs)	RTX (in combination with GCs)
Utility score	**Uncontrolled**	0.71*	0.671
	Remission	0.84	0.837
	Non-remission	0.754	0.754

Abbreviations: AAV, anti-neutrophil cytoplasmic antibody–associated vasculitis; CYC, cyclophosphamide; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; NICE, National Institute for Health and Care Excellence; RTX, rituximab; SMC, Scottish Medicines Consortium

*Utility value adjusted to reflect fact that AAV is rarely left untreated

Health-related quality of life data

The remaining studies reported HRQoL/impact of symptoms using a range of generic and disease-specific measures, including, Sino-Nasal Outcomes Test-22 (SNOT-22), SNOT-25, Nasal Obstruction Symptom Evaluation (NOSE), and SF-36. As these studies did not report utility data, they were not used to inform the model. Further details of these studies are reported in Appendix H.

B.3.4.4 Adverse reactions

GC therapies are associated with numerous side effects and the toxicity increases with daily and cumulative dose (96, 109). Several AEs are considered in the model, including infections, CV disease, renal disease, bone disease, and ocular disease to reflect potential additional benefits of treatment with avacopan, given its potential GC sparing property.

Utility decrements due to GC-related AEs are applied in each cycle that a patient experiences such events. Utility decrements for infections and ocular disease are only applied in the cycle when the event occurs, whereas utility decrements for CV events, renal disease and bone disease event are applied for the remainder of the time-horizon. Utility decrements are differentiated between the acute phase of an event and the follow-up period. A pragmatic literature search was conducted to source utility data for AEs; for more details on included studies see Section B.3.4.5 and Table 41.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Base-case utility inputs

In the ADVOCATE trial, the HRQoL was assessed with the SF-36 and the EQ-5D-5L questionnaires. The assessments were made on day 1 (pre-dosing) and at weeks 4, 10, 16, 26, 39, 52, and 60. In the base-case, the model used health state utilities derived from responses to the EQ-5D-5L using the cross-walk mapping value set (112). Alternative values based on the EQ-5D-5L value set for England have been included as an optional scenario analysis.

The utilities for model states were obtained by taking the mean of pooled patient utilities at weeks 4, 26, and 52, stratified by the treatment arm and disease state (active disease, remission, and relapse) according to definitions of remission and relapse used in the trial. Stratification by treatment was done to incorporate differences in HRQoL that may emerge, for example, as a result of reduced use of GCs with avacopan and, therefore, fewer GC-related adverse events. The utilities for model states, by treatment, are presented in Table 39.

The HRQoL of patients in the ESRD health state was calculated using data obtained from the literature according to the type of treatment that an ESRD patient may receive. This was based on the approach used in a previous NICE single technology appraisal for patiromer (115). This considered that ESRD patients may be treated with either peritoneal dialysis, haemodialysis, or renal transplant. The distribution of ESRD patients across these potential treatments was sourced from the 20th Annual Report of the Renal Association (116). The health state utilities for patients undergoing each treatment were sourced from a UK study published in 2005 (117).

These data for peritoneal dialysis and haemodialysis were combined to provide the weighted average health state utility for patients receiving dialysis in ESRD. Throughout the progression through model cycles, the ESRD health state was decomposed into 2 substates for dialysis or renal transplant using the proportion of patients requiring renal transplant. The overall utility of the ESRD health state was then obtained as the weighted mean of these 2 substates. The utilities used and proportions for ESRD treatments are presented in Table 39.

The starting age of the model cohort was 60 years. Data on the UK population norm health state utilities (Table 40) was used to adjust the utilities of all modelled health states to account for changes due to aging (118). The adjustment was based on movement between 5-year age groups and was calculated relative to the age group containing the mean age of the ADVOCATE trial cohort at baseline (61-65 years).

Table 39. Summary of utility inputs

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)
Avacopan + SoC			
Active disease	0.708 (0.022)	0.664-0.751	3.4.5
Remission	0.790 (0.011)	0.767-0.812	3.4.5
Relapse	0.738 (0.055)	0.629-0.847	3.4.5
GC + SoC			
Active disease	0.697 (0.024)	0.649-0.744	3.4.5
Remission	0.766 (0.012)	0.741-0.790	3.4.5
Relapse	0.678 (0.056)	0.566-0.790	3.4.5
ESRD utilities			

Peritoneal dialysis	0.530 (0.027)	0.477-0.583	3.4.5
Haemodialysis	0.443 (0.023)	0.399-0.487	3.4.5
Renal transplant	0.712 (0.036)	0.641-0.783	3.4.5
ESRD distribution			
Peritoneal dialysis	20.5%	Fixed	3.4.5
Haemodialysis	69.8%	Fixed	3.4.5
Renal transplant	9.7%	Fixed	3.4.5
Abbreviations: ESRD, end-stage renal disease; GC, glucocorticoid; SoC, standard of care			

Table 40. EQ-5D index population norms (UK-specific time trade-off value sets) according to age

Age group, years	Utility value	Utility adjustment
≤30	0.938	1.162
31-35	0.915	1.133
36-40	0.907	1.124
41-45	0.882	1.093
46-50	0.864	1.070
51-55	0.834	1.034
56-60	0.822	1.019
61-65	0.807	1.000
66-70	0.804	0.996
71-75	0.779	0.965
76-80	0.753	0.933
81-85	0.699	0.865
>85	0.650	0.805

Alternative utility values for GC AEs

There are potential adverse reactions associated with treatment that may affect patients' QoL. GCs are a particular concern and, in high doses, are associated with AEs including infections, bone disease, bone fractures, cataracts, new-onset diabetes, new-onset hypertension, weight gain, and psychiatric disorders (82, 109). In the modelled base case, the impact of treatment-related AEs was accounted for via the treatment specific health-state utilities derived from the ADVOCATE trial data.

As a separate scenario analysis, an alternative approach to the use of treatment-specific health-state utilities was developed for modelling the QoL impact of AEs associated with GC use. The 5 types of adverse events included in the model are

infections, CV events, renal disease, bone disease, and ocular disease. In this scenario analysis, the impact of infections and ocular disease was modelled by applying a utility decrement to a health-state utility only in the model cycle in which the event occurs, whereas CV events, renal disease, and bone disease result a permanent utility loss.

A pragmatic literature search was conducted to source utility data for adverse events. A utility decrement for CV event and renal disease was sourced from a large US population study (119). The utility decrement due to infection was assumed to be -0.1, given the lack of literature data. The utility decrement for bone disease was derived based on data reported in the ERG critique of the submission in Technology Appraisal 464 (120). An average utility value for 5-year age groups was derived from utility multipliers for hip, spine, shoulder, and wrist fractures. The weighted utility multipliers in first and subsequent years after a fracture were multiplied by the baseline utility for each age group to estimate a utility decrement for the model.

The decrease in utility associated with ocular disease is derived from a literature review of studies of cataract surgery (121). The difference in utility levels before and after surgery was assumed to be equivalent to a one-time utility decrease associated with cataract-induced vision loss. It is assumed that patients would undergo surgery halfway through the first year on average following which utility will be restored to pre-cataract levels. A utility decrement of one-half of the annual utility loss is thus applied in the first year after diagnosis. The utility decrements used in this scenario analysis for GC-relates adverse events are summarised in Table 41.

Table 41. Summary of utilities used in scenario analysis of GC-related adverse events

GC-related adverse event	Utility value		Follow-up period	Reference
	Acute	Post-acute		
Infections	-0.10	NA	1 year	3.4.4
Cardiovascular event	-0.05	-0.05	Lifetime	3.4.4
Renal disease	-0.05	-0.05	Lifetime	3.4.4
Bone disease	0.00	0.00	Lifetime	3.4.4
Ocular disease	-0.05	N/A	1 year	3.4.4
Abbreviation: NA, not available				

B.3.5 Cost and healthcare resource use identification, measurement and valuation

A systematic literature review was conducted to identify costs associated with management of AAV and its complications (Appendix I).

The costs of drug treatments were estimated based on the dosage schedules pre-specified in the ADVOCATE trial protocol and combined with unit costs from the British National Formulary for the cost year 2019-20 (122). Costs associated with the administration of intravenous treatments were assumed to be equivalent to the cost of administration of chemotherapy with unit costs obtained from NHS Reference Costs for 2019-20 (123).

B.3.5.1. Intervention and comparators' costs and resource use

Induction and maintenance treatments (first 12 months)

The cost of the intervention included the acquisition and administration costs for avacopan, CYC, and RTX induction. In the base case, it was assumed that 64.8% of patients are treated with RTX and 35.2% are treated with CYC, based on the findings of the ADVOCATE trial. The dosage for avacopan is 30 mg twice daily for 52 weeks. Induction treatments included RTX 375 mg/m^2 body surface area (mean body surface area was 1.92 m^2, based on the ADVOCATE trial) weekly for 4 weeks and IV CYC 15 mg/kg on days 1, 15, 29, 49, 70, and 91. AZA was assumed in both the intervention and comparator arms from model cycle 4 until model cycle 13, with titration up to 2 mg/kg/d over 2 weeks starting with week 15 (mean weight was 77 kg, based on the ADVOCATE trial). In the comparator arm, patients were given prednisolone starting with 60mg/d in the first week, with a tapering regimen until model cycle 6. RTX and CYC were both assumed to be administered intravenously, with an administration cost of £406.04 for the first attendance and £341.30 for subsequent visits. Avacopan, AZA, and prednisone were administered orally, and no administration cost was assumed. The total cost of avacopan and GC treatment was adjusted based on the compliance rates reported in the ADVOCATE trial, which were 86.4% and 98.4%, respectively. Drug unit costs used in the model are reported

in Table 42 and the total cost of the intervention and comparator treatments in the first 12 months in the model are reported in Table 43.

Maintenance treatments (after 12 months)

If patients remain in remission after 12 months, they were assumed to be given maintenance therapy with AZA for 24 months (from month 6 to month 30). A cost of £3.78 per cycle was added until cycle 32 for patients remaining in remission, which corresponds to 2 mg/kg/d.

Refractory disease treatments

No further induction treatments were assumed after patients transition to refractory disease. The same per-cycle cost of treatment was applied as in remission, corresponding to AZA 2 mg/kg/d.

Table 42. Drug unit costs

Drug acquisition cost			
Intervention/ comparator	**Dose (quantity)**	**Price**	**Source**
Avacopan PAS price	10 mg (1)	[redacted]	Vifor
RTX (IV)	500 mg/50mL (1)	£785.84	BNF (124)
RTX (IV)	100 mg/10mL (2)	£314.33	
CYC (IV)	500 mg	£9.66	
CYC (IV)	1,000 mg	£17.91	
AZA (PO)	25 mg (28)	£1.99	
AZA (PO)	50 mg (56)	£2.52	
Prednisone (PO)	5 mg (28)	£1.08	
Drug administration cost			
Service		**Unit cost**	**Source**
SB14Z: deliver complex chemotherapy, including prolonged infusional treatment, at first attendance		£406.04	NHS Reference Costs 2019-20 (123)
SB15Z: deliver subsequent elements of a chemotherapy cycle		£341.30	
Abbreviations: AZA, azathioprine; BNF, British National Formulary; CYC, cyclophosphamide; IV, intravenous; NHS, National Health Service; PO, prednisone by mouth; RTX, rituximab			

Table 43. Unit costs associated with the technology in the economic model (first 12 months)

Items	Avacopan + CYC/RTX	Reference in submission	CYC/RTX + GCs	Reference in submission
Avacopan (PAS price)	[redacted]	Table 42	£0.00	Table 42
CYC (acquisition) for 35.2%	£165.42	Table 42	£165.42	Table 42
CYC (administration) for 35.2%	£2,112.54	Table 42	£2,112.54	Table 42
RTX (acquisition) for 64.8%	£5,029.34	Table 42	£5,029.34	Table 42
RTX (administration) for 64.8%	£1,429.94	Table 42	£1,429.94	Table 42
Azathioprine	£38.21	Table 42	£38.21	Table 42
Prednisolone	£0.00	Table 42	£19.66	Table 42
Monitoring cost	£2,432.56	Table 42	£2,432.56	Table 42
Total (PAS price)	**£**[redacted]		**£7,535.76**	
Abbreviations: CYC, cyclophosphamide; GC, glucocorticoid; PAS, patient access scheme; RTX, rituximab				

B.3.5.2. Health-state unit costs and resource use

Cost of monitoring

Management of AAV requires regular monitoring to assess disease status and identify treatment-related adverse events (7, 62). The frequency of clinic visits and laboratory tests per health state were obtained from the ERG re-analysis reported in TA308 (8), which were based on clinical expert opinion (Table 44). Data on frequency of tests and visits were combined with unit costs from NHS Refence Costs 2019-20 (Table 45). No data were available for the ESRD state; we assume that patients in this state require the same monitoring and maintenance costs as in the active disease state.

Table 44. Monitoring and maintenance costs per cycle

Health state	Treatment	Monitoring costs per cycle		Follow-up visit costs per cycle	
		Number of events per 6 months	Cost per cycle	Number of events per 6 months	Cost per cycle
Induction treatment	CYC-based	22	£6.64	13	£336.16
	Non-CYC based	0	£0.00		
Remission	AZA maintenance	13 blood tests and 12 LFTs	£6.32		£51.72
Refractory disease			£6.32		£77.58
ESRD		22	£6.64		£336.16
Death		0	£0.00		£0.00
Abbreviations: AZA, azathioprine; CYC, cyclophosphamide; ESRD, end-stage renal disease; LFT, Liver-function test					

Table 45. Unit costs of follow-up visits and monitoring tests

Item	Unit cost	Reference
Blood test	£1.81	DAPS - DAPS03 Integrated Blood Services
Liver function test	£1.20	DAPS - DAPS04 Clinical Biochemistry
Outpatient visit	£155.15	Rheumatology consultant-led outpatient visit
Source: National Health Service Reference Costs 2019-20 (123)		

Hospitalisation cost

To account for the cost of inpatient hospital treatment for AAV relapse and treatment-related AEs, data were obtained on the frequency of length of hospitalisation between weeks 0 and week 52 in the ADVOCATE trial (

Table 46). This was combined with unit costs derived from the NHS Reference Costs 2019-20 (123). The unit cost used in the model was estimated as the weighted average of elective and non-elective inpatient admissions corresponding to HRG codes DZ29G-J. The weighted cost was adjusted for the length of stay observed in the ADVOCATE trial based on the mean length of stay and mean excess day cost reported in the NHS Reference Costs schedule (Table 47).

Table 46. Frequency and length of hospital admission in the ADVOCATE trial

Parameter	Avacopan	GC SoC
Mean no. of hospitalisations	0.47	0.68
Mean length of stay	13.80	19.60
Mean cost of hospitalisation in the first 52 weeks	£2,947.82	£5,802.48
Mean cycle cost of hospitalisation	£226.76	£446.34
Abbreviations: GC, glucocorticoid; SoC, standard of care		

Table 47. Unit costs of hospital admission

HRG code	Description*	Mean LOS	Mean cost	Mean cost per excess day
DZ29G	With Interventions	8.91	£5,598	£493
DZ29H	Without interventions, with CC score 5+	5.53	£3,045	£324
DZ29J	Without interventions, with CC score 2-4	4.01	£1,937	£363
DZ29K	Without interventions, with CC score 0-1	2.77	£1,464	£385
Weighted average		5.16	£2,849	£396
Abbreviations: CC, co-morbidity and complication; HRG, Healthcare Resource Group; LOS, length of stay *Granulomatous, allergic alveolitis or autoimmune lung disease				

Cost of ESRD

The cost of treatment of end stage renal disease was based on Kent et al. (125). The cost of maintenance dialysis in the model corresponds to the annual cost of dialysis initiated in a previous annual period and inflated to the 2020 cost year using the NHS price index (£27,038). The cost of renal transplant was £28,517 in the first year and £1,331 in subsequent years, based on the same study. The probability of receiving a renal transplant, peritoneal dialysis, or haemodialysis were based on the NICE technology appraisal of patiromer for the treatment of hyperkalaemia (TA623) (115) (

Table 48). It was assumed that peritoneal dialysis and haemodialysis carry the same cost from an NHS and Personal and Social Services perspective.

Table 48. Treatment modality in ESRD based on TA623

Treatment	Proportion of patients with ESRD	Proportion of patients with maintenance dialysis
Peritoneal dialysis	20.5%	22.7%
Haemodialysis	69.8%	77.3%
Renal transplant	9.7%	N/A
Abbreviations: ESRD, end-stage renal disease; N/A; not applicable		

B.3.5.3. Adverse reaction unit costs and resource use

The model uses two alternative sources of AE data, as described in Section B.3.3.5. This section outlines the unit costs and resource use informing both approaches. The base-case model uses AEs from the ADVOCATE trial, whereas the costs of GC-related AEs from CPRD have been included as a scenario analysis.

Unit costs of adverse events from ADVOCATE

The unit costs for AEs reported in the ADVOCATE trial were derived from NHS Reference Costs 2019-20 (122, 123). The full list of AE unit costs is included in Table 36.

Unit costs of hospitalisation

In the model base-case, the cost of treatment of adverse events was assumed to be accounted for within the hospitalisation data derived from ADVOCATE. The mean number of hospital admissions and length of stay were obtained from the avacopan and GC SoC arms of the ADVOCATE trial. These data were combined with hospital unit costs from NHS Reference Costs 2019-20 to estimate the total cost of inpatient hospital treatment for patients induced with avacopan and GC SoC (

Table 46 and Table 47).

Unit costs of adverse events from CPRD

A scenario analysis explored adverse event costs based on the incidence of GC-related AEs obtained from CPRD. The cost associated with GC-related infections is calculated as a weighted average based on the number of events for different infection types taken from the CPRD study (101) and associated costs derived from the NHS Reference Costs 2019-20 (122, 123). All costs associated with infections are assumed to be incurred in the cycle the event occurs, there are no associated follow-up costs in subsequent cycles. The estimation method for the cost of infection is summarised in Table 49.

Table 49. Cost of infections

GC-related events	Number of events in CPRD	Costs	
		Unit cost	Reference
Upper respiratory infection	[redacted]	£1,214	Assumption: same cost as lower respiratory infection
Lower respiratory infection	[redacted]	£1,214	Weighted average Unspecified Acute Lower Respiratory Infection with Interventions: DZ22K-Q Total HRG
Gastrointestinal infection	[redacted]	£1,366	Weighted average Gastrointestinal Infections with Multiple Interventions: FD01A-J Total HRG
Skin/wound infection	[redacted]	£1,479	Weighted average Skin Disorders without Interventions: JD07A-K Total HRG
Urinary infection	[redacted]	£1,725	Weighted average Kidney or Urinary Tract Infections, with Interventions: LA04H-S Total HRG

Abbreviations: CPRD, Clinical Practice Research Datalink; GC, glucocorticoid; HRG, Healthcare Resource Group

The cost of CV AEs was derived as a weighted mean of the costs of coronary heart disease (CHD), stroke, and hypertension, based on the incidence of these events

observed in the CPRD study (Table 50). The method of estimating the unit costs for each component of CV disease is reported in Table 51. The cost of CHD was derived from a study by Walker et al. (126). The cost of stroke was based on an aggregate modelling study of the stroke pathway in the United Kingdom (127). The cost of hypertension was based on annual follow-up in primary care as described in NICE guideline NG136, which includes an appointment with a general practitioner, recommended laboratory tests, and daily amlodipine (128).

Table 50. Proportion of patients with cardiovascular adverse events in the CPRD study

Event	Cases*
Vascular disease/CHD	[redacted]
Stroke	[redacted]
Hypertension	[redacted]
Abbreviations: CHD, coronary heart disease; CPRD, Clinical Practice Research Datalink *Patients may have >1 event; percentages do not sum to 100%	

Table 51. Cost of cardiovascular AEs

Event	Description	First year cost	Subsequent year cost	Reference
CHD	Annual healthcare cost	£1,780.00	£1,109.00	Walker et al. (2016)
Stroke	Annual NHS and social care cost	£18,081.00	£7,759.00	Patel et al. (2019)
Hypertension	Annual GP appointment	£37.40	£37.40	NICE NG136, PSSRU 2018
	Albumin:creatinine ratio test	£1.11	£0.00	NHS Reference Costs: DAPS04 Clinical Biochemistry
	HbA1C test	£2.51	£0.00	NHS Reference Costs: DAPS05 Haematology
	Electrolytes	£1.97	£0.00	NHS Reference Costs: DAPS03 Integrated Blood Services
	Creatinine	£1.97	£0.00	NHS Reference Costs: DAPS03 Integrated Blood Services
	eGFR	£1.97	£0.00	NHS Reference Costs: DAPS03 Integrated Blood Services

	Cholesterol	£1.97	£0.00	NHS Reference Costs: DAPS03 Integrated Blood Services
	Electrocardiogram	£38.31	£0.00	NHS Reference Costs: HRG EY51Z
	Amlodipine once daily: £0.85 per 28 tablets	£11.09	£11.09	NICE/BNF 2020
	Hypertension total	£98.30	£48.49	
Weighted annual cost		**£3,962.16**	**£1,818.86**	
Weighted cost per cycle		**£303.74**	**£139.43**	

Abbreviations: CHD, coronary heart disease; BNF, British National Formulary; eGFR, estimated glomerular filtration rate; GP, general practitioner; HbA1C, glycated hemoglobin; HRG, Health Resource Group; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSSRU, Personal and Social Services Research Unit

The cost of bone disease was estimated using the frequency and distribution of osteoporotic fractures (Table 52) combined with the unit cost of fractures based on the NICE technology appraisal for bisphosphonates for treating osteoporosis TA464 (120) (Table 53). The cost of osteoporotic fractures was calculated as a weighted average of rates of hip, spine, shoulder and wrist fractures reported in the literature. Distributions of fractures by site for 5-year age groups from 50 to 89 years were multiplied by the cost of treatment for each fracture in first and subsequent years estimated in the ERG analysis. The annual costs used in the model are reported in Table 54. The per-cycle cost in the model was estimated by multiplying the annual costs by the age-adjusted risk of osteoporotic fracture estimated using the QFracture risk calculator (https://qfracture.org/index.php).

Table 52. Distribution of fractures by site, ERG analysis in TA46

Age group, years	Hip	Spine	Shoulder	Wrist
Men and women*				
50-54	8%	35%	17%	41%
55-59	8%	35%	17%	41%
60-64	15%	26%	12%	48%
65-69	20%	33%	11%	37%
70-74	26%	25%	15%	35%
75-79	33%	33%	15%	19%

80-84	44%	29%	12%	16%
≥85	55%	23%	8%	14%
Women				
50-54	6%	22%	17%	56%
55-59	6%	22%	17%	56%
60-64	11%	19%	15%	55%
65-69	15%	26%	11%	48%
70-74	21%	23%	19%	37%
75-79	28%	27%	13%	31%
80-84	38%	25%	14%	23%
≥85	53%	18%	9%	19%
Men				
50-54	10%	48%	16%	25%
55-59	10%	48%	16%	25%
60-64	18%	32%	8%	41%
65-69	24%	40%	11%	25%
70-74	31%	27%	10%	32%
75-79	38%	39%	16%	7%
80-84	49%	32%	9%	9%
≥85	57%	28%	7%	8%
*Weighted average based on proportion of women in model population				

Table 53. Treatment cost of fractures based on TA464

Type of cost	Hip	Spine	Shoulder	Wrist
First year	£8,235	£4,173	£1,305	£861
Subsequent years	£106	£332	£70	£70

Table 54. Annual cost of osteoporotic fracture by age group

Age group, years	First year	Subsequent years
50-54	£2,683.38	£164.58
55-59	£2,683.38	£164.58
60-64	£2,821.55	£141.68
65-69	£3,440.73	£163.48
70-74	£3,670.62	£144.86
75-79	£4,447.46	£167.99
80-84	£5,059.37	£159.98
≥85	£5,709.68	£149.71

For the purposes of costing ocular disease, treatment is assumed to involve cataract surgery in the first year after developing the AE. No excess cost of treatment is

assumed in subsequent years. The standard approach to cataract surgery is phacoemulsification surgery with intra-ocular lens implantation. The cost of this procedure was estimated using the approach taken in the NICE guideline for the management of cataracts in adults (NG77) (129), which estimated a weighted mean based on the type of procedure reported in NHS Reference Costs 2014-15. This method was replicated in combination with NHS Reference Costs 2019-20 (123) (Table 55).

Table 55. Cost of cataract surgery based on NICE NG77

HRG code*	N (used for weighting)	Weight	Cost
BZ34A: Elective inpatients	247	0.00	£1,717.00
BZ34B: Elective inpatients	631	0.00	£1,657.00
BZ34C: Elective inpatients	1409	0.01	£1,529.00
BZ34B: Contracted elective inpatient†	0	0.00	£0.00
BZ34C: Contracted elective inpatient†	0	0.00	£0.00
BZ34A: Day case	15038	0.06	£974.00
BZ34B: Day case	64411	0.24	£938.00
BZ34C: Day case	187663	0.70	£900.00
BZ34A: Contracted day case†	0	0.00	£0.00
BZ34B: Contracted day case†	0	0.00	£0.00
BZ34C: Contracted day case†	0	0.00	£0.00
Weighted mean cost			**£919.03**
Weighted cost per cycle			**£70.45**

Abbreviations: HRG, healthcare resource group; NHS, National Health Service
*HRG case-mix codes derived from NHS Reference Costs 2019-20
†Excluded from the current analysis as category not found in NHS Reference Costs 2019-20. A test using original data from NG77 demonstrated that the contracted categories have a very small impact on the weighted mean

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1. Summary of base-case analysis inputs

A summary of base-case settings applied in the model is included in Table 56.

Table 56. Summary of variables applied in the economic model

Variable	Value	Low	High	Source for interval	Probabilistic distribution	Reference to section in submission	Reference to the literature
Model settings							
Time horizon	40 years	5 years	40 years	NICE reference case – lifetime horizon	Not varied	B.3.2.3	NICE Guide to the methods of technology appraisal
Starting age	60 years	N/A	N/A	Not varied	Not varied	B.3.2.1	ADVOCATE trial
Discount rate for costs	3.5%	1.5%	5.0%	NICE reference case	Not varied	B.3.2.3	NICE Guide to the methods of technology appraisal
Discount rate for outcomes	3.5%	1.5%	5.0%	NICE reference case	Not varied	B.3.2.3	NICE Guide to the methods of technology appraisal
Clinical inputs							
Patients treated with RTX	64.8%	58.0%	71.0%	±10%	Beta (134.6, 73.1)	B.3.5.1	ADVOCATE trial
Mean body weight	77.07 kg	Not varied				B.3.5.1	ADVOCATE trial
Mean body surface area	1.92 m^2	Not varied				B.3.5.1	ADVOCATE trial
Compliance with avacopan	86.4%	Not varied				B.3.5.1	ADVOCATE trial

Compliance with GCs	98.4%	Not varied				B.3.5.1	ADVOCATE trial
Remission rate at 26 weeks, avacopan	72.3%	64.8%	78.9%	95% CI	Beta (111.2, 42.6)	B.3.3.2	ADVOCATE trial
Remission at 26 weeks, GC SoC	70.1%	62.5%	77.0%	95% CI	Beta (106.7, 45.5)	B.3.3.2	ADVOCATE trial
Remission rate at 52 weeks, avacopan	65.7%	57.9%	72.8%	95% CI	Beta (101.8, 53.2)	B.3.3.1	ADVOCATE trial
Remission at 52 weeks, GC SoC	54.9%	46.9%	62.6%	95% CI	Beta (84.2, 69.2)	B.3.3.1	ADVOCATE trial
Remission rate at 60 weeks, avacopan	62.0%	55.0%	70.0%	95% CI	Beta (103, 63)	B.3.3.1	ADVOCATE trial
Remission at 60 weeks, GC SoC	50.6%	43.0%	58.0%	95% CI	Beta (83, 81)	B.3.3.1	ADVOCATE trial
Remission rate, no GC, CPRD	[redacted]	[redacted]	[redacted]	95% CI	[redacted]	B.3.3.2	CPRD study
Remission rate, low-dose GC, CPRD	[redacted]	[redacted]	[redacted]	95% CI	[redacted]	B.3.3.2	CPRD study
Relapse rate years 1 and 2, no GC, CPRD	[redacted]	[redacted]	[redacted]	95% CI	[redacted]	B.3.3.1	CPRD study
Relapse rate years 3+, no GC, CPRD	[redacted]	[redacted]	[redacted]	95% CI	[redacted]	B.3.3.1	CPRD study

Relapse rate years 1 and 2, low-dose GC, CPRD	[redacted]	[redacted]	[redacted]	95% CI	[redacted]	B.3.3.1	CPRD study
Relapse rate years 3+, low-dose GC, CPRD	[redacted]	[redacted]	[redacted]	95% CI	[redacted]	B.3.3.1	CPRD study
ESRD rate at 6 months	0.06	0.06	0.07	+/- 10%	Log normal (0.06, 0.05)	B.3.3.3	(96)
ESRD rate at 7.1 years	0.14	0.13	0.15	±10%	Log normal (0.14, 0.05)	B.3.3.3	(96)
Adjustment of hazard rate of ESRD based on eGFR from ADVOCATE	0.71	0.64	0.78	±10%	Log normal (0.71, 0.05)	B.3.3.3	Estimated from ADVOCATE trial and Gercik et al. (103)
ESRD rate, high-dose GC, CPRD	[redacted]	[redacted]	[redacted]	Poisson distribution based on CPRD data		B.3.3.3	CPRD study
ESRD rate, low-dose GC, CPRD	[redacted]	[redacted]	[redacted]	Poisson distribution based on CPRD data		B.3.3.3	CPRD study
ESRD rate, no GC, CPRD	[redacted]	[redacted]	[redacted]	Poisson distribution based on CPRD data		B.3.3.3	CPRD study
eGFR drop with relapse (mL/min)	10	Tested in scenario analysis				B.3.3.3	Assumption supported by clinical expert opinion

eGFR recovery at induction, avacopan (mL/min)	5.8	4.8	6.8	95% CI	Log normal (5.8, 0.09)	B.3.3.3	(65)
eGFR recovery at induction, GC SoC (mL/min)	2.9	1.9	3.9	95% CI	Log normal (2.9, 0.18)	B.3.3.3	(65)
eGFR recovery at remission, avacopan (mL/min)	7.3	6.3	8.3	95% CI	Log normal (7.3, 0.07)	B.3.3.3	(65)
eGFR recovery at remission, GC SoC (mL/min)	4.1	3.1	5.1	95% CI	Log normal (4.1, 0.13)	B.3.3.3	(65)
Peritoneal dialysis	20.5%	Not varied				B.3.5.2	NICE TA623 (115)
Haemodialysis	69.8%	Not varied				B.3.5.2	NICE TA623 (115)
Renal transplant	9.7%	Not varied				B.3.5.2	NICE TA623 (115)
Infection rate, high-dose GC, CPRD	[redacted]	[redacted]	[redacted]	95% CI	[redacted]	B.3.3.5	CPRD study (101)
Infection rate, low-dose GC, CPRD	[redacted]	[redacted]	[redacted]	95% CI	[redacted]	B.3.3.5	CPRD study (101)
Infection rate, no GC, CPRD	[redacted]	[redacted]	[redacted]	95% CI	[redacted]	B.3.3.5	CPRD study (101)

CV event rate, high-dose GC, CPRD	[redacted]	[redacted]	[redacted]	95% CI	[redacted]	B.3.3.5	CPRD study (101)
CV event rate, low-dose GC, CPRD	[redacted]	[redacted]	[redacted]	95% CI	[redacted]	B.3.3.5	CPRD study (101)
CV event rate, no GC, CPRD	[redacted]	[redacted]	[redacted]	95% CI	[redacted]	B.3.3.5	CPRD study (101)
Bone disease event rate, high-dose GC, CPRD	[redacted]	[redacted]	[redacted]	95% CI	[redacted]	B.3.3.5	CPRD study (101)
Bone disease event rate, low-dose GC, CPRD	[redacted]	[redacted]	[redacted]	95% CI	[redacted]	B.3.3.5	CPRD study (101)
Bone disease event rate, no GC, CPRD	[redacted]	[redacted]	[redacted]	95% CI	[redacted]	B.3.3.5	CPRD study (101)
Ocular disease event rate, high-dose GC, CPRD	[redacted]	[redacted]	[redacted]	95% CI	[redacted]	B.3.3.5	CPRD study (101)
Ocular disease event rate, low-dose GC, CPRD	[redacted]	[redacted]	[redacted]	95% CI	[redacted]	B.3.3.5	CPRD study (101)
Ocular disease event rate, no-dose GC, CPRD	[redacted]	[redacted]	[redacted]	95% CI	[redacted]	B.3.3.5	CPRD study (101)

RR of death in year one	6.31	3.62	10.98	95% CI	Normal (6.31, 1.88)	B.3.3.4	(105)
RR of death in years 2+	2.51	1.88	3.36	95% CI	Normal (2.51, 0.38)	B.3.3.4	(105)
RR of death in ESRD	10.30	10.00	10.60	95% CI	Normal (10.30,0.15)	B.3.3.4	(107)
% of deaths in 1st year attributed to GC infection	50%	37%	63%	95% CI	Beta (28, 28)	B.3.3.4	(11)
% of severe infections avoided with avacopan	73%	66%	80%	+/- 10%	Beta (102.6, 37.76)	B.3.3.4	ADVOCATE trial
Time on treatment with GC in refractory disease	[redacted]	N/A	N/A	Not varied	Not varied	B.3.3.6	Assumption based on CPRD analysis
Utility inputs							
EQ-5D-5L utility in active disease, ITT population, both trial arms	0.780	0.751	0.809	95% CI	Beta (636.34, 179.90	B.3.4.5	ADVOCATE trial and UK EQ-5D-5L value set: (130)
EQ-5D-5L utility in active disease, ITT population, avacopan arm	0.780	0.741	0.820	95% CI	Beta (340.57, 96.00)	B.3.4.5	
EQ-5D-5L utility in active	0.779	0.736	0.822	95% CI	Beta (292.07, 82.86)	B.3.4.5	

disease, ITT population, GC SoC arm							
EQ-5D-3L utility in active disease, ITT population, both trial arms	0.702	0.670	0.734	95% CI	Beta (572.86, 242.83)	B.3.4.5	ADVOCATE trial and UK EQ-5D-3L crosswalk value set: (112)
EQ-5D-3L utility in active disease, ITT population, avacopan arm	0.708	0.664	0.751	95% CI	Beta (307.34, 126.94)	B.3.4.5	
EQ-5D-3L utility in active disease, ITT population, GC SoC arm	0.697	0.649	0.744	95% CI	Beta (261.41, 113.86)	B.3.4.5	
EQ-5D-5L utility in remission, ITT population, both trial arms	0.842	0.827	0.856	95% CI	Beta (2152.36, 405.10)	B.3.4.5	ADVOCATE trial and UK EQ-5D-5L crosswalk value set: (130)
EQ-5D-5L utility in remission, ITT population, avacopan arm	0.849	0.828	0.869	95% CI	Beta (1037.73, 185.00)	B.3.4.5	
EQ-5D-5L utility in remission, ITT population, GC SoC arm	0.834	0.814	0.854	95% CI	Beta (1116.97, 222.16)	B.3.4.5	
EQ-5D-3L utility in remission,	0.778	0.761	0.795	95% CI	Beta (1939.42, 553.73)	B.3.4.5	ADVOCATE trial and UK

ITT population, both trial arms							EQ-5D-3L crosswalk value set: (112)
EQ-5D-3L utility in remission, ITT population, avacopan arm	0.790	0.767	0.812	95% CI	Beta (1010.83, 269.19)	B.3.4.5	
EQ-5D-3L utility in remission, ITT population, GC SoC arm	0.766	0.741	0.790	95% CI	Beta (929.46, 284.73)	B.3.4.5	
EQ-5D-5L utility in relapse, ITT population, both trial arms	0.760	0.673	0.846	95% CI	Beta (73.67, 23.32)	B.3.4.5	ADVOCATE trial and UK EQ-5D-5L crosswalk value set: (130)
EQ-5D-5L utility in relapse, ITT population, avacopan arm	0.806	0.707	0.905	95% CI	Beta (50.47, 12.16)	B.3.4.5	
EQ-5D-5L utility in relapse, ITT population, GC SoC arm	0.740	0.624	0.856	95% CI	Beta (41.47, 14.58)	B.3.4.5	
EQ-5D-3L utility in relapse, ITT population, both trial arms	0.696	0.611	0.780	95% CI	Beta (81.84, 35.76)	B.3.4.5	ADVOCATE trial and UK EQ-5D-3L crosswalk value set: (112)
EQ-5D-3L utility in relapse, ITT population, avacopan arm	0.738	0.629	0.847	95% CI	Beta (47.20, 16.78)	B.3.4.5	
EQ-5D-3L utility in relapse, ITT	0.678	0.566	0.790	95% CI	Beta (46.59, 22.14)	B.3.4.5	

population, GC SoC arm							
Utility in peritoneal dialysis	0.53	0.48	0.58	±10%	Beta (180.02, 159.64)	B.3.4.5	NICE TA623 (115)
Utility in haemodialysis	0.44	0.40	0.49	±10%	Beta (213.53, 268.47)	B.3.4.5	
Utility after renal transplant	0.71	0.64	0.78	±10%	Beta (109.92, 44.46)	B.3.4.5	
Cost inputs							
Cost of avacopan 10mg tablet (PAS price)	[redacted]	Not varied				B.3.5.1	Vifor
Cost of CYC 500 mg	£9.66	Not varied				B.3.5.1	BNF online (124)
Cost of CYC 1000 mg	£17.91	Not varied				B.3.5.1	
Cost of RTX 100 mg/10 mL	£314.33	Not varied				B.3.5.1	
Cost of RTX 500 mg/50 mL	£785.84	Not varied				B.3.5.1	
Cost of AZA 25 mg	£1.99	Not varied				B.3.5.1	
Cost of AZA 50 mg	£2.52	Not varied				B.3.5.1	
Cost of prednisone 5 mg/pack size 28	£1.08	Not varied				B.3.5.1	

Cost of IV drug administration, first attendance	£406.04	£365.44	£446.64	+/- 10%	Gamma (384.15, 1.06)	B.3.5.1	NHS Reference costs 2019-20: HRG SB14Z (123)
Cost of IV drug administration, subsequent attendance	£341.30	£307.17	£375.43	+/- 10%	Gamma (384.15, 0.89)	B.3.5.1	NHS Reference costs 2019-20: HRG SB15Z (123)
Cost of blood test	£1.81	£1.63	£1.99	+/- 10%	Gamma (384.15, 0.00)	B.3.5.2	NHS Reference costs 2019-20: DAPS04 (123)
Cost of liver function test	£1.20	£1.08	£1.32	+/- 10%	Gamma (384.15, 0.00)	B.3.5.2	NHS Reference costs 2019-20: DAPS04 (123)
Cost of outpatient visit	£155.15	£139.64	£170.67	+/- 10%	Gamma (384.15, 0.40)	B.3.5.2	NHS Reference costs 2019-20, Rheumatology consultant-led outpatient visit (123)
Cost of maintenance dialysis	£27,037.71	£24,333.94	£29,741.48	95% CI	Gamma (384.15, 70.38)	B.3.5.2	(125)

Cost of renal transplant, first year	£28,516.75	£25,665.08	£31,368.43	95% CI	Gamma (384.15, 74.23)	B.3.5.2	(125)
Cost of renal transplant, subsequent years	£1,330.67	£1,197.60	£1,463.74	95% CI	Gamma (384.15, 3.46)	B.3.5.2	(125)
Abbreviations: AZA, azathioprine; CI, confidence interval; CPRD, Clinical Practice Research Datalink; CV, cardiovascular; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; GC, glucocorticoid; ITT, intention to treat; IV, intravenous; NICE, National Institute for Health and Care Excellence; RR, relative risk; SoC, standard of care							

B.3.6.2 Model assumptions

Table 57. Summary of base-case model assumptions

Assumption	Justification
Treatment effect	
The full treatment effect of avacopan compared to GC SoC is applied for 52 weeks in the model based on the ADVOCATE trial (model cycles 1-13). The treatment effect between weeks 52 and 60 is derived from extension data from the ADVOCATE trial (cycles 14 and 15). No treatment effect is assumed beyond month 15 (cycle 16). In cycle 16, a reduced treatment effect is applied based on a linear waning effect.	The treatment effect of avacopan is sustained for up to 3 months after discontinuation of treatment with a constant waning effect based on advice from UK clinical experts (including investigators from the ADVOCATE study)
Treatment pathway in AAV	
No GC use is assumed alongside avacopan treatment	This assumption is in line with the ADOCATE trial protocol. In real-life practice, treatment with GCs may continue in combination with avacopan. This assumption was tested in a scenario analysis
Patients in refractory disease are assumed to be treated with AZA until ESRD or death	Patients with refractory disease were assumed to have low-grade disease that required ongoing treatment with AZA, in line with the recommendation by the ERG in the NICE technology appraisal of RTX in AAV (TA308)
ESRD	
Relapse is associated with a drop of 10 mL/min in eGFR	Relapse is associated with substantial worsening of renal function and increase in the risk of ESRD (102, 131)
An increase of 1 point in eGFR is associated with a 10% decrease in the hazard rate of ESRD	Assumption based on Gercik et al. (103)
Mortality	
The probability of death directly attributed to AAV relapse is assumed to be the same irrespective of induction treatment. The probability of death due to GC-related infections is lower for avacopan-treated patients due to GC-sparing. A smaller proportion of patients treated with avacopan die from ESRD due to higher improvements in eGFR and fewer relapses.	Around half of all deaths in AAV are attributed to GC-related infections (11)
Refractory disease	
The probability of ESRD in refractory disease is equal to the probability of ESRD in relapse	Refractory disease is associated with worsening renal function akin to relapse, as advised by UK clinical experts

Abbreviations: AAV, anti-neutrophil cytoplasmic antibody–associated vasculitis; AZA, azathioprine; eGFR, estimated glomerular filtration rate; ERG, Evidence Review Group; ESRD, end-stage renal disease; GC, glucocorticoid; NICE, National Institute for Health and Care Excellence; SoC, standard of care; UK, United Kingdom

B.3.7 Base-case results

B.3.7.1. Model base-case settings

Table 58. Model base-case settings

Setting	Base case	Justification
Population	Adults with GPA and MPA	ADVOCATE ITT population
Age at start	60 years	
Intervention	Avacopan in combination with CYC or RTX	ADVOCATE
Comparator	CYC or RTX in combination with GCs	
Discount rate (costs)	3.5%	NICE reference case
Discount rate (outcomes)	3.5%	
Time horizon	Lifetime (40 years)	
Avacopan cost (PAS price)	[redacted]	Vifor
Number of induction treatment courses	3	Patients are assumed to receive re-induction therapy in line with clinical guidelines. A maximum of three induction courses are set in the model based on maximum recommended cumulative dose of CYC
No. of induction treatment courses with avacopan	1	Patients are re-induced with GC SoC in case of relapse after induction with avacopan
Drug wastage	Included	Cost of IV treatments assumed to include use of full vials
Mortality data source	UK life tables	Source reflects UK population mortality
Mortality adjustment in AAV and ESRD	Literature	Source reflects UK population mortality
Source of data for remission and relapse	ADVOCATE trial	Consistent with model population
ESRD data source	Literature	Source reflects UK population
Health state utility values	Treatment-specific utilities	Reflects model population and impact of treatments and AEs on patient HRQoL

Abbreviations: AAV, anti-neutrophil cytoplasmic antibody–associated vasculitis; AE, adverse event; ESRD, end-stage renal disease; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; ITT, intention-to-treat; IV, intravenous; HRQoL, health-related quality of life; MPA, microscopic polyangiitis; SoC, standard of care; UK, United Kingdom

B.3.7.2. Base-case incremental cost-effectiveness analysis results

Table 59. Base-case results

	Total			Incremental			
Technologies	**Costs**	**LYG**	**QALYs**	**Costs**	**LYG**	**QALYs**	**ICER, £/QALY**
AVA + CYC/RTX	£[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,537
CYC/RTX + GC	£124,679	9.30	6.07	-	-	-	-
Abbreviations: AVA, avacopan; CYC, cyclophosphamide; GC, glucocorticoid; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; RTX, rituximab							

Table 60. Summary of disaggregated results of the base-case analysis

Outcomes	**Technology**		**Incremental**
	AVA + CYC/RTX	**CYC/RTX + GC**	
Costs			
Drug costs	[redacted]	[redacted]	[redacted]
Resource use*	[redacted]	[redacted]	[redacted]
ESRD	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Health outcomes			
Life year	[redacted]	9.30	[redacted]
QALYs	[redacted]	6.07	[redacted]
Abbreviations: AVA, avacopan; CYC, cyclophosphamide; ESRD, end-stage renal disease; GC, glucocorticoid; QALY, quality-adjusted life year; RTX, rituximab *Cost of treatment of AEs included in resource use category in the model base case			

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

The combined uncertainty propagated by all parameters in the model was characterised using a probabilistic sensitivity analysis. All uncertain parameter values were sampled from probability distributions listed in Table 56. The model analysis was repeated 5,000 times to estimate the probabilistic cost-effectiveness results. The uncertainty in the incremental cost and QALYs was illustrated using a scatter diagram mapped on the cost effectiveness plane in Figure 15.

The cost-effectiveness acceptability curve (CEAC) in Figure 16 reported the proportion of simulations with an ICER below the willingness-to-pay threshold per QALY. The CEAC was reported for WTP thresholds between £0 to £100,000 per QALY.

B.3.8.2 Parameter distributions and sources

Probability distributions were assigned to parameter values based on published 95% ranges reported in the original studies which estimated the parameter. In the absence of a published range, a 10% deviation from the mean was used to compute the lower and upper bound for each parameter. The type of distribution which was appropriate for the type of parameter was selected (beta distribution for transition probabilities and utility values, gamma distribution for costs, lognormal distribution for event rates). Cholesky decomposition was used to adjust the remission rates at week 26 and 52 weeks, which were assumed to be closely correlated.

B.3.8.3 Probabilistic sensitivity analysis results

In the probabilistic analysis, the mean ICER was £18,909. Based on the cost-effectiveness acceptability curve, the probability of cost-effectiveness of avacopan was 55% at £20,000 per QALY and 80% at £30,000 per QALY.

Table 61. Base case probabilistic results

Technologies	Total		Incremental		
	Costs	QALYs	Costs	QALYs	ICER, £/QALY
AVA + CYC/RTX	[redacted]	[redacted]	[redacted]	[redacted]	£18,909
CYC/RTX + GC	£125,774	6.09	Reference	Reference	Reference

Abbreviations: AVA, avacopan; CYC, cyclophosphamide; GC, glucocorticoid; QALY, quality-adjusted life year; RTX, rituximab

Figure 15. Cost-effectiveness plane and scatter diagram

Figure 16. Cost-effectiveness acceptability curve

B.3.8.4 Differences between deterministic and probabilistic model results

There were no significant differences between the ICER estimates based on the deterministic and probabilistic analyses. Minor differences can be explained by sampling error within the PSA and had no impact on the analysis conclusions.

B.3.8.5 Deterministic sensitivity analysis

One-way sensitivity analyses were conducted to identify the model parameters with the largest impact on the model results.

B.3.8.6 Parameter ranges for the deterministic sensitivity analysis

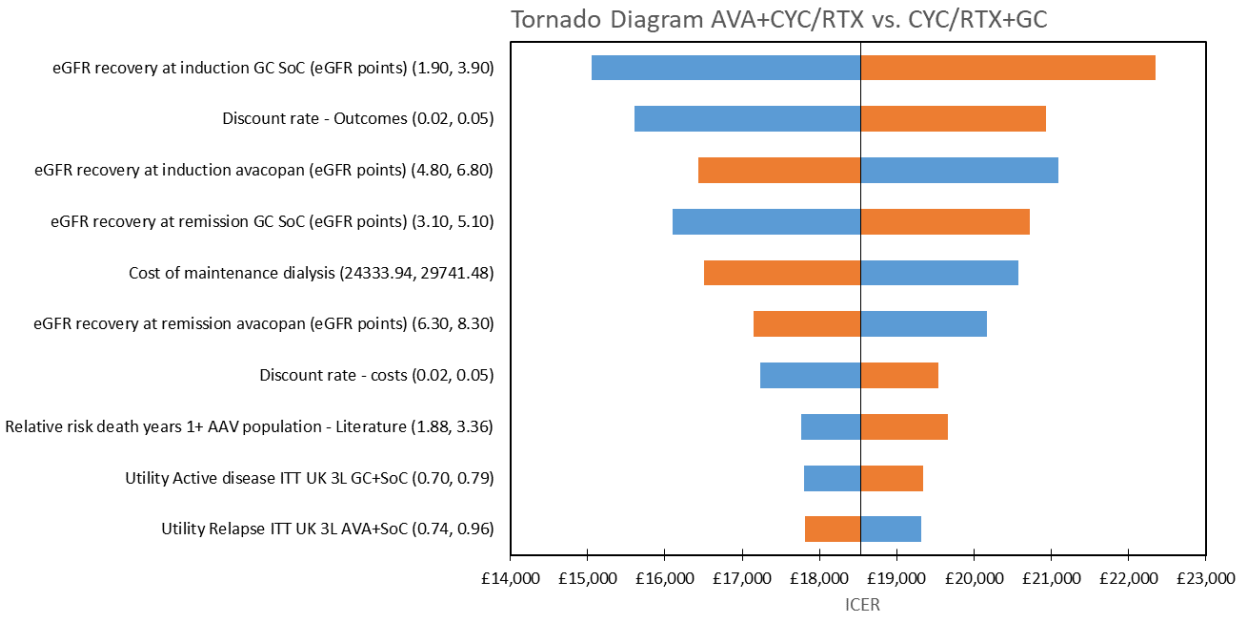
All uncertain model parameters were varied individually using the ranges reported in Table 56.

B.3.8.7 Results of the deterministic sensitivity analysis

The results were presented in the tornado plot in Figure 17.

The model results were sensitive to the eGFR improvement reported in the ADVOCATE trial. Other parameters which contributed to model uncertainty was the discount rate for outcomes and costs, and the cost of maintenance dialysis, which is the main component of the cost of ESRD. Nevertheless, the model results were reasonably robust in the presence of uncertainty, and at the PAS price avacopan was ICER was expected to be in the range of £15,000-£22,000 per QALY depending on the parameter values used.

Figure 17. Tornado diagram



B.3.8.8 Scenario analysis

Scenario analyses were conducted to assess the impact of key assumptions used in the model. The rationale for each scenario was described in Table 62 and the impact

of alternative assumptions on the ICER compared to the base case was explored in Table 63.

Table 62. Summary of scenario analysis inputs

Scenario	Base case	Alternative assumption(s)	Rationale
Time horizon	Lifetime (40 years)	5, 10 and 20 years	Explore shorter time horizon
Discount rate	3.5%	1.5%, 5.0%	Explore alternative discount rates for costs and outcomes
Number of induction courses	3	1, 2	Explore impact of reducing the maximum number of re-inductions
No. of re-induction courses with avacopan	0	1, 2	Explore the impact of re-induction with avacopan after one or two relapses
Treatment effect after avacopan discontinuation	Waning treatment effect for 3 months after discontinuation	No treatment effect after 52 weeks, waning treatment effect for 6 months	The extrapolation of the treatment effect of avacopan beyond 60-week ADVOCATE extension data is uncertain and is supported with expert opinion. This scenario explored a shorter or longer period of treatment effect persistence
GC use alongside avacopan treatment	No GC use based on ADVOCATE protocol	GC use tapered to 60mg/day	The model base case assumes no GC use alongside avacopan in line with the ADVOCATE trial protocol. This analysis explores a real-life scenario with avacopan in combination with GCs
Data source for probability of ESRD	Literature	CPRD	Explore impact of using real-world evidence from CPRD
eGFR decrease with each relapse	10 ml/min	5ml/min, 20 ml/min	Explore alternative assumptions for change in renal

			function after relapse as advised by clinical experts
Effect of eGFR decrease on probability of ESRD	HR 0.90 (based on Gercik et al.)	HR 0.96 (based on Brix et al.)	Test the impact of an alternative data source
Hospitalisation data from ADVOCATE	Included	Not included	Explore the impact of hospitalisation costs from ADVOCATE trial
Health state utility values	Treatment-specific	Not treatment-specific	Explore the impact of using the same health state utility values in the avacopan and SoC arm

Table 63. Scenario analysis results

Scenario	Assumption	Incr. costs	Incr. QALYs	ICER
Base case		[redacted]	[redacted]	£18,537
Time horizon	5 years	[redacted]	[redacted]	£75,316
	10 years	[redacted]	[redacted]	£28,214
	20 years	[redacted]	[redacted]	£18,833
Discount rate	1.5%	[redacted]	[redacted]	£14,508
	5.0%	[redacted]	[redacted]	£22,057
Number of induction courses	1	[redacted]	[redacted]	£24,797
	2	[redacted]	[redacted]	£21,414
No. of re-inductions with avacopan	1	[redacted]	[redacted]	£17,698
	2	[redacted]	[redacted]	£19,194
Treatment effect after avacopan discontinuation	No treatment effect after 52 weeks	[redacted]	[redacted]	£19,259
	Waning treatment effect for 6 months	[redacted]	[redacted]	£16,549
GC use alongside avacopan treatment		[redacted]	[redacted]	£18,596
ESRD probability from CPRD		[redacted]	[redacted]	£23,351
eGFR decrease with relapse	5ml/min	[redacted]	[redacted]	£24,869
	20 ml/min	[redacted]	[redacted]	£12,534
Effect of eGFR decrease on probability of ESRD	HR 0.96	[redacted]	[redacted]	£31,655
Hospitalisation data from ADVOCATE	Not included	[redacted]	[redacted]	£24,433
Health state utility values	Not treatment-specific	[redacted]	[redacted]	£19,559

B.3.9 Subgroup analysis

The cost-effectiveness analysis was conducted for patient subgroups pre-specified in the ADVOCATE trial protocol. The following subgroups were included:

- Newly diagnosed AAV
- Relapsed AAV
- GPA
- MPA
- RTX background therapy
- CYC background therapy
- MPO positive
- PR3 positive

The subgroup analyses were informed by remission data at week 26 and week 52 reported in Table 24 and EQ-5D-5L subgroup data from the ADVOCATE trial. All other clinical inputs were assumed to be the same as in the base case analysis based on the ADVOCATE ITT population. The cost of induction treatment was adjusted accordingly in the RTX and CYC subgroups.

Table 64. Results of the cost-effectiveness analysis within the subgroups in the ADVOCATE trial

Subgroup	Δ Costs	Δ QALYs	ICER per QALY
Newly diagnosed AAV	[redacted]	[redacted]	£33,537
Relapsed AAV	[redacted]	[redacted]	£15,267
GPA	[redacted]	[redacted]	£51,991
MPA	[redacted]	[redacted]	£467
RTX background therapy	[redacted]	[redacted]	£17,731
CYC background therapy	[redacted]	[redacted]	£25,471
MPO positive	[redacted]	[redacted]	£13,668
PR3 positive	[redacted]	[redacted]	£54,284

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Internal validation

Internal quality control was conducted to ensure both accuracy and consistency in formulas and model outputs. The following steps were taken:

1. All worksheets and associated formulae were examined for potential sources of error
2. Verification was conducted, adjusting input parameters and observing model behaviour
3. Functionalities (restore defaults, DSA, PSA) where run to verify that they work appropriately

Step 1:

All sheets were checked for accuracy of coding, with attention paid to the calculations section of the model. These worksheets contain the underlying engine of the model computing the accrued costs, life-years and quality adjusted life year (QALYs).

Step 2:

A model verification process was conducted, whereby key input parameters were manipulated and model behaviour observed. Inconsistent model behaviour can be used to identity errors that may have been overlooked by manual inspection. The procedures conducted, as well as expected model outputs are presented in Table 65.

Table 65. Outcome of internal model validation

Procedure	Implementation	Expectation	Check
All utilities set to 1	• Set all health state utilities to 1 • Set AE utilities to 0 • Set utility norms (used for age adjustment) to 1	LY = QALYs	✓
Increase age of patients	Increase age from 60 to 65	LY and QALYs lower than in the base-case	✓

Cost per induction course equal to AVA costs in all arms	• Set induction costs equal in all arms • Set maintenance and refractory disease costs equal to zero	Drug costs equal in all AVA arms, and across CYC/RTX arms	✓
All costs set to 0		No costs	✓
Same treatment effect Induction costs equal to AVA costs across all arms and other drug costs set to zero	Literature data: • Set remission rate at week 52 in AVA arm equal to CYC/RTX arms • Set AEs rates to zero CPRD data: • Set relative risk of relapse to 1 • Set ESRD rate in AVA arm equal to CYC/RTX arms • Set AEs rates to zero Mortality data: • Set infection mortality adjustment to zero Costs • Set induction costs equal in all arms • Set maintenance and refractory disease costs equal to zero	LY and QALYs equal across all arms Drug costs, Resources used costs and ESRD costs equal across all arms. No cost of AEs	✓
Abbreviations: AE, adverse event; AVA, avacopan; CYC, cyclophosphamide; ESRD, end-stage renal disease; LY, life year; QALY, quality-adjusted life years; RTX, rituximab			

Step 3:

Several model functionalities were tested to ensure they work appropriately. The "restore defaults" functionality was tested by manipulating inputs, and verifying that they were restored to default values, and that the model results produced were identical to the base-case values. The DSA and PSA functionalities were also run, and the results investigated for inconsistencies to identify any potential error.

External validation

An assessment of the predictive accuracy of a model should be carried out by comparing simulated outcomes to observed data (132). External validation for

predicted endpoints in the model was carried using previous epidemiological studies in AAV.

The predicted overall survival in the model (Figure 18) was compared to OS in an observational cohort of 465 patients with GPA in the UK with a mean age 60 years (Figure 19) (105). The cohort of patients diagnosed between 2003 and 2013 was deemed to be the most relevant dataset for comparison given improvements in survival in AAV in recent decades due to improved disease management. OS predicted in the model is similar to the validation cohort: 1 and 2-year survival in both was between 90-95% and 5-year survival around 80-85%.

An alternative validation cohort for overall survival is Flossman et al., who analysed data for 535 AAV patients recruited to four multicentre RCTs in 15 countries between 1995 and 2002 (Figure 20) (10).OS in Flossman et al. is similar to the current model and Wallace et al. at 1 year, however it is lower in future years after recruitment. At 5 years less than 80% of patients remain alive. The mean age in Flossman et al. (61 years) was similar to the starting age in the model cohort and in Wallace et al. (60 years). The difference in survival could be explained by the fact that Wallace et al. recruited patients diagnosed after 2003 with a better prognosis due to improvements in disease management. This is demonstrated by differences in all-cause mortality in patients recruited at different time points in Wallace at al. Another explanation could be that Wallace et al. was restricted to UK patients with better AAV outcomes and/or lower background mortality compared to countries included in Flossman et al., and therefore Wallace et al. matches the population included in our model.

Figure 18. Overall survival predicted in the model

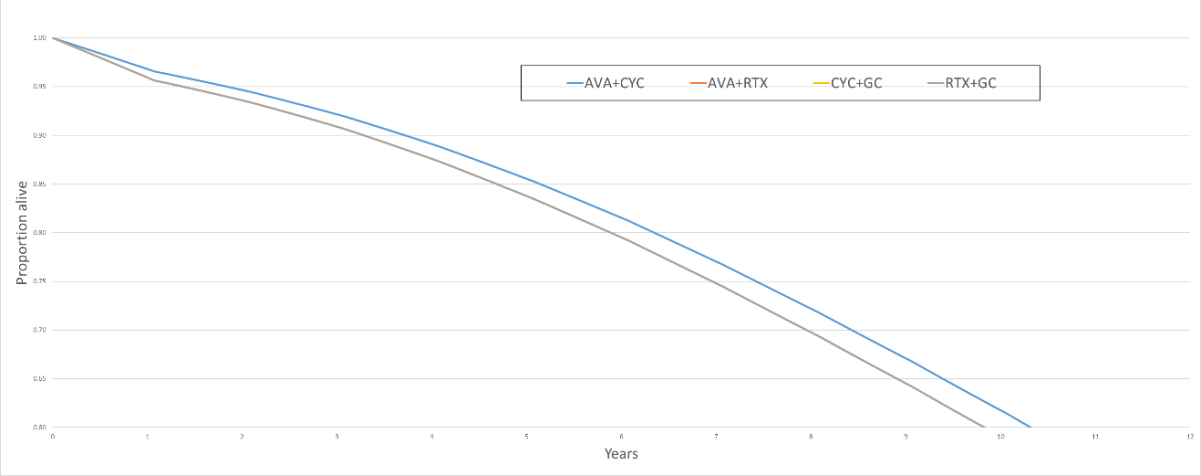


Figure 19. Survival reported in Wallace et al. Semin Arthritis Rheum 2016;45(4):483-9

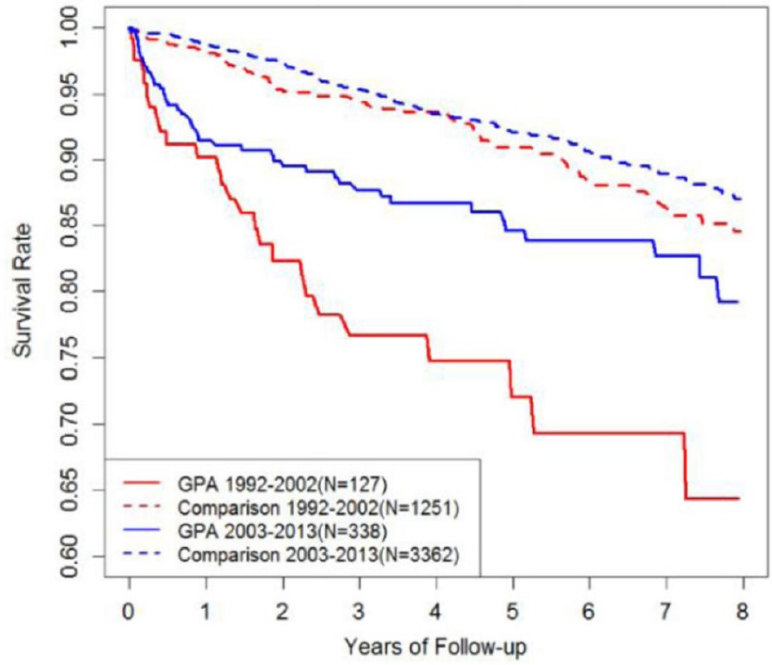
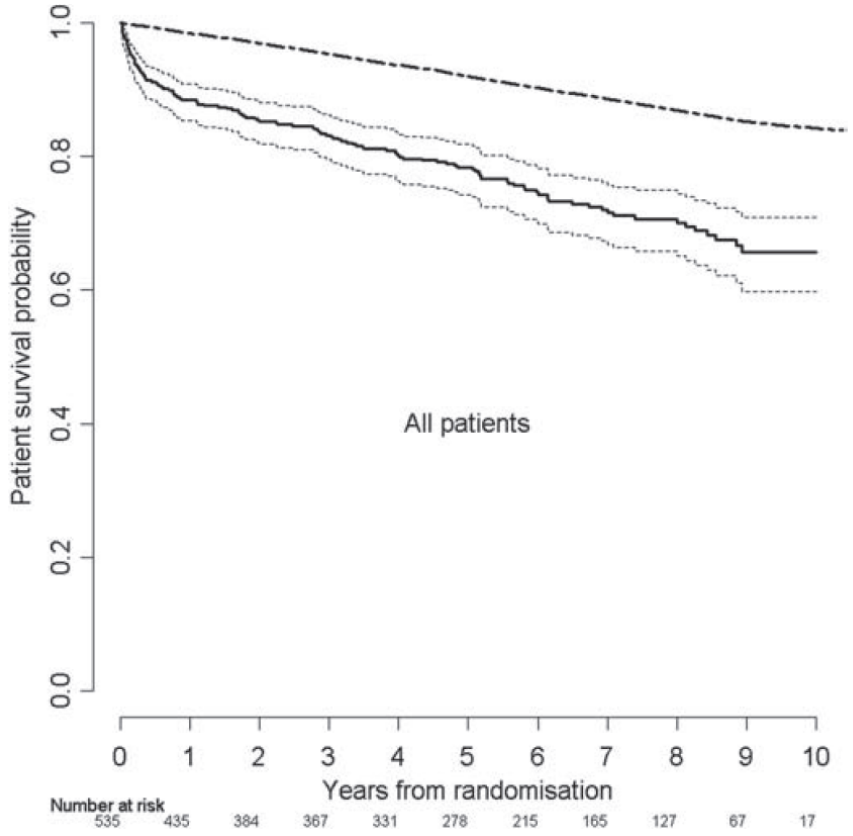


Figure 20. Overall survival reported in Flossman et al.



B.3.11 Interpretation and conclusions of economic evidence

The cost-effectiveness analysis showed that at the PAS price, avacopan in combination with RTX or CYC is expected to be a cost-effective strategy for the treatment of AAV, compared to CYC or RTX in combination with GCs. In the base case analysis, the ICER was £18,537 per QALY gained. The treatment strategy with avacopan was expected to have a higher cost (£[redacted]) and generate more QALYs ([redacted]) and life-years ([redacted]) over a patient's lifetime. The cost of adding avacopan to the standard of care for the induction of remission in AAV was partially offset by downstream cost savings from reduced healthcare management costs, in particular the cost of maintenance dialysis and renal transplant to treat ESRD. Avacopan was also associated with a benefit in terms of life-years and QALYs gained from slowing down progression to ESRD and avoiding the harmful effects of glucocorticoid therapy. The model results were shown to be robust in sensitivity and scenario

analyses. Parameters and assumptions associated with the probability of ESRD had the largest impact on model uncertainty.

The systematic literature review did not identify any previously published economic evaluations of avacopan in AAV. The de novo economic analysis presented here adds new information to support the use of avacopan in addition to the recommended standard of care for the treatment of AAV in the UK.

The population of the economic evaluation is consistent with the population identified in the decision problem, which includes all patients with AAV. The model was informed by data from the ADVOCATE trial, which recruited both newly diagnosed and relapsing patients. The trial was not restricted by induction treatment, and included patients with CYC or RTX induction treatment, which is representative of clinical practice in England. The cost-effectiveness analysis results were reported for subgroups of interest which were pre-specified in the ADVOCATE trial. The cost-effectiveness analysis results based on strata of the ITT population were subject to uncertainty due to the reduced sample size, but the trial randomisation was assumed to be preserved across all subgroups.

The model structure was broadly based on the structure used in the NICE Technology Appraisal for RTX in combination with GCs for treating AAV (TA308) (8). Several improvements to the model structure were made based on the feedback from the ERG in TA308 in order to better represent the treatment pathway in AAV. The health consequences and costs of ESRD were explicitly included in the model as a separate health state. A novel approach for modelling the decrease in renal function was applied based on published literature and clinical expert opinion. This allowed the model to capture the long-term benefits of preserving renal function by preventing relapse of AAV.

Clinical inputs which were key to assessing the cost-effectiveness of avacopan were identified from the ADVOCATE trial, where possible, enhancing the validity of the model results. This includes estimates of the treatment effect of avacopan in terms of reducing relapse and improvement in eGFR at week 26 and 52. The treatment effect

of avacopan beyond the horizon of the ADVOCATE trial was limited to 3 months based on advice from clinical experts, which represents a conservative assumption.

The cost-effectiveness analysis relied on assumptions for some of the model parameters in the absence of published data, which contributed to model uncertainty. The extrapolation of renal function and probability of ESRD was based on an assumed reduction in eGFR of 10ml/min for each relapse, which was based on clinical expert opinion. This corresponds to a 2.9-fold increase in the hazard rate of ESRD. This assumption was deemed to be appropriate and sufficiently conservative, given that previous observational studies have reported a 9-fold increase in the risk of ESRD for relapsing patients (102). This parameter value was tested in scenario analyses.

Given the significant impact of ESRD on survival, QoL, and cost of treatment, further evidence of the impact of AAV relapse on ESRD using observational studies and real-world registries could reduce the uncertainty around these parameters values and, subsequently, reduce the uncertainty in the cost-effectiveness analysis.

B.4 References

1. Bekker P, Dairaghi D, Seitz L, Leleti M, Wang Y, Ertl L, et al. Characterization of pharmacologic and pharmacokinetic properties of CCX168, a potent and selective orally administered complement 5a receptor inhibitor, based on preclinical evaluation and randomized phase 1 clinical study. PLoS One. 2016;11(10):e0164646.

2. ChemoCentryx. Clinical study report. 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. 2020.

3. Jayne DRW, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol. 2007;18(7):2180-8.

4. Jayne DRW, Bruchfeld AN, Harper L, Schaier M, Venning MC, Hamilton P, et al. Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis. J Am Soc Nephrol. 2017;28(9):2756-67.

5. McKinney EF, Willcocks LC, Broecker V, Smith KG. The immunopathology of ANCA-associated vasculitis. Semin Immunopathol. 2014;36(4):461-78.

6. Kitching AR, Anders HJ, Basu N, Brouwer E, Gordon J, Jayne DR, et al. ANCA-associated vasculitis. Nat Rev Dis Primers. 2020;6(1):71.

7. Ntatsaki E, Carruthers D, Chakravarty K, D'Cruz D, Harper L, Jayne D, et al. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology (Oxford). 2014;53(12):2306-9.

8. NICE. Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis. Technology appraisal guidance [TA308] 2014 [Available from: https://www.nice.org.uk/Guidance/TA308].

9. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med. 2013;369(5):417-27.

10. Flossmann O, Berden A, de Groot K, Hagen C, Harper L, Heijl C, et al. Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis. 2011;70(3):488-94.

11. Little MA, Nightingale P, Verburgh CA, Hauser T, De Groot K, Savage C, et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. Ann Rheum Dis. 2010;69(6):1036-43.

12. Yates M, Watts R. ANCA-associated vasculitis. Clin Med (London). 2017;17(1):60.

13. Falk RJ, Hogan S, Carey TS, Jennette JC. Clinical course of anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and systemic vasculitis. The Glomerular Disease Collaborative Network. Ann Intern Med. 1990;113(9):656-63.

14. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med. 1992;116(6):488-98.

15. Jennette JC, Falk RJ. Small-vessel vasculitis. N Engl J Med. 1997;337(21):1512-23.

16. Jayne D. The diagnosis of vasculitis. Best Pract Res Clin Rheumatol. 2009;23(3):445-53.

17. Seo P, Stone JH. The antineutrophil cytoplasmic antibody-associated vasculitides. Am J Med. 2004;117(1):39-50.

18. Rowaiye OO, Kusztal M, Klinger M. The kidneys and ANCA-associated vasculitis: from pathogenesis to diagnosis. Clin Kidney J. 2015;8(8):343-50.

19. Corral-Gudino L, Borao-Cengotita-Bengoa M, Del Pino-Montes J, Lerma-Márquez JL. Overall survival, renal survival and relapse in patients with microscopic polyangiitis: a systematic review of current evidence. Rheumatology (Oxford). 2011;50(8):1414-23.

20. Englund M, Merkel PA, Tomasson G, Segelmark M, Mohammad AJ. Comorbidities in patients with antineutrophil cytoplasmic antibody-associated vasculitis versus the general population. J Rheumatol. 2016;43(8):1553-8.

21. Jayne D. Evidence-based treatment of systemic vasculitis. Rheumatology (Oxford). 2000;39(6):585-95.

22. Koldingsnes W, Nossent H. Predictors of survival and organ damage in Wegener's granulomatosis. Rheumatology (Oxford). 2002;41(5):572-81.

23. Berti A, Felicetti M, Monti S, Ortolan A, Padoan R, Brunori G, et al. Disease and treatment-related morbidity in young and elderly patients with granulomatosis with polyangiitis and microscopic polyangiitis. Semin Arthritis Rheum. 2020;50(6):1441-8.

24. Qasim A, Patel J. ANCA positive vasculitis. StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2021.

25. Novick TK, Chen M, Scott J, Cortazar FB, Ayoub I, Little MA, et al. Patient outcomes in renal-limited antineutrophil cytoplasmic antibody vasculitis with inactive histology. Kidney Int Rep. 2018;3(3):671-6.

26. Stone JH. Limited versus severe Wegener's granulomatosis: baseline data on patients in the Wegener's granulomatosis etanercept trial. Arthritis Rheum. 2003;48(8):2299-309.

27. Liu LJ, Chen M, Yu F, Zhao MH, Wang HY. Evaluation of a new algorithm in classification of systemic vasculitis. Rheumatology (Oxford). 2008;47(5):708-12.

28. Watts RA, Scott DG, Jayne DR, Ito-Ihara T, Muso E, Fujimoto S, et al. Renal vasculitis in Japan and the UK--are there differences in epidemiology and clinical phenotype? Nephrol Dial Transplant. 2008;23(12):3928-31.

29. O'Donnell JL, Stevanovic VR, Frampton C, Stamp LK, Chapman PT. Wegener's granulomatosis in New Zealand: evidence for a latitude-dependent incidence gradient. Intern Med J. 2007;37(4):242-6.

30. Watts RA, Gonzalez-Gay MA, Lane SE, Garcia-Porrua C, Bentham G, Scott DG. Geoepidemiology of systemic vasculitis: comparison of the incidence in two regions of Europe. Ann Rheum Dis. 2001;60(2):170-2.

31. Cao Y, Schmitz JL, Yang J, Hogan SL, Bunch D, Hu Y, et al. DRB1*15 allele is a risk factor for PR3-ANCA disease in African Americans. J Am Soc Nephrol. 2011;22(6):1161-7.

32. Mahr A, Specks U, Jayne D. Subclassifying ANCA-associated vasculitis: a unifying view of disease spectrum. Rheumatology (Oxford). 2019;58(10):1707-9.

33. Watts RA, Mooney J, Skinner J, Scott DGI, Macgregor AJ. The contrasting epidemiology of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis. Rheumatology (Oxford). 2012;51(5):926-31.

34. Lyons PA, Rayner TF, Trivedi S, Holle JU, Watts RA, Jayne DR, et al. Genetically distinct subsets within ANCA-associated vasculitis. N Engl J Med. 2012;367(3):214-23.

35. Weng CH, Liu ZC. Drug-induced anti-neutrophil cytoplasmic antibody-associated vasculitis. Chin Med J (Engl). 2019;132(23):2848-55.

36. Willeke P, Schlüter B, Sauerland C, Becker H, Reuter S, Jacobi A, et al. Farm exposure as a differential risk factor in ANCA-associated vasculitis. PLoS One. 2015;10(9):e0137196.

37. Xiao H, Hu P, Falk RJ, Jennette JC. Overview of the pathogenesis of ANCA-associated vasculitis. Kidney Dis (Basel). 2016;1(4):205-15.

38. Merkel PA, Jayne DR, Luqmani R, Shetty T, Close D. P2_175 Assessment of current treatment practice and unmet clinical needs in ANCA associated vasculitis. Rheumatology (Oxford). 2017;56((Suppl 3)):iii164.

39. Xie G, Roshandel D, Sherva R, Monach PA, Lu EY, Kung T, et al. Association of granulomatosis with polyangiitis (Wegener's) with HLA-DPB1*04 and SEMA6A gene variants: evidence from genome-wide analysis. Arthritis Rheum. 2013;65(9):2457-68.

40. Scott J, Hartnett J, Mockler D, Little MA. Environmental risk factors associated with ANCA associated vasculitis: a systematic mapping review. Autoimmun Rev. 2020;19(11):102660.

41. Houben E, Groenland SL, van der Heijden JW, Voskuyl AE, Doodeman HJ, Penne EL. Relation between duration of the prodromal phase and renal damage in ANCA-associated vasculitis. BMC Nephrol. 2017;18(1):378.

42. Rutherford P, Goette D, Stamm M, Liu X. Abstract number: 2724. Variable Response to Induction Therapy and Significant Burden of Treatment Adverse Events over the First 12 Months in Incident ANCA-Associated Vasculitis (AAV) Patients – a

Study of Routine Clinical Practice in the EU. 2018 American College of Rheumatology Annual Meeting; Chicago, IL.

43. Watts RA, Mahr A, Mohammad AJ, Gatenby P, Basu N, Flores-Suárez LF. Classification, epidemiology and clinical subgrouping of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Nephrol Dial Transplant. 2015;30(Suppl 1):i14-22.

44. Jennette JC, Nachman PH. ANCA glomerulonephritis and vasculitis. Clin J Am Soc Nephrol. 2017;12(10):1680-91.

45. Furuta S, Jayne DR. Antineutrophil cytoplasm antibody-associated vasculitis: recent developments. Kidney Int. 2013;84(2):244-9.

46. Halbwachs L, Lesavre P. Endothelium-neutrophil interactions in ANCA-associated diseases. J Am Soc Nephrol. 2012;23(9):1449-61.

47. Kettritz R. Vasculitis: a CLEAR argument for targeting complement in ANCA vasculitis. Nat Rev Nephrol. 2017;13(8):448-50.

48. Basu N, McClean A, Harper L, Amft EN, Dhaun N, Luqmani RA, et al. The characterisation and determinants of quality of life in ANCA associated vasculitis. Ann Rheum Dis. 2014;73(1):207-11.

49. Hirahara S, Katsumata Y, Harigai M, Kawaguchi Y, Yamanaka H. AB0571 A cross-sectional study of health-related quality of life assessed by the SF-36 and the EQ-5D-5l in patients with ANCA-associated vasculitis. Ann Rheum Dis. 2016;75(Suppl 2):1099-100.

50. Tomasson G, Boers M, Walsh M, LaValley M, Cuthbertson D, Carette S, et al. Assessment of health-related quality of life as an outcome measure in granulomatosis with polyangiitis (Wegener's). Arthritis Care Res. 2012;64(2):273-9.

51. Brezinova P, Englbrecht M, Lovric S, Samann A, Strauss B, Wolf G, et al. Coping strategies and depressiveness in primary systemic vasculitis--what is their impact on health-related quality of life? Rheumatology (Oxford). 2013;52(10):1856-64.

52. Benarous L, Terrier B, Laborde-Casterot H, Berezne A, Dunogue B, Cohen P, et al. Employment, work disability and quality of life in patients with ANCA-associated vasculitides. The EXPOVAS study. Clin Exp Rheumatol. 2017(1 Suppl 103):S40-S6.

53. Carpenter DM, Thorpe CT, Lewis M, Devellis RF, Hogan SL. Health-related quality of life for patients with vasculitis and their spouses. Arthritis Rheum. 2009;61(2):259-65.

54. Suka M, Hayashi T, Kobayashi S, Ito S, Yumura W, Ozaki S. Improvement in health-related quality of life in MPO-ANCA-associated vasculitis patients treated with cyclophosphamide plus prednisolone: an analysis of 18 months of follow-up data from the JMAAV study. Mod Rheumatol. 2012;22(6):877-84.

55. Tomasson G, Boers M, Walsh M, Cuthbertson D, Carette S, Davis JC, et al. Measurement of health-related quality of life among patients with ANCA-AAV using the SF-36. Clin Exp Immunol. 2011;164(S1):83-4.

56. Hinojosa-Azaola A, Jimenez-Gonzalez A, Alcocer-Castillejos N. Patient and physician perspectives on the impact of health-related quality of life in Mexican patients with ANCA-associated vasculitis. Rheumatol Int. 2018;38(4):631-40.

57. McClean A, Basu N, Jones D, Morgan M, Bosch J, Harper L. Severe fatigue and psychological morbidity in ANCA-associated vasculitis. Presse Medicale. 2013;42(4 Pt 2):749-50.

58. Rutherford P, Götte D. Anti-neutrophil cytoplasmic autoantibody-associated vasculitis: from diagnosis to outcomes. EMJ Nephrol. 2020;8(Suppl 4):2-16.

59. O'Malley L, Druce KL, Chanouzas D, Morgan MD, Jones R, Jayne DRW, et al. The longitudinal course of fatigue in antineutrophil cytoplasmic antibody-associated vasculitis. J Rheumatol. 2020;47(4):572-9.

60. Herlyn K, Hellmich B, Seo P, Merkel PA. Patient-reported outcome assessment in vasculitis may provide important data and a unique perspective. Arthritis Care Res (Hoboken). 2010;62(11):1639-45.

61. NHS. Clinical Commissioning Policy: Rituximab for the treatment of ANCA-associated vasculitis in adults. London, United Kingdom: National Health Service England; 2015.

62. Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis. 2016;75(9):1583-94.

63. Langford CA. Cyclophosphamide as induction therapy for Wegener's granulomatosis and microscopic polyangiitis. Clin Exp Immunol. 2011;164(Suppl 1):31-4.

64. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363(3):221-32.

65. Jayne DRW, Merkel PA, Schall TJ, Bekker P. Avacopan for the treatment of ANCA-associated vasculitis. N Engl J Med. 2021;384(7):599-609.

66. Faurschou M, Ahlström MG, Lindhardsen J, Baslund B, Obel N. Impact of pre-existing co-morbidities on mortality in granulomatosis with polyangiitis: a cohort study. Rheumatology (Oxford). 2016;55(4):649-53.

67. Mourguet M, Chauveau D, Faguer S, Ruidavets JB, Béjot Y, Ribes D, et al. Increased ischemic stroke, acute coronary artery disease and mortality in patients with granulomatosis with polyangiitis and microscopic polyangiitis. J Autoimmun. 2019;96:134-41.

68. Suppiah R, Judge A, Batra R, Flossmann O, Harper L, Höglund P, et al. A model to predict cardiovascular events in patients with newly diagnosed Wegener's

granulomatosis and microscopic polyangiitis. Arthritis Care Res (Hoboken). 2011;63(4):588-96.

69. Tan JA, Dehghan N, Chen W, Xie H, Esdaile JM, Avina-Zubieta JA. Mortality in ANCA-associated vasculitis: ameta-analysis of observational studies. Ann Rheum Dis. 2017;76(9):1566-74.

70. Luqmani R, Suppiah R, Edwards CJ, Phillip R, Maskell J, Culliford D, et al. Mortality in Wegener's granulomatosis: a bimodal pattern. Rheumatology (Oxford). 2011;50(4):697-702.

71. Grayson PC, Cuthbertson D, Carette S, Hoffman GS, Khalidi NA, Koening CL, et al. New features of disease after diagnosis in 6 forms of systemic vasculitis. J Rheumatol. 2013;40(11):1905-12.

72. Booth AD, Almond MK, Burns A, Ellis P, Gaskin G, Neild GH, et al. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. Am J Kidney Dis. 2003;41(4):776-84.

73. Faurschou M, Westman K, Rasmussen N, de Groot K, Flossmann O, Höglund P, et al. Brief Report: long-term outcome of a randomized clinical trial comparing methotrexate to cyclophosphamide for remission induction in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2012;64(10):3472-7.

74. Harper L, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. Ann Rheum Dis. 2012;71(6):955-60.

75. Karras A, Pagnoux C, Haubitz M, Groot Kd, Puechal X, Tervaert JWC, et al. Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. Ann Rheum Dis. 2017;76(10):1662.

76. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaître O, Cohen P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014;371(19):1771-80.

77. Walsh M, Merkel PA, Mahr A, Jayne D. Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody–associated vasculitis: A meta-analysis. Arthritis Care Res (Hoboken). 2010;62(8):1166-73.

78. Turnbull J, Harper L. Adverse effects of therapy for ANCA-associated vasculitis. Best Pract Res Clin Rheumatol. 2009;23(3):391-401.

79. Jayne D, Potarca A, Schall T, Hilson J, Becker P. FP167 Adverse events with glucocorticoid standard of care versus avacopan in anca-associated vasculitis: observations from the CLEAR trial. Nephrol Dial Transplant. 2018;33(Suppl 1):i85-i6.

80. King C, Harper L. Avoidance of harm from treatment for ANCA-associated vasculitis. Curr Treatm Opt Rheumatol. 2017;3(4):230-43.

81. Hellmich B, Geetha D, Goette D, Priyanka K, Nagaraj K, Rutherford PA. Adverse events due to glucocorticoids in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis are frequent and often severe: a systematic review.

82. Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Höglund P, et al. Damage in the anca-associated vasculitides: long-term data from the European Vasculitis Study group (EUVAS) therapeutic trials. Ann Rheum Dis. 2015;74(1):177-84.

83. R H, R L, G C, P A. Could anti-CD20 therapy jeopardise the efficacy of a SARS-CoV-2 vaccine? European journal of cancer (Oxford, England : 1990). 2020;136.

84. Chilimuri S, Department of Medicine BHS, Bronx, NY, USA, Mantri N, Department of Medicine BHS, Bronx, NY, USA, Zahid M, Department of Medicine BHS, Bronx, NY, USA, et al. COVID-19 vaccine failure in a patient on rituximab therapy. Rheumatology Advances in Practice. 2021;5(2).

85. Bonelli M, Mrak D, Perkmann T, Haslacher S, Aletaha D. SARS-CoV-2 vaccination in rituximab-treated patients: evidence for impaired humoral but inducible cellular immune response. 2021.

86. Spiera S, Jinich S, Jannat-Khah D. Rituximab, but not other antirheumatic therapies, is associated with impaired serological response to SARS- CoV-2 vaccination in patients with rheumatic diseases. 2021.

87. ChemoCentryx. Clinical study report. 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. 2016.

88. Merkel PA, Niles J, Jimenez R, Spiera RF, Rovin BH, Bomback A, et al. Adjunctive treatment with avacopan, an oral C5a receptor inhibitor, in patients with antineutrophil cytoplasmic antibody–associated vasculitis. ACR Open Rheumatol. 2020;2(11):662-71.

89. ChemoCentryx. Clinical study report. 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. 2016.

90. Ehlers L, Wiebe E, Freier D, Hermann S, Miloslavsky E, Zhang Y, et al. AB1310 Prospective use of the Glucocorticoid Toxicity Index (GTI) in a cohort of vasculitis patients. Ann Rheum Dis. 2019;78(Suppl 2):2117-8.

91. Smith R, Jayne D, Merkel P. A randomized, controlled trial of rituximab versus azathioprine after induction of remission with rituximab for patients with ANCA-associated vasculitis and relapsing disease. 2019 ACR/ARTP Annual Meeting2019.

92. Charles P, Terrier B, Perrodeau E, Cohen P, Faguer S, Huart A, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis. 2018(77):1144-50.

93. Rutherford P, Goette D, Stamm M, Liu X. Real world experience in ANCA-associated vasculitis (AAV) – a complex pathway of patient referral, diagnosis and management. 2018 American Society of Nephrology Kidney Week; San Diego, CA.

94. Puéchal X, Pagnoux C, Perrodeau É, Hamidou M, Boffa JJ, Kyndt X, et al. Long-term outcomes among participants in the WEGENT trial of remission-maintenance therapy for granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis. Arthritis Rheumatol. 2016;68(3):690-701.

95. Charles P, Perrodeau É, Samson M, Bonnotte B, Néel A, Agard C, et al. Long-term rituximab use to maintain remission of antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med. 2020;173(3):179-87.

96. Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Höglund P, et al. Glucocorticoid treatment and damage in the anti-neutrophil cytoplasm antibody-associated vasculitides: long-term data from the European Vasculitis Study Group trials. Rheumatology (Oxford). 2015;54(3):471-81.

97. Montante A, Le Bras A, Pagnoux C, Perrodeau E, Ravaud P, Terrier B, et al. Cost-effectiveness of rituximab versus azathioprine for maintenance treatment in antineutrophil cytoplasmic antibody-associated vasculitis. Clin Exp Rheumatol. 2019;37(2 suppl 117):137-43.

98. Harland D, Naisbett-Groet, B., Chang, S., Sungher, D. K., Sawyer, L., Diamantopoulos, A. Mabthera (rituximab) for the treatment of severe granulomatosis with polyangiitis (Gpa) and microscopic polyangiitis (Mpa)--a cost-utility model for the United Kingdom. Value Health. 2014;17(7):A382.

99. Scottish Medicines Consortium (SMC). Rituximab (MabThera®) in combination with glucocorticoids for the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) 2013 [Available from: https://www.scottishmedicines.org.uk/medicines-advice/rituximab-mabthera-fullsubmission-89413/.

100. National Institute for Health and Care Excellence (NICE). Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis 2014 [Available from: https://www.nice.org.uk/guidance/ta308.

101. PHMR. An Investigation of the Adverse Outcomes and Resource Use Associated with Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis (AAV) in England and Their Relationship with Glucocorticoid (GC) Treatment: A Clinical Practice Research Datalink. London, UK: PHMR Ltd.; 2019.

102. Wester Trejo MAC, Floßmann O, Westman KW, Höglund P, Hagen EC, Walsh M, et al. Renal relapse in antineutrophil cytoplasmic autoantibody-associated vasculitis: unpredictable, but predictive of renal outcome. Rheumatology (Oxford). 2019;58(1):103-9.

103. Gercik O, Bilgin E, Solmaz D, Cakalagaoglu F, Saglam A, Aybi O, et al. Histopathological subgrouping versus renal risk score for the prediction of end-stage renal disease in ANCA-associated vasculitis. Ann Rheum Dis. 2020;79(5):675-6.

104. ONS. National life tables, UK: 2015 to 2017. London, UK: Office for National Statistics; 2018.

105. Wallace ZS, Lu N, Unizony S, Stone JH, Choi HK. Improved survival in granulomatosis with polyangiitis: a general population-based study. Semin Arthritis Rheum. 2016;45(4):483-9.

106. Jayne D. Treating vasculitis with conventional immunosuppressive agents. Cleve Clin J Med. 2012;79(suppl 2):S46-S9.

107. Choi H, Kim M, Kim H, Pyo Lee J, Lee J, Tak Park J, et al. Excess mortality among patients on dialysis: comparison with the general population in Korea. Kidney Res Clin Pract. 2014;33(22):89-94.

108. McGregor JG, Hogan SL, Hu Y, Jennette CE, Falk RJ, Nachman PH. Glucocorticoids and relapse and infection rates in anti-neutrophil cytoplasmic antibody disease. Clin J Am Soc Nephrol. 2012;7(2):240-7.

109. Manson SC, Brown RE, Cerulli A, Vidaurre CF. The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. Respir Med. 2009;103(7):975-94.

110. Ware JEJ, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.

111. EuroQol Group. EQ-5D User Guides 2019 [Available from: [Available from: https://euroqol.org/publications/user-guides/].

112. van Hout B, Janssen MF, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.

113. Cazzador D, Padoan R, Colangeli R, Pendolino AL, Felicetti M, Zanoletti E, et al. Health-related quality of life in patients with ANCA-associated vasculitis and sinonasal involvement: a single-center cross-sectional study. J Clin Rheumatol. 2020.

114. Ara R, Brazier J. Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). Value in Health. 2008;11(7):1131-34.

115. NICE. Patiromer for treating hyperkalaemia [Available from: https://www.nice.org.uk/guidance/ta623/resources/patiromer-for-treating-hyperkalaemia-pdf-82609015577029].

116. UK Renal Registry. 20th Annual Report of the Renal Association. Nephron. 2018;139(suppl 1):1-372.

117. Lee AJ, Morgan CLI, Conway P, Currie CJ. Characterisation and comparison of health-related quality of life for patients with renal failure. Curr Med Res Opin. 2005;21(11):1777-83.

118. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value Health. 2011;14(4):539-45.

119. Sullivan PW, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. Med Decis Making. 2006;26(4):410-20.

120. NICE. Bisphosphonates for treating osteoporosis. Technology appraisal guidance [Available from: https://www.nice.org.uk/guidance/ta464/resources/bisphosphonates-for-treating-osteoporosis-pdf-82604905556677].

121. Lansingh VC, Carter MJ. Use of Global Visual Acuity Data in a time trade-off approach to calculate the cost utility of cataract surgery. Arch Ophthalmol. 2009;127(9):1183-93.

122. NHS. Reference costs 2017/18. London, UK: National Health Service; 2018.

123. NHS. 2019/20 National cost collection data 2020 [Available from: https://www.england.nhs.uk/national-cost-collection/.

124. Leahy TP, Ramagopalan S, Sammon C. The use of UK primary care databases in health technology assessments carried out by the National Institute for health and care excellence (NICE). BMC health services research. 2020;20(1):1-9.

125. Kent S, Schlackow I, Lozano-Kühne J, Reith C, Emberson J, Haynes R, et al. What is the impact of chronic kidney disease stage and cardiovascular disease on the annual cost of hospital care in moderate-to-severe kidney disease? BMC Nephrol. 2015;16(1):65.

126. Walker S, Asaria M, Manca A, Palmer S, Gale CP, Shah AD, et al. Long-term healthcare use and costs in patients with stable coronary artery disease: a population-based cohort using linked health records (CALIBER). Eur Heart J Qual Care Clin Outcomes. 2016;2(2):125-40.

127. Patel A, Berdunov V, Quayyum Z, King D, Knapp M, Wittenberg R. Estimated societal costs of stroke in the UK based on a discrete event simulation. Age Ageing. 2020;49(2):270-6.

128. NICE. Hypertension in adults: diagnosis and management [Available from: https://www.nice.org.uk/guidance/ng136].

129. NICE. Cataracts in adults: management [Available from: https://www.nice.org.uk/guidance/ng77].

130. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: an EQ-5D-5L value set for England. Health Econ. 2018;27(1):7-22.

131. Goceroglu A, Berden AE, Fiocco M, Flossmann O, Westman KW, Ferrario F, et al. ANCA-associated glomerulonephritis: risk factors for renal relapse. PLoS One. 2016;11(12):e0165402.

132. DM E, W H, JJ C, J T, KM M, JB W. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. Medical decision making : an international journal of the Society for Medical Decision Making. 2012;32(5).

133. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Medicine. 2009;151(4):264-9.

134. NICE. Guide to the methods of technology appraisal 2013 [Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781.

135. NICE. Single technology appraisal: User guide for company

evidence submission template 2017 [Available from: https://www.nice.org.uk/guidance/pmg24/resources/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pdf-72286715419333.

136. CRD. Systematic reviews: CRD's guidance for undertaking systematic reviews in health care York, UK: University of York; 2009 [Available from: https://www.york.ac.uk/crd/SysRev/!SSL!/WebHelp/SysRev3.htm].

137. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 Chichester, UK: Cochrane; 2019 [Available from: https://training.cochrane.org/handbook/archive/v6].

138. NICE. Appendix H Appraisal checklists, evidence tables, GRADE and economic profiles [Available from: https://www.nice.org.uk/process/pmg20/resources/appendix-h-appraisal-checklists-evidence-tables-grade-and-economic-profiles-pdf-8779777885].

139. Faurschou M, Sigaard L, Bjorner JB, Baslund B. Impaired health-related quality of life in patients treated for Wegener's granulomatosis. J Rheumatol. 2010;37(10):2081-5.

140. Srouji IA, Andrews P, Edwards C, Lund VJ. General and rhinosinusitis-related quality of life in patients with Wegener's granulomatosis. Laryngoscope. 2006;116(9):1621-5.

141. Pugnet G, Pagnoux C, Terrier B, Perrodeau E, Puéchal X, Karras A, et al. Rituximab versus azathioprine for ANCA-associated vasculitis maintenance therapy: impact on global disability and health-related quality of life. Clin Exp Rheumatol. 2016;34(3 Suppl 97):S54-9.

142. Walsh M, Mukhtyar C, Mahr A, Herlyn K, Luqmani R, Merkel PA, et al. Health-related quality of life in patients with newly diagnosed antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Care Res (Hoboken). 2011;63(7):1055-61.

143. Weiner M, Goh SM, Mohammad AJ, Hruskova Z, Tanna A, Sharp P, et al. Organ damage and hospitalization in elderly patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Rheumatology (Oxford). 2017;56(suppl 3):iii32.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avacopan for maintenance treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

Clarification questions

November 2021

File name	Version	Contains confidential information	Date
ID1581 avacopan clarification questions to PM for company AIC_021221_final	v1.0	Yes	02 Dec 2021

Section A: Clarification on effectiveness data

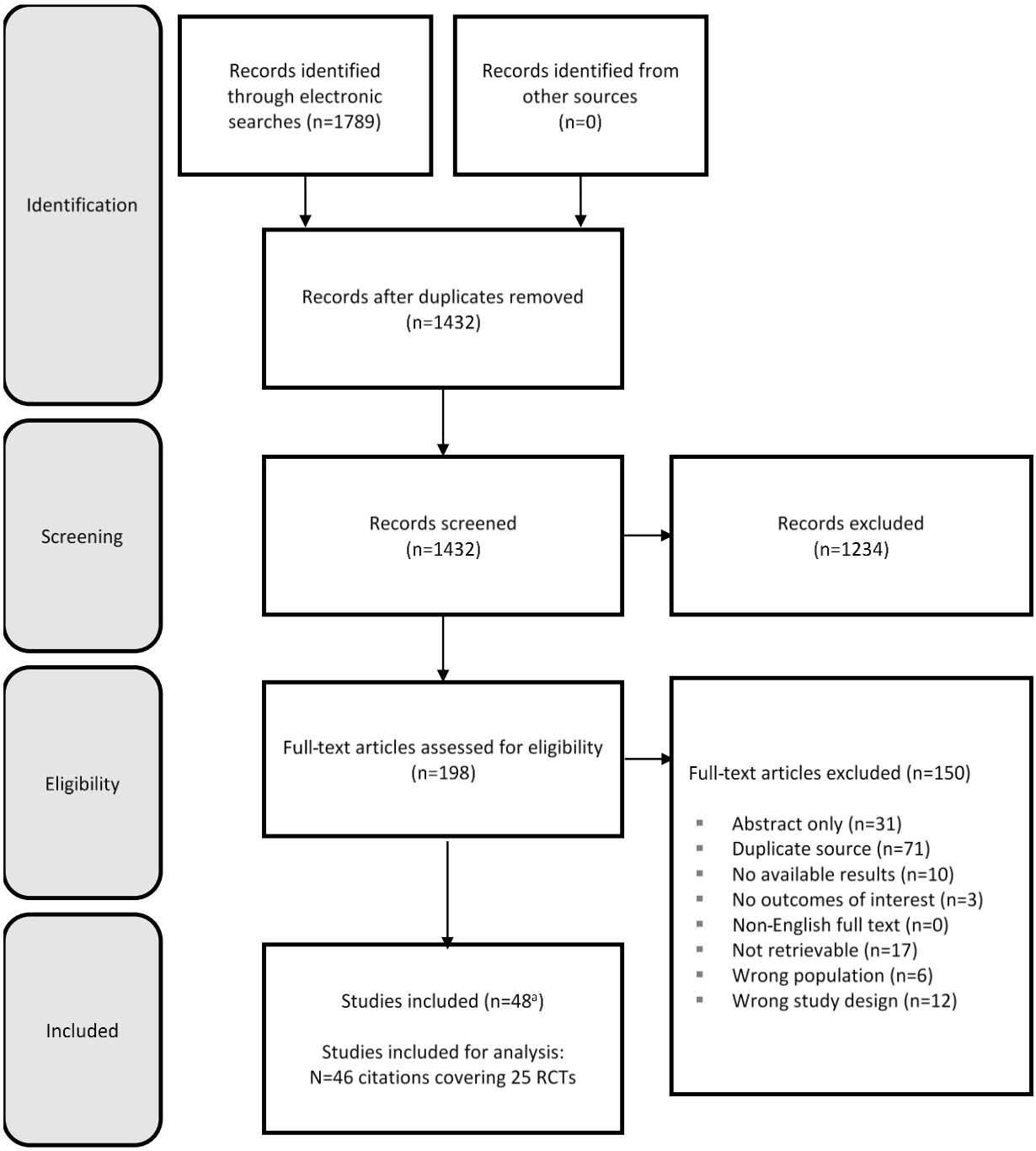
Literature searches

A1. Please provide a PRISMA flow diagram for the clinical effectiveness update searches for 2020 and 2021. Currently only the 2018 search results are presented in a flow diagram (Figure 21; App D).

RESPONSE:

The PRISMA flow diagrams for the 2018, 2020 and 2021 searches are shown in Figure 1, Figure 2, and Figure 3, respectively.

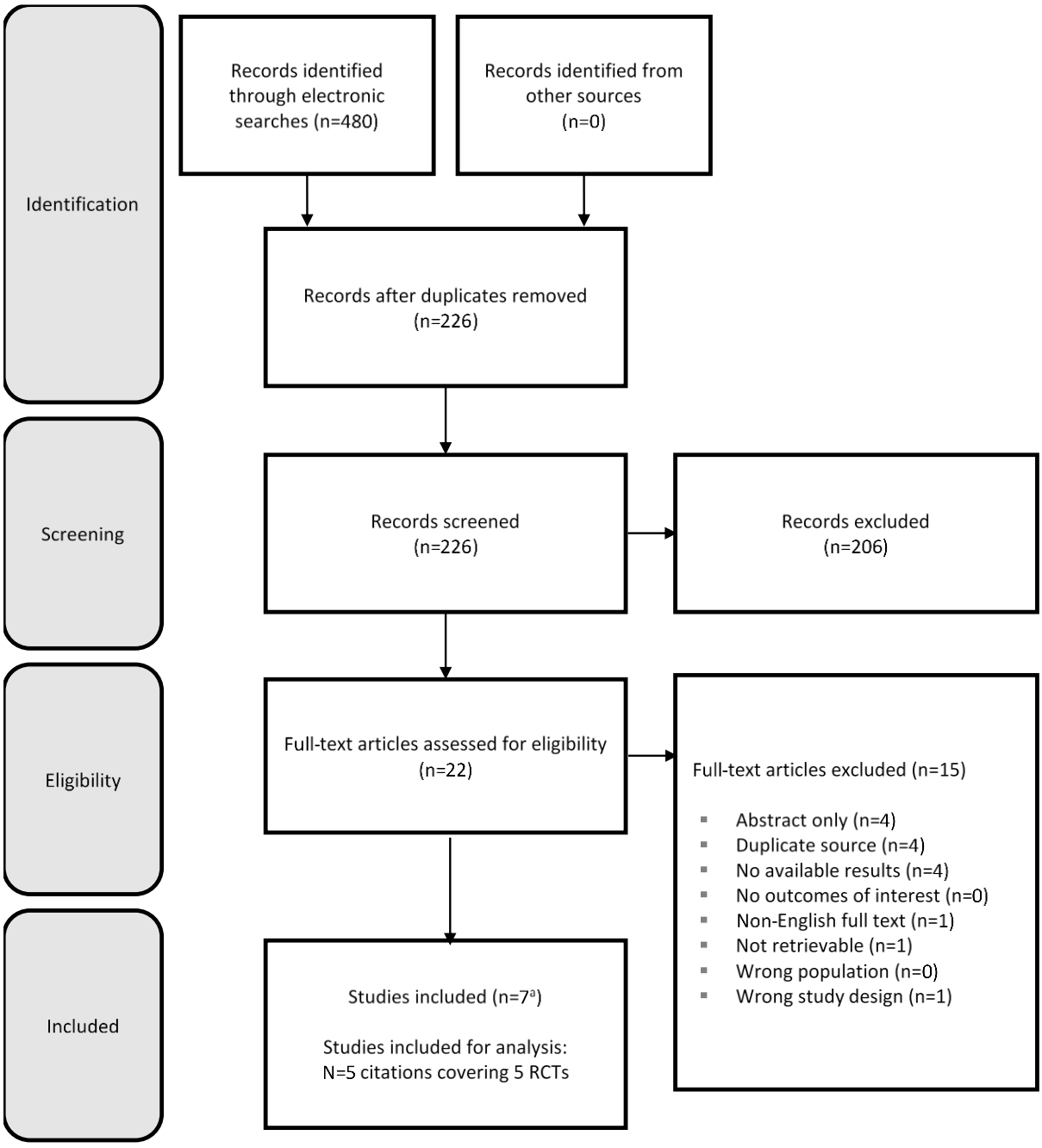
Figure 1. PRISMA flow diagram, 2018 literature search



Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT, randomised controlled trial

[a]Two studies identified by the 2018 literature search had a non-PICOS comparator as a treatment arm; therefore, data for these studies were not extracted into the data extraction table for analysis

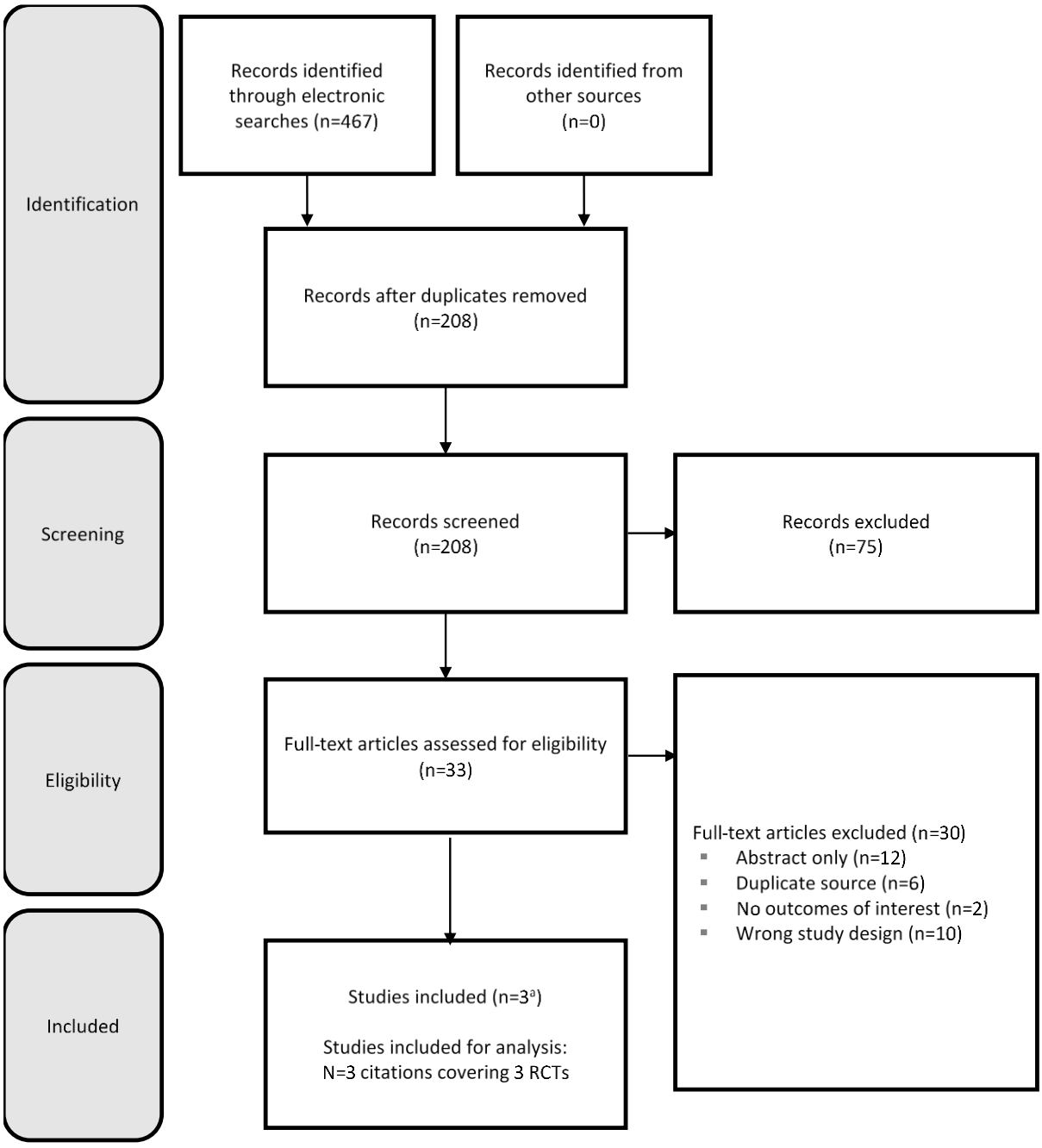
Figure 2. PRISMA flow diagram, 2020 literature search



Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT, randomised controlled trial

[a]Two studies identified by the 2020 literature search had a non-PICOS comparator as a treatment arm; therefore, data for these studies were not extracted into the data extraction table for analysis

Figure 3. PRISMA flow diagram, 2021 literature search



Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT, randomised controlled trial

[a] One study identified was the ADVOCATE trial, fully published as a peer-reviewed article. This study had been previously reported by Vifor as a clinical study report.

A2. Please provide the number of records retrieved for each of the Cochrane Library databases in the 2020 update searches. Only the total number of records is currently provided (p.7; App D).

RESPONSE:

The total number of records retrieved from the databases searched in 2018, 2020 and 2021 (before and after deduplication), including the Cochrane Library databases, are shown in Table 1.

Table 1. Total number of records found, before and after deduplication, in the 2018, 2020 and 2021 searches

Source	Records found	After deduplication
2018 Searches		
CDSR	3	3
DARE	7	7
HTAD	2	2
Medline	277	276
Embase	902	660
CENTRAL	365	326
Clinicaltrials.gov	103	103
WHO ICTRP	130	55
Total	**1,789**	**1,432**
2020 Searches		
CDSR	3	N/A
Epistemonikos	27	26
Medline	321	38
Embase	1052	134
CENTRAL	531	16
Clinicaltrials.gov	119	12
WHO ICTRP	Unavailable	N/A
Total	**2,053**	**226**
2021 Searches		
CDSR	3	1
Epistemonikos	61	33
Medline	351	21

Embase	1,185	100
CENTRAL	606	10
Clinicaltrials.gov	127	14
WHO ICTRP	187	29
Total	**2,520**	**208**
Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials (CENTRAL); CDSR, Cochrane Database of Systematic Reviews; DARE, Database of Abstracts of Reviews of Effects; HTAD, Health Technology Assessment Database; WHO-ICTRP, World Health Organisation-International Clinical Trials Registry Platform		

A3. Please confirm whether the language and date limits stated in the CS (p.2 App D) were included in the search strategies, or whether these were applied as screening criteria. If they were in the search strategies, then please provide updated strategies including the relevant search lines and results of the limits.

RESPONSE:

No language or date limits were applied to the clinical systematic literature review (SLR) searches. Non-English language studies were excluded during screening.

A4. Please confirm whether the NHSEED database was searched for the HRQoL and the Cost and healthcare resource identification searches (as stated on p. 2; App H, and p.2; App I). If so, please provide the search strategies used for this database.

RESPONSE:

The NHS Economic Evaluations Database (NHSEED) was searched for the economic evaluations review but not for the HRQoL or the cost and healthcare resource utilisation reviews.

A5. Please provide details of the HRQoL Embase search conducted on 17 June 2021. The strategy provided on p.11 App H appears to be 16 June 2020 search strategy.

RESPONSE:

The HRQoL Embase search was as follows:

Database: Embase <1974 to 2021 Week 23>

Search Strategy:
1 ANCA associated vasculitis/ (7080)
2 (("anca associated" or anca-associated or "anti neutrophil cystoplasmic antibody" or "anti-neutrophil cystoplasmic antibody" or "pauci-immune" or pauci-immune) adj2 (vasculitis or vasculitide$)).ti,ab. (5752)
3 Wegener granulomatosis/ (13708)
4 ((wegener$ or polyangiitide$ or polyangiitis) adj2 granulomatos$).ti,ab. (11408)
5 microscopic polyangiitis/ (3444)
6 microscopic polyangiiti$.ti,ab. (3007)
7 or/1-6 (22847)
8 quality adjusted life year/ or quality of life index/ (31887)
9 Short Form 12/ or Short Form 20/ or Short Form 36/ or Short Form 8/ (39566)
10 "International Classification of Functioning, Disability and Health"/ or "Ferrans and Powers Quality of Life Index"/ (3153)
11 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (44144)
12 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (2562)
13 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab. (10262)
14 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab. (1628)
15 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab. (473)
16 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab. (1045)
17 (short form$ or shortform$).ti,ab. (50136)
18 ("European Organization for Research and Treatment of Cancer Quality of Life Questionnaire" or EORTC-QLQ).ti,ab. (9053)
19 "health related quality of life".ti,ab. (69494)
20 (Quality adjusted life or Quality-adjusted-life).ti,ab. (21641)
21 "assessment of quality of life".ti,ab. (3103)
22 (euroqol or euro qol or euroqual or euro qual or eq5d or eq 5d or eq-5d or eq5-d or eq-sdq or eqsdq).ti,ab. (23456)
23 (qol or hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab. (112242)
24 (hye or hyes).ti,ab. (142)
25 health$ year$ equivalent$.ti,ab. (42)
26 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab. (2512)
27 (quality time or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or index of well being).ti,ab. (1280)
28 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab. (5498)
29 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab. (27760)
30 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab. (13330)

31 15d.ti,ab. (2680)
32 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab. (664)
33 illness state$.ti,ab. (208)
34 (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$ or evaluat$ or scale$ or instrument$ or weight$ or information or data or unit or units or mean or cost$ or expenditure$ or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status)).ti,ab. (60161)
35 (utilities or disutili$).ti,ab. (13227)
36 (Severity Weighted Assessment Tool or SWAT or mSWAT).ti,ab. (1314)
37 (patient$ adj2 (attitude$ or compliance or "non compliance" or adheren$ or "non adherence" or participation or "non participation" or preference$ or satisf$ or dissatisf$ or toleran$ or intoleran$ or "reported outcome" or "reported outcomes")).ti,ab. (213431)
38 patient reported outcome/ or (patient reported outcome$ or (patient adj2 (outcome measure$ or outcome tool$ or outcome assess$ or outcome instrument$ or outcome questionnaire$ or outcome survey$ or outcome score$ or outcome scale$)) or PROM or PROMS).ti,ab. (54891)
39 or/8-38 (520534)
40 7 and 39 (284)
41 limit 40 to (english language and yr="1998-Current") (277)

A6. Please provide details of all searches conducted for NICE health technology appraisals (via the NICE website) for the cost-effectiveness, HRQoL and cost and healthcare resource identification literature reviews.

RESPONSE:

Health technology appraisals on the NICE website were hand-searched. No electronic searches of appraisals were conducted.

Decision Problem

A7. Priority question: The final NICE scope states that the intervention is avacopan. Table 1 of the company submission states that the intervention is avacopan in combination with SoC (i.e., CYC [Cyclophosphamide], followed by AZA[Azathioprine]/MMF[Mycophenolate mofetil], or RTX[Rituximab). In Appendix D (section D 1.1.), it is stated that glucocorticosteroids were part of the intervention.

a. **Please provide references to support the claim that CYC, followed by AZA/MMF, or RTX reflect SoC in the UK NHS setting.**

b. Please provide evidence that the SoC was similar within the intervention and control groups in the relevant trials (including the ADVOCATE trial).

RESPONSE:

a. Combination therapy with glucocorticoids (GCs) and cyclophosphamide (CYC) is currently standard therapy for remission induction (1, 2). NHS England will routinely fund the use of rituximab (RTX) for the treatment of AAV as an option for inducing remission in adults, if:

- The disease has remained active or progressed, or has relapsed, despite a course of CYC lasting 3-6 months; OR
- CYC is contraindicated (as defined in the summary of product characteristics) or not tolerated; OR
- The person has not completed their family and treatment with CYC may materially affect their fertility; OR
- The person has had uroepithelial malignancy

Where RTX is used instead of CYC, GCs are still used at standard doses but should also be used as pre-medication for RTX (1, 2).

Long-term therapy with CYC has been used to maintain remission, but the toxicity associated with this makes it an unattractive option and is not common clinical practice in the UK. As such, following induction of remission, azathioprine (AZA) or methotrexate (MTX) can be used as maintenance therapy (1). MTX should not be used in those with organ-threatening or renal disease. Mycophenolate mofetil (MMF) may be used for remission maintenance if there is intolerance to AZA (1). In addition, in patients with RTX-induced remission, remission maintenance with RTX is an option (1).

The British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) in 2014 (3) have published consensus recommendations based on varying levels of evidence to try and harmonise therapy and refine treatment strategies. These guidelines are developed using

processes which NICE have accredited and are also closely aligned with guidelines from the European League Against Rheumatism (EULAR), published in 2016 (4).

b. Avacopan, in combination with a RTX or CYC regimen, is indicated for the treatment of adult patients with severe, active GPA or MPA. In line with its indication, avacopan was administered in combination with RTX or CYC, with/without GCs, in all three trials (Table 2).

   To ensure SoC was similar within the intervention and control groups, patients were stratified by RTX/CYC use prior to randomisation in the ADVOCATE, CLEAR and CLASSIC studies.

Table 2. Treatment arms in the three avacopan trials

	Treatment arms
ADVOCATE (5, 6)	• Avacopan 30 mg twice daily plus CYC followed by AZA (N=59) or RTX (N=107) plus prednisone-matching placebo • Tapering oral regimen of prednisone plus CYC followed by AZA (N=57) or RTX (N=107) plus avacopan-matching placebo During the study, extra GC treatment, i.e., treatment that was not provided as prednisone study medication must have been avoided as much as possible. However, subjects who experienced a relapse of their AAV during the study may have been treated with IV GCs and/or oral GCs, tapered according to the subject's condition.
CLEAR (7, 8)	• Avacopan plus CYC (N=16) or RTX (N=5) plus no oral GCs • Placebo plus CYC (N=17) or RTX (N=3) plus a full starting dose of oral GCs • Avacopan plus CYC (N=17) or RTX (N=5) plus a two-thirds reduced starting dose of oral GCs
CLASSIC (9, 10)	• Avacopan 10 mg twice daily plus CYC (N=0) or RTX (N=12) plus GCs • Avacopan 30 mg twice daily plus CYC (N=2) or RTX (N=13) plus GCs • Placebo twice daily plus CYC (N=1) or RTX (N=12) plus GCs If necessary, rescue GCs were given to subjects with worsening disease.
Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; AZA, azathioprine; CYC, cyclophosphamide; GC, glucocorticoid; RTX, rituximab	

A8. The company submission states: "*In the ADVOCATE trial, over 52 weeks, GC exposure was 63% lower in the avacopan-based regimen group, with a mean cumulative GC dose during the treatment period of 1,348.9 mg for an avacopan group versus 3,654.5 mg for prednisone group driven by study design (Figure 5)*".

a. Please explain how the benefits of Avacopan were distinguished from the effects of GC.

b. Please provide results that compare Avacopan alone as the intervention (as per the final NICE scope).

RESPONSE:

The ADVOCATE study protocol envisioned the use of some GCs in both groups as a function of administration during screening and prior to randomisation; as co-administration with RTX (to prevent hypersensitivity reactions per the RTX prescribing information), and to manage adrenal insufficiency for example. During the trial, extra IV and/or oral GC treatment was administered to subjects who experienced a relapse of their AAV, tapered according to the subject's condition, which is in line with the anticipated use of avacopan in clinical practice. Such GC use was reasonably well balanced between the two groups; therefore, the benefits can be ascribed to the avacopan treatment arm and compared to the tapered GC dosing regimen in the comparator arm.

Avacopan demonstrated a true GC sparing effect. In the ADVOCATE trial, over 52 weeks, GC exposure was 63% lower in the avacopan-based regimen group, with a mean cumulative GC dose during the treatment period of 1,348.9 mg for the avacopan group versus 3,654.5 mg for the prednisone group driven by study design (6).

In the ADVOCATE trial, the use of avacopan was associated with statistically less GC-induced toxicity relative to prednisone for both scores of the Glucocorticoid Toxicity Index (GTI), a measure of side effects related to the use of GCs comprising the Cumulative Worsening Score (CWS) and the Aggregate Improvement Score (AIS). The GTI-CWS captures cumulative GC

toxicity regardless of whether it is permanent or transient. The GTI-CWS can only increase or remain the same over time; a lower score indicates lower GC toxicity. The GTI-AIS captures both worsening and improvement in GC toxicity. New or worsening toxicities contribute a positive score and improvement in existing toxicities contributes a negative score; a lower score indicates lower GC toxicity (11). In the ADVOCATE trial, the least-squares mean (LSM) for the GTI-CWS at week 13 was 36.6 in the prednisone group compared with 25.7 in the avacopan-based regimen group (p=0.0140). At week 26 GTI-CWS was 56.6 in the prednisone group and 39.7 in the avacopan group (p=0.0002). The LSM for the GTI-AIS at week 13 was 23.2 in the prednisone group compared with 9.9 in the avacopan group (p=0.003); at week 26 GTI-AIS was 23.4 in the prednisone group and 11.2 in the avacopan group (p=0.008) (5, 6).

Accordingly, in the ADVOCATE trial, the incidence of GC-related adverse events (AEs) was reduced with an avacopan-based regimen compared with prednisone-based regimen. Treatment with the avacopan-based regimen was associated with a significantly lower number of potentially GC-related AEs (based on European Alliance of Associations of Rheumatology criteria) compared with the prednisone arm (66% vs 81% of patients, respectively). A statistically significant difference was found in the endocrine/metabolic (12% vs 28%) and dermatological (7% vs 16%) systems ($p<0.05$). Metabolic effects included diabetes, Cushingoid signs (facial swelling and weight gain), and adrenal insufficiency (5, 6). These findings reinforced results from the Phase 2 CLEAR trial, which also showed a higher number of potentially GC-related AEs in patients receiving SoC compared with an avacopan-based regimen (7, 8).

a. Avacopan is intended to be used in combination regimen with RTX or CYC for the treatment of adults with severe, active GPA or MPA, as per the marketing authorisation. The study protocol envisioned the use of some GCs in both groups; as such, avacopan has not been investigated as a monotherapy.

A9. The ADVOCATE clinical study report (CSR) states: "*subjects received appropriate prophylactic therapy during the course of the study*".

a. Please provide a refined list of the concomitant medications taken by participants and the number of patients (by arm) that were on these medications (please avoid listing pharmacological group names (e.g., NSAIDs) or brand products (e.g., Advil), rather than the list of individual pharmacological agents (e.g., Ibuprofen).

b. Please provide a list of the non-protocol specified concomitant medications administered to patients during the treatment period.

c. Please clarify if the extra IV/ oral glucocorticoid treatment (not provided as prednisone study medication) was administered to patients as rescue medication and specify how many patients on each arm received rescue GCs through the treatment period.

RESPONSE:

a. The most common concomitant medication in the ADVOCATE study was combinations of sulfonamides and trimethoprim, which was a protocol-recommended preventative treatment for *Pneumocystis jirovecii* infection: 92.7% and 91.6% in the prednisone and avacopan groups, respectively (6). Concomitant medications are listed in Table 14.1.8 of the ADVOCATE CSR.

b. Non-protocol allowed concomitant medications included RTX, AZA, CYC, mycophenolate, MTX, methotrexate sodium, cyclosporine, tacrolimus, alemtuzumab, belimumab, abatacept or other immunosuppressants (6). The incidence on non-protocol concomitant medication use across all the study periods in the prednisone- and avacopan-based groups is summarised in Table 14.1.9 of the ADVOCATE CSR.

c. During the ADVOCATE study, extra GC treatment, i.e., treatment that was not provided as prednisone study medication was avoided as much as possible. However, the protocol allowed subjects who experienced a relapse of their

AAV during the study to be treated with IV GCs and/or oral GCs, tapered according to the subject's condition (5, 6).

The incidence of concomitant GC use across all the study periods in the prednisone- and avacopan-based groups is shown in Table 3.

Table 3. Concomitant glucocorticoid use was comparable between the study arms in ADVOCATE

	Prednisone-based regimen (N=164), n (%)	**Avacopan-based regimen (N=166), n (%)**
Day 1 to 29	141 (86.0)	138 (83.1)
Day 30 to 183	56 (34.1)	52 (31.3)
Day 184 to end of treatment[a]	64 (39.0)	45 (27.1)
Day 1 to 183	149 (90.9)	143 (86.1)
Day 1 to end of treatment[a]	149 (90.9)	145 (87.3)
Day 1 to end of 60-week study period	151 (92.1)	146 (88.0)
End of treatment[a] to week 60	57 (34.8)	49 (29.5)
[a] End of treatment is day 365 or early termination visit		

A10. There are three major clinicopathologic variants of autoantibody-associated vasculitis (AAVs), namely: microscopic polyangiitis (MPA); granulomatosis with polyangiitis (GPA); and eosinophilic granulomatosis with polyangiitis (EGPA). Yet, the NICE final scope does not specify MPA and GPA as the population's variants of interest. Please justify why only data for patients with these two variants were included in this submission.

RESPONSE:

AAVs are a collection of relatively rare autoimmune diseases characterised by inflammatory cell infiltration causing necrosis of blood vessels. GPA and MPA are the main forms of the disease that also carry the most severe complications, with EGPA the rarer variant, having a distinctive clinical phenotype and treatment pathway (12).

Avacopan was only studied (ADVOCATE, CLASSIC AND CLEAR) in patients with active GPA or MPA and, therefore, is only indicated, in combination with a RTX or CYC regimen, for the treatment of adult patients with severe, active GPA or MPA; EGPA is not part of the marketing authorisation for avacopan.

Trials and data analysis

A11. Priority question: The Clinical Study Report (CSR) for the ADVOCATE trial appears to be incomplete.

Please provide the complete CSR for the ADVOCATE trial.

RESPONSE:

The complete ADVOCATE trial CSR, along with supporting tables and appendices, is provided alongside our responses to the clarification questions.

A12. Priority question: The comparators section of Table 1 of the company submission lists a separate heading for maintenance treatment, suggesting that this is a subgroup of the relevant population for which avacopan is being evaluated. Yet, Patients who have reached the stage of maintenance treatment must have already responded.

a. Given that the population in the final NICE scope is restricted to newly diagnosed or relapsed, can the company please confirm that they are not considering those eligible for maintenance treatment as a separate subgroup.

b. Please confirm that the comparators listed under maintenance treatment are not relevant for the decision problem (except insofar as they are subsequent treatment to the comparators listed under remission indication should patients have remission induced and thus be eligible for maintenance treatment).

RESPONSE:

a. Maintenance treatment is warranted following induction of remission to prevent relapse (as per the NHS, BSR/BHPR and EULAR guidelines) (1-4), and is, therefore, not considered as a separate subgroup.

Once remission is achieved, avacopan treatment can be continued during the maintenance phase to prevent disease relapse.

b. Under current SoC (as per the NHS, BSR/BHPR and EULAR guidelines) (1-4), AZA or MTX can be used as maintenance therapy in patients who achieve remission with CYC. MTX should not be used in those with organ-threatening or renal disease. MMF may be used for remission maintenance if there is intolerance to AZA. In addition, in patients with RTX-induced remission, remission maintenance with RTX is an option (1-4).

   As such, the relevant comparators considered for the scope of this submission are:

   - CYC in combination with GCs, followed by AZA/MMF in combination with low-dose GCs
   - RTX in combination with GCs, followed by RTX in combination with low-dose GCs

A13. Table 1 of the company submission states: "*MTX and MMF are recommended as alternatives to CYC/AZA or RTX for remission induction in patients with localised disease at low risk of suffering organ damage. These patients were not studied in ADVOCATE and so they are not relevant comparators for avacopan*."

a. Please confirm that the population in the decision problem does not include patients with localised disease at low risk of suffering organ damage.

b. Please explain what is meant by low risk in the above quote. Is this equivalent to "non-organ-threatening disease" as stated in the NICE Scope?

c. If, on the other hand, patients with localised disease at low risk of suffering organ damage are to be included in the Decision problem, then please include an analysis with the appropriate comparators, including MTX and MMF.

RESPONSE:

a. The use of avacopan, in combination with a CYC or RTX regimen, is indicated for severe, active GPA or MPA. As such, the population in the decision problem did not include patients with localised disease at low risk of suffering organ damage, and MTX and MMF were not considered as relevant comparator treatments.

b. In the CS, severe AAV (also referred to as 'organ-threatening' disease) is defined as disease activity that threatens the function of the affected organ and has the potential to cause permanent organ damage or to threaten the patient's life unless effective therapy is implemented quickly. Non–organ-threatening disease describes patients with no evidence of organ damage.

c. Not applicable.

A14. The process for data extraction of included studies is not reported in the company submission (CS).

Please provide the details of the process, the number of reviewers involved, and how disagreements were resolved.

RESPONSE:

Data from records meeting criteria for inclusion were extracted by 1 reviewer into a focused data extraction table developed and standardised for this project. To ensure that the final data extraction table was of the highest quality, a second reviewer checked and validated the information by conducting an independent internal data check once all required data were entered to identify and rectify any errors in data extraction or data entry.

A15. Please clarify how many reviewers were involved in the quality assessment process, and how disagreements were resolved.

RESPONSE:

Quality assessment of clinical trials was performed according to the methodology outlined in the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2). The

quality assessment process was carried out by a single analyst who was required to answer specific questions for each study regarding selection, performance, attrition, and detection bias. A second analyst checked and validated the findings regarding the study quality; if a consensus could not be achieved, a third reviewer was consulted.

A16. The company submission states that 12.1% of enrolled subjects in the ADVOCATE trial were from study sites in the UK.

a. Please provide the number of UK patients randomised and publish the baseline characteristics of these patients by study arm.

b. Please discuss the generalisability of the study baseline characteristics to the general UK population.

RESPONSE:

a. A total of 40 UK patients were included in the ADVOCATE study, of which 17 received an avacopan-based regimen and 13 received a prednisone-based regimen. The demographic and baseline characteristics of the UK patients included in the ADVOCATE study are summarised in Table 11 and Table 12 (Appendix A), respectively.

   In the ADVOCATE trial ITT population, the mean age of recruited subjects was 60.9 years, with the majority between the ages of 51 and 75 years (224 subjects [67.7%]). More male subjects than female subjects were randomised to treatment and most subjects were white and not Hispanic or Latino. Most subjects enrolled in the study were newly diagnosed with AAV (69.4%) with a median duration of disease of approximately 0.2 months. The incidence of subjects with GPA was higher than those with MPA (54.8% vs 45.2%); most subjects were anti-MPO positive (57.0%), and most subjects were taking IV RTX as the SoC treatment (2, 65).

   Similarly, the mean age of the UK patients included in the ADVOCATE trial (N=40) was 57.9 years, with the majority between the ages of 51 and 75 years (30 subjects [75%]). More male subjects than female subjects were

randomised to treatment (60% vs 40%) and most subjects were white. Most UK patients enrolled in the study were newly diagnosed with AAV (72.5%); and most subjects were anti-MPO positive (52.5%). Approximately 50% of patients were taking IV RTX as the SoC treatment at baseline.

The mean baseline Birmingham Vasculitis Activity Score (BVAS) and Vasculitis Damage Index (VDI) scores of the whole ADVOCATE trial ITT population was similar to the UK patient subgroup of the ADVOVATE trial.

b. The findings of the Clinical Practice Research Datalink (CPRD) study that we conducted indicate that the baseline demographics and characteristics of the population included in the ADVOCATE trial are generalisable to the UK AAV population. The majority of AAV (MPA and GPA) patients included in the CPRD study were male (55.2%) and the mean age was 62 years (IQR: 53-73) (13).
In addition, a retrospective clinical audit of healthcare records of 300 UK AAV patients indicates a higher proportion receive CYC induction therapy but otherwise the demographic and clinical characteristics of the patients are similar to those in the ADVOCATE study (14). This provides reassurance that the findings of the ADVOCATE trial are generalisable to the treatment of people with AAV in the UK.

A17. Adverse events (AEs) data for all three relevant studies have been included in the CS.

a. Please provide the follow-up period for AE data in the ADVOCATE trial.

b. Please provide the terminology used for adverse events reporting.

c. Please provide the metric used to classify severity of treatment-emergent adverse events (TEAEs).

d. Please compare and tabulate the moderate-severity TEAEs between avacopan-based and prednisone-based treatment arms, across the CLEAR, CLASSIC, and ADVOCATE trials.

RESPONSE:

a. All AEs were monitored until resolution or, if the AE was determined to be chronic, until a cause was identified. The final scheduled AE assessment occurred at week 60, eight weeks after discontinuation of avacopan treatment.

b. AEs in the ADVOCATE trial were coded using MedDRA version 19.1, MedDRA version 17.1 in the CLASSIC trial, and MedDRA version 14.0 in the CLEAR trial.

c. An AE was considered treatment-emergent if the start date/time of the event was on or after the date/time of first dose of study medication. The severity of each AE was determined by the Investigator using the following scale:

    - Mild (Grade 1): no limitation of usual activities
    - Moderate (Grade 2): some limitation of usual activities
    - Severe (Grade 3): inability to carry out usual activities
    - Life-threatening (Grade 4): an immediate risk of death
    - Death (Grade 5)

For a summary of moderate treatment-emergent AEs (TEAEs) in the ADVOCATE trial by system organ class refer to

d. Table 4 (source: Table 14.3.1.7 of the ADVOCATE CSR).

For a summary of moderate TEAEs in the CLEAR trial by system organ class during the 84-day treatment period, refer to

Table 5 (source: Table 14.3.1.12 of the CLEAR CSR).

For a summary of moderate TEAEs in the CLASSIC trial by system organ class during the 84-day treatment period, refer to Table 6 (source: Table 14.3.1.12 of the CLASSIC CSR).

Table 4. Summary of moderate treatment-emergent adverse events by system class in the ADVOCATE trial

	Prednisone-based regimen (N=164)	**Avacopan-based regimen (N=166)**
Any moderate TEAEs	68 (41.5)	82 (49.4)
Infections and infestations	49 (29.9)	39 (23.5)
Gastrointestinal disorders	29 (17.7)	31 (18.7)
Musculoskeletal and connective tissue disorders	29 (17.7)	33 (19.9)
General disorders and administration site conditions	31 (18.9)	23 (13.9)
Skin and subcutaneous tissue disorders	21 (12.8)	15 (9.0)
Nervous system disorders	14 (8.5)	27 (16.3)
Investigations	19 (11.6)	26 (15.7)
Respiratory, thoracic and mediastinal disorders	27 (16.5)	27 (16.3)
Metabolism and nutrition disorders	19 (11.6)	16 (9.6)
Vascular disorders	15 (9.1)	17 (10.2)
Blood and lymphatic system disorders	17 (10.4)	17 (10.2)
Injury, poisoning and procedural complications	15 (9.1)	9 (5.4)
Psychiatric disorders	12 (7.3)	8 (4.8)
Immune system disorders	16 (9.8)	15 (9.0)
Renal and urinary disorders	11 (6.7)	15 (9.0)
Cardiac disorders	7 (4.3)	13 (7.8)
Eye disorders	3 (1.8)	9 (5.4)
Ear and labyrinth disorders	3 (1.8)	4 (2.4)
Hepatobiliary disorders	0 (0.0)	3 (1.8)
Reproductive system and breast disorders	2 (1.2)	1 (0.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	6 (3.7)	2 (1.2)
Endocrine disorders	4 (2.4)	1 (0.6)
Abbreviations: TEAE, treatment-emergent adverse event		

Table 5. Summary of moderate treatment-emergent adverse events by system class in the CLEAR trial

	Placebo + full-dose GCs (N=23)	Avacopan + low-dose GCs (N=22)	Avacopan + no GCs (N=22)
Any moderate TEAEs	9 (39.1)	7 (31.8)	9 (40.9)
Infections and infestations	2 (8.7)	3 (13.6)	3 (13.6)
Gastrointestinal disorders	3 (13.0)	3 (13.6)	1 (4.5)
Musculoskeletal and connective tissue disorders	1 (4.3)	2 (9.1)	1 (4.5)
General disorders and administration site conditions	1 (4.3)	1 (4.5)	2 (9.1)
Nervous system disorders	0 (0.0)	1 (4.5)	1 (4.5)
Investigations	2 (8.7)	2 (9.1)	3 (13.6)
Respiratory, thoracic and mediastinal disorders	2 (8.7)	1 (4.5)	1 (4.5)
Metabolism and nutrition disorders	1 (4.3)	0 (0.0)	0 (0.0)
Vascular disorders	1 (4.3)	2 (9.1)	2 (9.1)
Blood and lymphatic system disorders	0 (0.0)	1 (4.5)	0 (0.0)
Injury, poisoning and procedural complications	1 (4.3)	0 (0.0)	0 (0.0)
Psychiatric disorders	1 (4.3)	1 (4.5)	0 (0.0)
Renal and urinary disorders	1 (4.3)	1 (4.5)	1 (4.5)
Cardiac disorders	1 (4.3)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	1 (4.5)
Reproductive system and breast disorders	0 (0.0)	1 (4.5)	1 (4.5)
Abbreviations: GC, glucocorticoid; TEAE, treatment-emergent adverse event			

Table 6. Summary of moderate treatment-emergent adverse events by system class in the CLASSIC trial

	Placebo + SoC (N=13)	Avacopan 10 mg + SoC (N=13)	Avacopan 30 mg + SoC (N=16)
Any moderate TEAEs	5 (38.5)	7 (53.8)	7 (43.8%)
Infections and infestations	1 (7.7)	0 (0.0)	0 (0.0)

Gastrointestinal disorders	0 (0.0)	1 (7.7)	1 (6.3)
Musculoskeletal and connective tissue disorders	1 (7.7)	0 (0.0)	1 (6.3)
General disorders and administration site conditions	1 (7.7)	1 (7.7)	2 (12.5)
Skin and subcutaneous tissue disorders	1 (7.7)	3 (23.1)	0 (0.0)
Nervous system disorders	3 (23.1)	0 (0.0)	1 (6.3)
Investigations	1 (7.7)	3 (23.1)	0 (0.0)
Vascular disorders	1 (7.7)	2 (15.4)	2 (12.5)
Injury, poisoning and procedural complications	1 (7.7)	1 (7.7)	0 (0.0)
Renal and urinary disorders	0 (0.0)	1 (7.7)	0 (0.0)
Cardiac disorders	0 (0.0)	0 (0.0)	3 (18.8)
Eye disorders	0 (0.0)	1 (7.7)	0 (0.0)
Abbreviations: SoC, standard of care; TEAE, treatment-emergent adverse event			

A18. Please discuss the results of the use of immunosuppressants and corticosteroids outcome in the ADVOCATE trial.

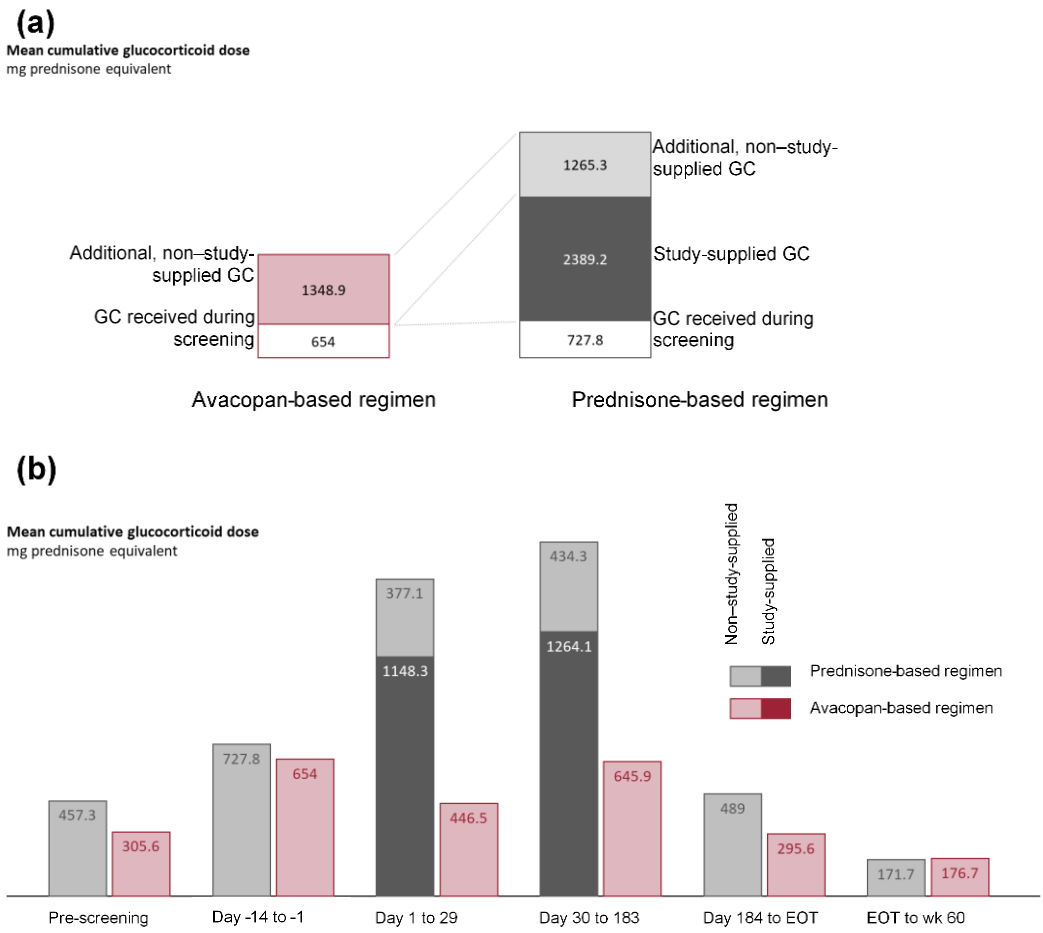
RESPONSE:

In the ADVOCATE trial, over 52 weeks, GC exposure was 63% lower in the avacopan-based regimen group, with a mean cumulative GC dose during the treatment period of 1,348.9 mg for the avacopan group vs 3,654.5 mg for the prednisone group driven by study design (Figure 4). Sources of additional, non–study-supplied GCs in both groups were tapered in the first 4 weeks from pre-randomisation GC dosing, GC from co-administration with RTX (65% of all subjects) over first 4 weeks, and off-protocol GC use (for AAV relapse or no improvement in major BVAS item in the first 4 weeks) as prescribed by clinician. During the last 26 weeks of the treatment period, 39.0% of the prednisone group and 27.1% of the avacopan group received non-study supplied GCs; GC exposure was 40% lower in the avacopan-based regimen group, with a mean cumulative GC dose during the treatment period of 295.6 mg for the avacopan group vs 489.0 mg for the prednisone

group (5, 6). The difference in GC use between the treatment arms in the ADVOCATE trial corresponds to the potential steroid-sparing effect of avacopan.

The incidence of use of concomitant other non-protocol specified immunosuppressant drugs or other treatments for AAV was also lower in the avacopan-based regimen group (range: 8.4-27.1%) compared to the prednisone-based regimen group (range: 9.8-33.5%) across all study periods (6).

Figure 4. Mean cumulative glucocorticoid dose over time in the ADVOCATE trial (ITT population): (a) overall and (b) by time period (5)



Abbreviations: EOT, end of treatment; GC, glucocorticoid; wk, week

Eligibility criteria

A19. Priority question: The list of comparators as per Table 66 of the Appendix D differs from the list in the final scope issued by NICE.

Please explain and justify these differences.

RESPONSE:

The clinical SLR adopted a broad global scope, aiming to determine the clinical efficacy and tolerability of all commonly used treatments for MPA and GPA.

Combination therapy with GCs and CYC (followed by AZA/MMF) or RTX is currently standard therapy for remission induction in the United Kingdom (1, 2). These were, therefore, considered relevant comparators for the purposes of this submission.

MTX and MMF are recommended as alternatives to CYC (followed by AZA/MMF) or RTX for remission induction in patients with localised disease at low risk of suffering organ damage. However, the use of avacopan, in combination with a CYC or RTX regimen, is indicated for severe, active GPA or MPA. As such, MTX and MMF were not considered as relevant comparator treatments.

A20. Please justify exclusion of non-English studies; and the application of date limits (1998-present) as per the section D.1.1.1 of the Appendix D.

RESPONSE:

To date, the majority of journals publish in English resulting in limited amount of relevant non-English language scientific evidence. In addition, the quality of non-English language studies (i.e., study designs adopted) has been shown to be lower than that of English language studies, and errors may occur in the translation process. Furthermore, such studies will not have been conducted in the UK and, therefore, are less likely to be generalisable to an NHS setting. Consequently, non-English language studies were excluded at screening stage of the clinical SLR.

A21. In Appendix D (page 2), it states that the randomised trial filter was applied. Please justify why non-randomised studies were not eligible for inclusion.

RESPONSE:

The design of single arm trials has several limitations; and, despite their simplicity, the interpretation of the trial results can be complicated. In single arm trials, it is not possible to distinguish between the effect of the treatment, a placebo effect, and the effect of natural history.

In an attempt to include evidence of the highest quality (in line with NICE's preferred evidence hierarchy), only randomised control trials were considered in the clinical SLR and single arm trials were excluded.

A22. Please justify exclusion of paediatric patients as per Table 66 of the Appendix D as those aged 12 or older were eligible in the ADVOCATE (NCT02994927) trial.

RESPONSE:

The indication of avacopan for the treatment of severe, active GPA or MPA is limited to adult patients. As such, the clinical SLR excluded paediatric patients.

The mean age of recruited subjects in the ADVOCATE study was 60.9 years, with the majority between the ages of 51 and 75 years (224 subjects [67.7%]). Only 3 subjects were aged 12 to 17 years; of which, 2 were treated with an avacopan-based regimen and 1 was treated with a prednisone-based regimen (6).

A23. Please clarify other inconsistencies in eligibility criteria. For instance, the company submission states that the COMBIVAS trial was excluded for the following reason: "No outcome of interest". However, this trial measured e.g., time to clinical remission, time to first relapse, proportion of participants in sustained remission, proportion of participants complete remission, adverse effects which are all in line with the NICE scope and Table 66 of the Appendix D.

RESPONSE:

The COMBIVAS trial is investigating a number of outcomes relevant to the scope of the clinical SLR we conducted, including clinical efficacy and safety outcomes. However, the study is ongoing, and no data were published in the relevant publication identified during our review.

Accordingly, all studies investigating outcomes of interest that have no published results were excluded for the reason 'No outcome of interest'.

Baseline imbalances

A24. In the ADVOCATE (NCT02994927) trial, there were higher proportions of patients receiving glucocorticoids during the screening period in the prednisone group compared with avacopan.

Please clarify how these imbalances impacted the outcomes, including the Glucocorticoid Toxicity Index (GTI).

Response:

The prior GCs use during the screening period is summarised in Table 7.

Table 7. Summary of prior glucocorticoid use – ITT population

Screening Period	**Prednisone (N=164)**	**Avacopan (N=166)**
Glucocorticoids use, n (%)	135 (82.3)	125 (75.3)
Glucocorticoid total dose (mg prednisone-equivalent):		
Mean (SD)	727.8 (787.83)	654.0 (744.41)
Median (range)	430 (0-3,255)	415 (0-3,780)
Abbreviations: ITT, intent-to-treat; SD, standard deviation		

The incidence of prior GCs use was numerically higher in the prednisone group, but the difference between groups was not statistically different (p=0.119, chi-squared test). The mean and median total dose of prior GCs were similar between groups. In patients receiving oral GCs during the screening period, the dose needed to be tapered to a dose that did not exceed 20 mg prednisone equivalent on day 1 (first dosing day) of the study and to be tapered to zero over a 4-week period after day 1. The GTI measures change in GC toxicity rather than absolute GC toxicity to account for the effects of prior GC therapy and background rate of AEs. As the GTI measured CWS and AIS over the first and subsequent 13 weeks of the study, prior GC use is unlikely to have had a meaningful impact on the outcomes observed.

Generalisability

A25. The ADVOCATE (NCT02994927) trial enrolled patients from 143 centres worldwide; and 12.1% of subjects were from the UK.

Please clarify any impact on generalisability of the findings.

Response:

The baseline demographics and characteristics of the population included in the ADVOCATE trial are generalisable to the UK population.

In the ADVOCATE trial ITT population, the mean age of recruited subjects was 60.9 years, with the majority between the ages of 51 and 75 years (224 subjects [67.7%]). More male subjects than female subjects were randomised to treatment and most subjects were white and not Hispanic or Latino. Most subjects enrolled in the study were newly diagnosed with AAV (69.4%) with a median duration of disease of approximately 0.2 months. The incidence of subjects with GPA was higher than those with MPA (54.8% vs 45.2%); most subjects were anti-MPO positive (57.0%), and most subjects were taking IV RTX as the SoC treatment (2, 65).

Similarly, the mean age of the UK patients included in the ADVOCATE trial (N=40) was 57.9 years, with the majority between the ages of 51 and 75 years (30 subjects [75%]). More male subjects than female subjects were randomised to treatment (60% vs 40%) and most subjects were white. Most UK patients enrolled in the study were newly diagnosed with AAV (72.5%); and most subjects were anti-MPO positive (52.5%). Approximately 50% of patients were taking IV RTX as the SoC treatment at baseline.

The mean baseline Birmingham Vasculitis Activity Score (BVAS) and Vasculitis Damage Index (VDI) scores of the whole ADVOCATE trial ITT population was similar to the UK patient subgroup of the ADVOCATE trial.

Risk of bias assessments

A26. In Table 69 of Appendix D, the Risk of Bias 2 (ROB2) tool was used to evaluate the trials quality. However, the Cochrane Collaboration recommends using 5

domains (of bias) and an overall risk of bias assessment. Please supply the missing overall risk of bias assessments using appropriate risk of bias assessment tools such as the Cochrane Collaborations Risk of Bias 2 (RoB 2) tool; modify judgments using the signalling questions.

Response:

The quality of the 3 avacopan trials was assessed using the RoB 2 tool and was found to be high. The overall risk of bias was low for all 3 trials, see Table 8 for more details.

Table 8. Quality assessment of ADVOCATE, CLEAR, and CLASSIC trials

Trial name		**ADVOCATE**	**CLEAR**	**CLASSIC**
Overall risk of bias		**Low risk**	**Low risk**	**Low risk**
Selection bias (systematic differences between the comparison groups)	Was an appropriate method of randomisation used to allocate participants to treatment groups?	Yes	Yes	Yes
	Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
	Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
	Risk of selection bias	**Low risk**	**Low risk**	**Low risk**
Performance bias (systematic differences between groups in the care provided, apart from the intervention	Did the comparison groups receive the same care apart from the intervention(s) studied?	Yes	Yes	Yes
	Were participants receiving care kept “blind” to treatment allocation?	Yes	Yes	Yes

under investigation)	Were individuals administering care kept “blind” to treatment allocation?	Yes	Yes	Yes
	Risk of performance bias	**Low risk**	**Low risk**	**Low risk**
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)	Were all groups were followed up for an equal length of time?	Yes	Yes	Yes
	Were there any unexpected imbalances in drop-outs between groups?	No	No	No
	Did the analysis include an intention to treat analysis?	Yes	Yes	No
	Risk of attrition bias	**Low risk**	**Low risk**	**Low risk**
Detection bias (bias in how outcomes are ascertained, diagnosed, or verified)	Were investigators kept 'blind' to participants' exposure to the intervention?	Yes	Yes	Yes
	Risk of detection bias	**Low risk**	**Low risk**	**Low risk**
Reporting bias (bias in how outcomes are ascertained, diagnosed, or verified)	Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
	Risk of reporting bias	**Low risk**	**Low risk**	**Low risk**

Reliability and validity of outcome measures

A27. Please specify which reliable measurement tools or biomarkers were used to validate the measurement of remission.

Response:

Numerous instruments have been developed to measure disease activity in AAV and are frequently used to define primary or secondary outcomes in AAV trials. Testing for the presence of ANCA antibodies, along with clinical assessments and other blood tests for inflammatory markers, kidney function, and urine measurements for blood and protein, supports an AAV diagnosis. However, the utility of these clinical assessments alone as an indicator of disease activity or as a predictor of relapse has been inconsistent.

The Birmingham Vasculitis Activity Score (BVAS), originally published in 1994 and then revised in 1997 and 2009, is the only validated tool developed to date that can be used to accurately assess disease remission in AAV and is widely used in clinical practice and trials. The BVAS is a composite score that evaluates 56 clinical features from 9 organ systems that are attributed to active vasculitis. Each item is weighted according to the severity. A score of 0 is often adopted as the definition of disease remission in studies (15). The BVAS tool was used for assessing remission in the three avacopan trials, ADVOCATE, CLEAR and CLASSIC.

Section B: Clarification on cost-effectiveness data

Intervention and comparator

B1. Priority question: Patients transition from active disease to remission 1 in the first 6 model cycles but continue receiving induction therapy. Please clarify whether this is reflective of clinical practice?

Response:

The assumptions regarding the treatment of patients entering remission in the first 6 model cycles are reflective of clinical practice. We provide an explanation for each type of induction therapy below:

- For avacopan, it would be used for both induction and maintenance. Therefore, patients who achieve remission in any of the first 6 model cycles can be assumed to continue with avacopan, even though this may technically be for the purpose of maintenance.
- For RTX, the induction course of treatment takes place in the first model cycle. Therefore, there is no need to consider whether patients entering remission before cycle 6 remain on induction therapy or not.
- CYC is used for induction, but then must be withdrawn on account of its cumulative dose toxicity. The regimen for CYC induction used in ADVOCATE was 3 months in duration. Guidelines state that treatment courses of CYC should be maintained for at least 3 months (2, 3). Hence, although patients may enter remission in the first or second model cycle, they must continue to receive the full course of CYC in accordance with clinical guidance.
- Prednisone treatment is expected to be tapered rapidly in clinical practice and reduce to 5mg daily by 20 weeks. As prednisone requires tapering rather than stopping abruptly, we did not assume that prednisone treatment would be discontinued due to remission.

B2. Priority question: The company submission states: "*after the induction phase, patients induced with avacopan in combination with CYC or RTX were assumed to receive maintenance treatment with avacopan in combination with AZA for 7 model cycles followed by AZA alone for the remainder of the 26-cycle maintenance period*." Evidence for the effectiveness of avacopan is limited to the 52-week follow-up in ADVOCATE (equivalent to 6 cycles of induction and 7 cycles of maintenance).

a. **Presumably the assumption of 7 maintenance cycles of avacopan stems from the 52-week duration of ADVOCATE. Would this duration be expected in clinical practice or is it possible that more than 7 maintenance cycles would be provided?**

b. **Please clarify whether there are any restrictions to the length of time for which avacopan can be used as maintenance therapy in clinical practice?**

c. **The model includes additional options for assuming durations of avacopan maintenance therapy of 18 and 24 months. Please explain the assumptions, including a justification for their underlying rationale, clinical plausibility and model implementation, made for the clinical effectiveness of avacopan when modelled as a maintenance therapy beyond 6 months.**

d. **Please include the options in the model for assuming durations of maintenance therapy with avacopan of 12, 36 and 48 months.**

e. **Please include the options in the model to assume, for all durations specified above, the use of (relevant combinations of) the following maintenance therapies: azathioprine, avacopan, rituximab, cyclophosphamide, and mycophenolate mofetil, according to appropriate and clinically plausible assumptions for their clinical effectiveness and costs.**

Response:

a. There is no data to inform the effectiveness of avacopan treatment beyond the 52-week data from ADVOCATE. In the absence of longer-term data, clinicians may be cautious about extending the duration of use of avacopan. It is possible that some patients may continue avacopan maintenance treatment beyond 52 weeks if the treatment is still effective and tolerated. We will include options for longer duration of maintenance with avacopan and other treatments for the purposes of scenario analysis.

b. There is no restriction regarding the length of treatment; however, effectiveness data is limited to 52 weeks, which limits our ability to model the effect of treatment beyond 52 weeks.

c. The options for longer duration of avacopan maintenance were included for the purposes of exploratory scenario analysis and are highly uncertain due to absence of data on the effectiveness of avacopan maintenance treatment beyond the data horizon of the ADVOCATE trial. We have revisited the assumptions and the model and updated them in line with your requests. It is assumed that the treatment effect of avacopan after 52 weeks (in terms of the HR for the reduction in the hazard rate of relapse) is the same as the treatment effect observed in the ADVOCATE trial between weeks 26 and 52. It was assumed that avacopan is used in combination with RTX or AZA in line with its marketing authorisation.

d. This has been implemented in the updated model. Avacopan maintenance for >6 months can be switched on in “Model settings” cell C26. All the options for duration of maintenance can be selected from cell C27. The choice of AZA or RTX maintenance can be selected from cell C32.

e. The model assumes that avacopan will be used in combination with AZA or RTX in line with its marketing authorisation.

The model already includes the options for avacopan maintenance, which have been updated to include the options for length of maintenance treatment requested in B3(d).

AZA maintenance has already been implemented in the original model with effectiveness data from the ADVOCATE trial.

We have outlined the findings from a feasibility assessment for an indirect treatment comparison (ITC) between avacopan and RTX for the maintenance of remission in AAV. This assessment concluded that an ITC between treatments as they are intended to be used in clinical practice (AVA+RTX vs RTX) is not feasible in the absence of a trial which tested avacopan in combination with RTX for the maintenance of remission in AAV. We have outlined our rationale for the non-inclusion of RTX maintenance in Section B3.2.8 of the submission. In response to your request, we will include an adjustment to the baseline hazard rate of relapse to reflect the improved effectiveness of maintenance treatment through the addition of RTX instead of AZA, based treatment effectiveness data from the RITAZAREM trial. However, this non-adjusted naïve comparison should be treated as an exploratory analysis and its conclusions treated with caution due to the high uncertainty associated with this approach.

CYC is not used for the maintenance of remission in AAV in the UK and its inclusion in this analysis was not considered to be appropriate.

AZA is preferred over MMF for the maintenance of remission of AAV based on the results of the IMPROVE trial (4, 16). MMF was therefore not considered for inclusion in the analysis, given that AZA is a more relevant option in clinical practice.

Treatment effectiveness

B3. Priority question: The company submission states that "*The per-cycle probability of transitioning from active disease/relapse states to remission was derived based on the proportions of patients in remission at week 26 and from*

***ADVOCATE*", and "*These transition probabilities were assumed to apply to transitions from both the active disease state and the relapsed states to remission, for both the intervention and comparator*." Please clarify the following:**

a. **Please confirm whether this should read "proportions of patients in remission at week 26 from ADVOCATE" or whether another approach taken?**

b. **Were there any patients in ADVOCATE that experienced a remission and subsequent relapse prior to week 26? How were these patients dealt with in the estimation of the remission transition probability?**

c. **The submission states that this approach assumes a constant hazard over the 26 weeks. However, Table 14 of the CS shows that the majority of patients reaching remission did so after 4 weeks of treatment already. Why was this information not used and why was a constant hazard approach considered appropriate instead?**

d. **Please provide evidence to justify the assumption that the probability of transitioning to remission can be applied to transitions from both active disease and relapse 1 and 2 states, given that it was only estimated using data up to 26 weeks.**

e. **Why was a separate remission transition probability not estimated for transitioning from the last relapse tunnel state in which patients were assumed to receive maintenance treatment?**

Response:

a. Correct, this should read "proportions of patients in remission at week 26 from ADVOCATE".

b. The probability of relapse in the model was based on the proportion of patients in remission at week 26 and 52. Relapse prior to week 26 was not included in the model.

c. The use of constant hazards over time was a simplification to facilitate the extrapolation of the hazard rate of relapse beyond the horizon of the ADVOCATE trial. If remission at week 4 were to be included in the model, it is expected to be favourable for avacopan.

d. The ADVOCATE trial population included a mixture of newly diagnosed and relapsed patients. We assumed that the rate at which patients achieve remission is the same with each induction treatment, if the same treatments were used.

e. The last tunnel state in relapse (Tunnel 1.7 and Tunnel 2.7) represents refractory disease. No transitions to remission were possible from this health state.

B4. Priority question: The CS states that "Based on the CPRD study (101), the probability of moving from remission to relapse [redacted]. In the absence of long-term data for CYC or RTX, the relapse probability for these treatments was assumed to be [redacted]. The transition probability from remission to relapse after 2 years in remission is assumed to be [redacted], based on data from the CPRD study." Please clarify on which evidence in the CPRD study the assumed one-fifth probability of relapse after two years was based. How exactly were the one-fifth and two years decided upon?

Response:

The CPRD study provides the timings of changes in treatment for patients with AAV, which can be used as a proxy of changes in disease state. Specifically, Figure 8 in the CPRD study report (*Duration of episodes of no GC treatment in the AAV population. Upon failure patients restart GC treatment*) and Figure10 (*Duration of episodes of low dose GC (<30mg/day) and/or no GC treatment in the AAV population. Upon failure patients move to high dose treatment.*) from the CPRD study can provide information regarding the changing risk of relapse over time. This is because, upon relapse, patients would be expected to resume or escalate GC

treatment. Which data provides the best proxy depends on the assumptions made regarding changes in treatment occurring upon relapse.

Regardless of which data is used, these survival curves both indicate a rate of decay that has two distinct phases. The change in the underlying hazard would appear to occur at approximately [redacted] in both cases. When these curves are used to estimate a constant hazard for each phase, the hazard after [redacted] is approximately [redacted] of the hazard before [redacted]. It is in fact slightly above [redacted] based on Figure 8 and slightly below based on Figure 10 in the CPRD study report.

In the absence of any more direct long-term data on time to relapse, this was the approach taken to inform some appropriate assumptions regarding the changing risk of relapse over time.

B5. Priority question: The CS states that "the hazard ratio for the rate of relapse with avacopan between week 52 and 60 is derived from extension study data reported in the ADVOCATE clinical study report." Please clarify the following:

a. **Did any patients receive avacopan in this extension study?**

b. **What proportion of the ITT population were followed in this extension and how the characteristics of the patients included in the extension compared to the ITT population?**

c. **The extension took place after 52 weeks of avacopan, which is approximately double the length of the modelled induction period and efficacy data used from 26 weeks. What impact might this have on the HR estimated from this study?**

d. **Why was a HR used instead of making direct use of the avacopan data available?**

e. **Was the proportional hazards assumption tested? Please show the results of this testing. If PH is not met, please present a suitable alternative approach such as extrapolation of the data using non-PH models, or applying time-dependent HRs.**

Response:

a. No patients received avacopan in the extension study

b. The number of patients included in the extension study was 157 out of 165 patients in the prednisone arm and 158 out of 166 in the avacopan arm of ADVOCATE. Given the low drop-out rate, we do not expect the characteristics of the patient population in the extension study to differ substantially from those of the ITT population

c. The hazard ratio was estimated based on the number of patients in remission at week 52 and the proportion of patients who relapsed between week 52 and 60 (Table 9).

Table 9. Number of patients in remission, ADVOCATE

Parameter	Prednisone-based regimen	Avacopan-based regimen	HR
N	164	166	
In remission at week 26	115 (70.1%)	120 (72.3%)	
In remission at week 52	90 (54.9%)	109 (65.7%)	0.39
Relapsed between week 52-60	7 In remission: 83 (50.6%)	6 In remission: 103 (62.0%)	0.70

d. The hazard ratio was computed directly using the patient numbers in the ADVOCATE study using the method outlined in (c)

e. Proportional hazards were not assumed in the time period of 52 to 60 weeks. The hazard ratio was estimated as the difference in the proportions of patients remaining in remission at weeks 52 and week 60 of the study.

B6. Priority question: From week 60, it was assumed that the treatment effect of avacopan declined linearly over 3 months, with no residual treatment benefit after month 15. Please provide evidence or reasoning to justify the assumed 3 months of linearly declining residual benefit. Given that that HR increases from 0.39 to 0.7 over the extension follow-up period of 8 weeks,

would we expect any residual benefit to remain after week 60 given the assumption of linear decline in benefit?

Response:

There is uncertainty regarding the duration of any residual treatment effect of avacopan, hence the economic model was designed with alternative approaches built-in and to allow users to modify inputs and assumptions.

The full treatment effect of avacopan compared to GC SoC is applied for 52 weeks in the model based on the ADVOCATE trial (model cycles 1-13). In a UK advisory board, clinical experts (including investigators from the ADVOCATE study) were asked about the duration of any treatment effect following discontinuation of avacopan. Most responses (6/10) were for a waning period of '1-3 months' followed by (2/10) for '3-6 months'. On this basis, the model base case assumes that waning takes place over 3 model cycles. The period covered by treatment waning is, therefore, between weeks 52 and 64 (cycles 14-16).

For cycles 14 and 15 (weeks 52-60), the treatment effect is derived using data from the extension phase of the ADVOCATE trial – which provided the hazard ratio of 0.7. Cycle 16 is the final cycle in which any residual treatment effect is applied. In this cycle the transition probability to relapse is adjusted based on the transition probabilities for cycles 14-15 and 17+, assuming that waning occurs linearly.

Adverse events

B7. Priority question: Please include AE disutilities for all AEs in the model which affect more than 2% of either treatment arm and allow the option to use these disutilities when utilities are assumed to be equal across treatment groups.

Response:

Disutilities have been included for AEs which occurred in 2% or more of either treatment arm of the ADVOCATE trial. In order to activate these decrements, treatment-specific utilities have to be switched off and AE source set to ADVOCATE in the model settings sheet.

B8. Priority question: The model allows the option to include AE disutilities for infections, CV events, renal disease, bone disease and ocular disease. Please ensure that when this option is selected, costs are also included for these AEs.

Response:

In order to select AE disutilities and costs based on CPRD, the following steps should be taken:

1. Switch treatment-specific utilities off in “HRQoL data” D13
2. Set “AE source” to “CPRD” in C68, Model settings
3. Switch hospital cost data off in C70, Model settings

HRQoL

B9. Priority question: Why were the EQ-5D-5L data from ADVOCATE from weeks 10, 16, 39 and 60 not used to estimate the utility values used in the model.

Response:

The analysis of the EQ-5D-5L was used to estimate health state utilities for the model health states of active disease, remission and relapse. The pivotal ADVOCATE study reported the proportions of patients in remission after 26 and 52 weeks as a primary outcome, which provided the evidence to inform the distribution of patients between model health states. Therefore, the EQ-5D-5L data was analysed at 26 and 52 weeks to align with the timing of the reporting of health state occupancy from ADVOCATE.

B10. Priority question: Please clarify the number of respondents from ADVOCATE who provided data for each of the utility values per time point. Please also clarify how missing data was dealt with.

Response:

For the health state utilities in the ITT population, the numbers for each treatment, health state and time point are provided below.

Table 10. ADVOCATE trial respondents for each of the health state utilities (ITT population)

Health State	26 weeks	52 weeks
Active disease		
Both trial arms	57	54
Avacopan + SoC	30	29
Prednisone + SoC	27	25
Remission		
Both trial arms	149	133
Avacopan + SoC	74	68
Prednisone + SoC	75	65
Relapse		
Both trial arms	NA	13
Avacopan + SoC	NA	4
Prednisone + SoC	NA	9
Abbreviations: SoC, standard of care		

For missing data, no imputation was performed and only complete data at each time point was used in the analysis of the quality-of-life data.

B11. Please comment on the likelihood that the impact of AEs was captured within the EQ-5D self-reports at weeks 4, 26 and 52 given the recall period of "today" on the EQ-5D-5L

Response:

The recall period specified in EQ-5D-5L is a limitation, given that it may have failed to capture the impact of AEs which occurred on the days when it was not measured. However, given that it was assessed at the same time points in both the avacopan and GC arms of the study, we do not expect this to result in bias in favour of either treatment. Given that a lower incidence of GC-related AEs was observed in the avacopan arm of the ADVOCATE trial, if this method underestimated the impact of

AEs on quality of life, it would be in favour of GC SoC, thus representing a conservative scenario.

The model includes options for modelling the utility impact of AEs based on the ADVOCATE trial and CPRD which can be used for alternative analyses which do not assume that treatment-specific utilities based on EQ-5D-5L data from ADVOCATE capture the impact of treatment-related AEs.

Costs and resource use

B12. Priority question: Please include the cost of GC use in the model according to actual use in the trial and not based on protocol use. Please also appropriately account for this in terms of GC AEs.

Response:

The model includes an option to include GC use alongside avacopan in the Model Settings sheet cell C52. If this option is switched on, the cost and utility of GC AEs are applied to the avacopan arm of the model if CPRD is used as the selected data source for GC AEs. If ADVOCATE hospitalisation is selected as the source of GC AEs or if treatment-specific utilities are switched on, it is not possible to isolate the effect of GCs. We recommend that the impact of GC use alongside avacopan is tested using AE data from CPRD and treatment-specific utility values switched off.

B13. Priority question: The CS states on p.136 that the cost of treatment of adverse events was assumed to be accounted for within the hospitalisation data derived from ADVOCATE. The model includes the options to either in- or exclude hospitalisations data from ADVOCATE and to toggle between using either ADVOCATE or CPRD data as a source for AE estimates.

a. **Please confirm that using the option to include hospitalisations data from ADVOCATE overrides the use of all other AE cost estimates.**

b. **Please justify the assumption that all relevant costs for the treatment of all adverse events are captured by including hospitalisations data from ADVOCATE.**

Response:

a. That is correct. The Results sheet ('Resources used' and 'GC-related adverse event' rows) select the appropriate costs based on the selections in the drop-down menus for 'include hospitalisation data' and 'AE source'. If 'include hospitalisation data' is set to 'Yes', then ADVOCATE based hospitalisation costs are added to other costs presented within the resource use, and the 'GC-related adverse event' costs will return zero costs. Only if 'include hospitalisation data' is set to 'No' will the ADVOCATE based hospitalisation costs be supressed and AE costs will be presented in the 'GC-related adverse event' results using a method that depends on the AE source selected.

b. The list of AEs comprises serious TEAEs, and as such, their management and treatment is highly likely to require hospital attendance. Furthermore, many AEs may be identified and treated during hospital attendance for routine treatment monitoring. Therefore, this approach was considered appropriate for estimating the cost implications of AEs, and any other costs resulting from AEs is likely to be negligible. If all relevant costs are not captured using the data on hospitalisation in ADVOCATE, then this will likely bias the results against avacopan since the majority of AEs are more frequent in patients treated with GCs.

B14. Please justify the exclusion of additional monitoring costs for X-rays and CT-scans that were included in TA308 or include these costs.

Response:

The cost of X-rays and CT-scans have been included based on information in TA308. The updated values have been included in cells D153:154 and incorporated into the monitoring costs in the "Cost data" sheet.

B15. A reference is provided to the CPRD study, in which annual total health care resource use costs were estimated to fluctuate around £25,000.

a. Please comment on the comparability of the costs as estimated in this study and those included in the analysis.

b. Please justify why the model does not include the option to use estimates from this study to inform health care resource use costs or include the option in the model to use the estimates from this study.

Response:

a. We can compare annual costs between the CPRD study and the model by using the modelled costs over a 10-year horizon with discount rates set to 0%. Dividing these total costs for CYC/RTX+GC by the accrued patient life-years yields a crude annual cost approximation of £13.4k. This is considerably lower than the annual cost estimated from the CPRD study.

   There are, however, several reasons that we do not expect that these annual costs should be comparable, such as: 1) ADVOCATE was an international multi-centre study and levels of healthcare resource utilisation may not be equivalent between countries, and 2) Inclusion/exclusion criteria for enrolment on ADVOCATE may lead to some differences in resource use between the study populations, and the clinical trial context may also lead to differences in resource use.

b. We considered that the CRPD study was unsuitable for providing cost estimates for use in the cost-effectiveness model for two key reasons:

   1) The CPRD study did not include the costs of avacopan-treated patients, given that this treatment was not approved during the data collection period in CPRD. Therefore, it cannot provide information on changes to health care resource use and costs that result from treatment with avacopan.

   2) The cost estimates from CPRD were not stratified according to disease state, and it was not possible to match the estimates to the health states in our model. It therefore is not useful for estimating the impact of avacopan on the cost of treatment in AAV.

   Furthermore, the impact of avacopan is to help sustain AAV remission leading to reduced healthcare resource use. Hence, in general, if the model was to

use higher estimates of resource use or costs, it is likely that this would favour avacopan. Therefore, it is likely that the approach adopted can be considered conservative.

Other model input

B16. Priority question: Please provide details on whether and how clinical expert opinion was consulted in support of assumptions made in the model, provide the documentation of clinical expert opinion for each specific assumption, and indicate which assumptions were made in the absence of (documented) clinical expert opinion.

Response:

In the absence of published data to inform some of the model parameters and assumptions in the model, an advisory board was conducted with UK clinical experts. The advisory board consisted of 10 experts with experience of treating patients with AAV, including consultant nephrologists and rheumatologists from 10 different hospitals and units in the UK.

The clinical experts were asked to provide input for the following model assumptions:

1. *Q: What do you believe is the duration of any treatment effect following discontinuation of avacopan?*

   <1 month: One out of 10 (10%)
   1 to 3 months: 6 out of 10 (60%)
   3 to 6 months: 2 out of 10 (20%)
   >12 months: 1 out of 10 (10%)

   Nine out of 10 of the respondents believed that the treatment effect would persist for at least 1-3 months. This was the basis for our assumption of a waning treating effect for 3 months after discontinuation of avacopan

2. *Q: What do you believe is the probability of patients with refractory AAV developing ESRD?*

The majority of the experts (6/10) believed that the probability of refractory patients developing ESRD is greater than patients with relapsing AAV. In the absence of a specific estimate for this transition probability, we conservatively assumed that it is equal to the probability of ESRD in the relapse health state.

The increase in the probability of ESRD associated with AAV relapse has been documented in the clinical literature, as described in B.3.3.3 of the dossier. However, the precise impact of release on renal function (measured using eGFR) is unknown. Clinical experts in an advisory board in the Netherlands advised that each relapse is associated with a decrease in eGFR of 20ml/min. In our model, a decrease of 10ml/min was included, which represents a conservative case, based on further validation with clinical experts in Sweden and the UK

Model

B17. Please explain how the simulation results on sheet 'simulated HR' are used in the model.

Response:

The sheet 'simulated HR' is not used within the model.

Section C: Textual clarification and additional points

C1. Priority question: Please provide the tables, figures, and graphs from chapter 14 of the CSR of the ADVOCATE study.

Response:

The complete ADVOCATE trial CSR, along with supporting tables and appendices, is provided alongside our responses to the clarification questions.

References

1. Chalisey A, Karim M. Guidelines for the management of ANCA-associated vasculitis with renal involvement 2021 [Available from: https://www.nnuh.nhs.uk/publication/download/guidelines-for-the-management-of-anca-associated-vasculitis-v1-2
2. NICE. Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis. Technology appraisal guidance [TA308] 2014 [Available from: https://www.nice.org.uk/Guidance/TA308].
3. Ntatsaki E, Carruthers D, Chakravarty K, D'Cruz D, Harper L, Jayne D, et al. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology (Oxford). 2014;53(12):2306-9.
4. Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis. 2016;75(9):1583-94.
5. Jayne DRW, Merkel PA, Schall TJ, Bekker P. Avacopan for the treatment of ANCA-associated vasculitis. N Engl J Med. 2021;384(7):599-609.
6. ChemoCentryx. Clinical study report. 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. 2020.
7. Jayne DRW, Bruchfeld AN, Harper L, Schaier M, Venning MC, Hamilton P, et al. Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis. J Am Soc Nephrol. 2017;28(9):2756-67.
8. ChemoCentryx. Clinical study report. 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. 2016.
9. Merkel PA, Niles J, Jimenez R, Spiera RF, Rovin BH, Bomback A, et al. Adjunctive treatment with avacopan, an oral C5a receptor inhibitor, in patients with antineutrophil cytoplasmic antibody–associated vasculitis. ACR Open Rheumatol. 2020;2(11):662-71.
10. ChemoCentryx. Clinical study report. 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. 2016.
11. Ehlers L, Wiebe E, Freier D, Hermann S, Miloslavsky E, Zhang Y, et al. AB1310 Prospective use of the Glucocorticoid Toxicity Index (GTI) in a cohort of vasculitis patients. Ann Rheum Dis. 2019;78(Suppl 2):2117-8.
12. McKinney EF, Willcocks LC, Broecker V, Smith KG. The immunopathology of ANCA-associated vasculitis. Semin Immunopathol. 2014;36(4):461-78.
13. PHMR. An Investigation of the Adverse Outcomes and Resource Use Associated with Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis (AAV) in England and Their Relationship with Glucocorticoid (GC) Treatment: A Clinical Practice Research Datalink. London, UK: PHMR Ltd.; 2019.
14. Worthington D, Rutherford P. Reality of ANCA associated vasculitis (AAV) remission and relapse, prolonged use of glucorticosteroids and burden of disease – a real world study in the UK. UK Kidney week. 2020.

15. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Annals of the Rheumatic Diseases. 2009;68(12):1827.
16. Hiemstra TF, Walsh M, Mahr A, Savage CO, de Groot K, Harper L, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. Jama. 2010;304(21):2381-8.

Appendix A. Demographic and baseline characteristics of UK patients in the ADVOCATE trial

Table 11. Summary of demographic characteristics of UK patients in the ADVOCATE study (ITT populations)

ChemoCentryx, Inc.
Protocol CL010_168

Summary of Subject Demographics
(UK Patients Only in the Intent-to-Treat Population)

Demographic Variable Statistic/Category	Prednisone + Standard of Care (N=23)	Avacopan + Standard of Care (N=17)	Total (N=40)
Age at screening			
n	23	17	40
Mean	58.0	57.6	57.9
SD	15.09	11.94	13.67
Minimum	15	33	15
Median	60.0	57.0	59.5
Maximum	78	74	78
Age category, n (%)			
12-17 years	1 (4.3)	0 (0.0)	1 (2.5)
18-50 years	4 (17.4)	3 (17.6)	7 (17.5)
51-64 years	10 (43.5)	8 (47.1)	18 (45.0)
65-75 years	6 (26.1)	6 (35.3)	12 (30.0)
>75 years	2 (8.7)	0 (0.0)	2 (5.0)
Age at diagnosis of AAV			
n	23	17	40
Mean	57.9	57.5	57.7
SD	14.83	12.13	13.58
Minimum	16	33	16
Median	58.2	57.6	57.9
Maximum	78	74	78
Gender, n (%)			
Male	15 (65.2)	9 (52.9)	24 (60.0)
Female	8 (34.8)	8 (47.1)	16 (40.0)

Note: ANCA=Anti-Neutrophil Cytoplasmic Antibody, AAV=(ANCA)-associated vasculitis. %=100*n/N

Program name: demog.sas Run date: 24NOV2021 8:42 Database last modified: 27JAN2020 11:32

Summary of Subject Demographics
(UK Patients Only in the Intent-to-Treat Population)

Demographic Variable Statistic/Category	Prednisone + Standard of Care (N=23)	Avacopan + Standard of Care (N=17)	Total (N=40)
Race, n (%)			
Asian	2 (8.7)	0 (0.0)	2 (5.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
White	21 (91.3)	17 (100.0)	38 (95.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, n (%)			
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)
Not Hispanic or Latino	23 (100.0)	17 (100.0)	40 (100.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Not Reported	0 (0.0)	0 (0.0)	0 (0.0)
Country, n (%)			
United Kingdom	23 (100.0)	17 (100.0)	40 (100.0)
Geographic Region, n (%)			
Europe and Rest of World excluding Japan	23 (100.0)	17 (100.0)	40 (100.0)
Europe	23 (100.0)	17 (100.0)	40 (100.0)

Note: ANCA=Anti-Neutrophil Cytoplasmic Antibody, AAV=(ANCA)-associated vasculitis. %=100*n/N

Table 12. Summary of baseline characteristics of UK patients in the ADVOCATE study (ITT population)

Summary of Baseline Characteristics
(UK Patients Only in the Intent-to-Treat Population)

Baseline Characteristic Statistic/Category	Prednisone + Standard of Care (N=23)	Avacopan + Standard of Care (N=17)	Total (N=40)
AAV Status, n (%)			
Newly diagnosed	16 (69.6)	13 (76.5)	29 (72.5)
Relapsed	7 (30.4)	4 (23.5)	11 (27.5)
ANCA Positivity, n (%)			
PR3	11 (47.8)	8 (47.1)	19 (47.5)
MPO	12 (52.2)	9 (52.9)	21 (52.5)
Standard of Care Treatment, n (%)			
IV Rituximab	13 (56.5)	7 (41.2)	20 (50.0)
IV Cyclophosphamide	10 (43.5)	7 (41.2)	17 (42.5)
Oral Cyclophosphamide	0 (0.0)	3 (17.6)	3 (7.5)
IV or Oral Cyclophosphamide	10 (43.5)	10 (58.8)	20 (50.0)
Stratification Category, n (%)			
Rituximab, PR3+, Newly Diagnosed	2 (8.7)	1 (5.9)	3 (7.5)
Rituximab, PR3+, Relapsed Disease	3 (13.0)	3 (17.6)	6 (15.0)
Rituximab, MPO+, Newly Diagnosed	5 (21.7)	2 (11.8)	7 (17.5)
Rituximab, MPO+, Relapsed Disease	3 (13.0)	1 (5.9)	4 (10.0)
IV Cyclophosphamide, PR3+, Newly Diagnosed	5 (21.7)	2 (11.8)	7 (17.5)
IV Cyclophosphamide, PR3+, Relapsed Disease	1 (4.3)	0 (0.0)	1 (2.5)
IV Cyclophosphamide, MPO+, Newly Diagnosed	4 (17.4)	5 (29.4)	9 (22.5)
IV Cyclophosphamide, MPO+, Relapsed Disease	0 (0.0)	0 (0.0)	0 (0.0)
Oral Cyclophosphamide, PR3+, Newly Diagnosed	0 (0.0)	2 (11.8)	2 (5.0)
Oral Cyclophosphamide, PR3+, Relapsed Disease	0 (0.0)	0 (0.0)	0 (0.0)
Oral Cyclophosphamide, MPO+, Newly Diagnosed	0 (0.0)	1 (5.9)	1 (2.5)
Oral Cyclophosphamide, MPO+, Relapsed Disease	0 (0.0)	0 (0.0)	0 (0.0)

Note 1: ANCA=Anti-Neutrophil Cytoplasmic Antibody, AAV=ANCA-Associated Vasculitis, MPO=myeloperoxidase, PR3=proteinase-3, BMI=Body Mass Index, BVAS=Birmingham Vasculitis Activity Score, VDI=Vasculitis Damage Index, SF-36 v2=Short Form-36 version 2, EQ-5D-5L=EuroQOL-5D-5L Health Scale, eGFR=estimated glomerular filtration rate, UACR=urinary albumin:creatinine ratio, MCP-1=monoctye chemoattractant protein-1, RBC=Red Blood Cell, IVRS=Interactive Voice Response System. %=100*n/N
[1] Subjects can appear in more than one category

Summary of Baseline Characteristics
(UK Patients Only in the Intent-to-Treat Population)

Baseline Characteristic Statistic/Category	Prednisone + Standard of Care (N=23)	Avacopan + Standard of Care (N=17)	Total (N=40)
Type of AAV, n (%)			
Granulomatosis with polyangiitis (GPA)	17 (73.9)	8 (47.1)	25 (62.5)
Microscopic polyangiitis (MPA)	6 (26.1)	9 (52.9)	15 (37.5)
Duration of ANCA-Associated Vasculitis (Months)			
N	23	17	40
Mean	9.20	6.81	8.18
SD	17.466	16.038	16.705
Minimum	0.0	0.0	0.0
Median	0.20	0.23	0.23
Maximum	64.7	63.7	64.7
BVAS Entry Criteria [1], n (%)			
One or more major item	12 (52.2)	10 (58.8)	22 (55.0)
Three or more minor items	21 (91.3)	15 (88.2)	36 (90.0)
Two renal items of Proteinuria and hematuria	7 (30.4)	4 (23.5)	11 (27.5)
Renal Disease at Baseline, n (%)			
Yes	20 (87.0)	11 (64.7)	31 (77.5)
No	3 (13.0)	6 (35.3)	9 (22.5)
Smoking Status, n (%)			
Current	3 (13.0)	1 (5.9)	4 (10.0)
Former	8 (34.8)	7 (41.2)	15 (37.5)
Never	12 (52.2)	9 (52.9)	21 (52.5)

Note 1: ANCA=Anti-Neutrophil Cytoplasmic Antibody, AAV=ANCA-Associated Vasculitis, MPO=myeloperoxidase, PR3=proteinase-3, BMI=Body Mass Index, BVAS=Birmingham Vasculitis Activity Score, VDI=Vasculitis Damage Index, SF-36 v2=Short Form-36 version 2, EQ-5D-5L=EuroQOL-5D-5L Health Scale, eGFR=estimated glomerular filtration rate, UACR=urinary albumin:creatinine ratio, MCP-1=monoctye chemoattractant protein-1, RBC=Red Blood Cell, IVRS=Interactive Voice Response System. %=100*n/N
[1] Subjects can appear in more than one category

Table 2
Summary of Baseline Characteristics
(UK Patients Only in the Intent-to-Treat Population)

Baseline Characteristic Statistic/Category	Prednisone + Standard of Care (N=23)	Avacopan + Standard of Care (N=17)	Total (N=40)
Body Weight (kg)			
N	23	17	40
Mean	81.03	79.52	80.39
SD	16.913	16.830	16.677
Minimum	52.8	51.0	51.0
Median	78.60	83.00	79.40
Maximum	112.7	108.8	112.7
Height (cm)			
N	23	17	40
Mean	172.43	168.88	170.93
SD	8.267	7.696	8.125
Minimum	157.0	157.0	157.0
Median	174.00	168.00	170.00
Maximum	186.0	185.0	186.0
BMI (kg/m^2)			
N	23	17	40
Mean	27.19	27.96	27.52
SD	5.108	6.314	5.588
Minimum	20.4	19.5	19.5
Median	26.19	28.06	26.54
Maximum	36.5	38.9	38.9

Note 1: ANCA=Anti-Neutrophil Cytoplasmic Antibody, AAV=ANCA-Associated Vasculitis, MPO=myeloperoxidase, PR3=proteinase-3, BMI=Body Mass Index, BVAS=Birmingham Vasculitis Activity Score, VDI=Vasculitis Damage Index, SF-36 v2=Short Form-36 version 2, EQ-5D-5L=EuroQOL-5D-5L Health Scale, eGFR=estimated glomerular filtration rate, UACR=urinary albumin:creatinine ratio, MCP-1=monoctye chemoattractant protein-1, RBC=Red Blood Cell, IVRS=Interactive Voice Response System. %=100*n/N
[1] Subjects can appear in more than one category

Table 2
Summary of Baseline Characteristics
(UK Patients Only in the Intent-to-Treat Population)

Baseline Characteristic Statistic/Category	Prednisone + Standard of Care (N=23)	Avacopan + Standard of Care (N=17)	Total (N=40)
BVAS Score (Adjudicated)			
N	23	17	40
Mean	16.6	15.8	16.2
SD	5.45	6.01	5.63
Minimum	7	9	7
Median	16.0	14.0	15.5
Maximum	27	30	30
VDI Score (Adjudicated)			
N	23	17	40
Mean	0.8	0.5	0.7
SD	1.56	1.12	1.38
Minimum	0	0	0
Median	0.0	0.0	0.0
Maximum	6	4	6
SF-36 v2 Mental Component Score			
N	20	17	37
Mean	40.23	42.92	41.47
SD	16.038	10.650	13.711
Minimum	14.3	28.7	14.3
Median	39.08	38.92	38.92
Maximum	63.5	61.9	63.5

Note 1: ANCA=Anti-Neutrophil Cytoplasmic Antibody, AAV=ANCA-Associated Vasculitis, MPO=myeloperoxidase, PR3=proteinase-3, BMI=Body Mass Index, BVAS=Birmingham Vasculitis Activity Score, VDI=Vasculitis Damage Index, SF-36 v2=Short Form-36 version 2, EQ-5D-5L=EuroQOL-5D-5L Health Scale, eGFR=estimated glomerular filtration rate, UACR=urinary albumin:creatinine ratio, MCP-1=monoctye chemoattractant protein-1, RBC=Red Blood Cell, IVRS=Interactive Voice Response System. %=100*n/N
[1] Subjects can appear in more than one category

Summary of Baseline Characteristics
(UK Patients Only in the Intent-to-Treat Population)

Baseline Characteristic Statistic/Category	Prednisone + Standard of Care (N=23)	Avacopan + Standard of Care (N=17)	Total (N=40)
SF-36 v2 Physical Component Score			
N	20	16	36
Mean	41.26	36.43	39.11
SD	9.371	10.974	10.257
Minimum	22.9	17.6	17.6
Median	42.16	37.52	41.24
Maximum	56.5	55.7	56.5
EQ-5D-5L VAS Score			
N	22	17	39
Mean	67.0	58.8	63.5
SD	24.04	21.90	23.20
Minimum	20	30	20
Median	75.0	50.0	70.0
Maximum	95	100	100
EQ-5D-5L Index Score			
N	22	17	39
Mean	0.754	0.679	0.721
SD	0.1896	0.2821	0.2340
Minimum	0.40	0.01	0.01
Median	0.774	0.785	0.785
Maximum	1.00	1.00	1.00

Note 1: ANCA=Anti-Neutrophil Cytoplasmic Antibody, AAV=ANCA-Associated Vasculitis, MPO=myeloperoxidase, PR3=proteinase-3, BMI=Body Mass Index, BVAS=Birmingham Vasculitis Activity Score, VDI=Vasculitis Damage Index, SF-36 v2=Short Form-36 version 2, EQ-5D-5L=EuroQOL-5D-5L Health Scale, eGFR=estimated glomerular filtration rate, UACR=urinary albumin:creatinine ratio, MCP-1=monoctye chemoattractant protein-1, RBC=Red Blood Cell, IVRS=Interactive Voice Response System. %=100*n/N
[1] Subjects can appear in more than one category

Summary of Baseline Characteristics
(UK Patients Only in the Intent-to-Treat Population)

Baseline Characteristic Statistic/Category	Prednisone + Standard of Care (N=23)	Avacopan + Standard of Care (N=17)	Total (N=40)
eGFR			
N	22	16	38
Mean	57.0	60.4	58.5
SD	34.01	35.68	34.28
Minimum	17	17	17
Median	49.0	54.5	49.0
Maximum	138	120	138
eGFR (mL/min/1.73 m^2), n (%)			
<30	7 (30.4)	4 (23.5)	11 (27.5)
30-59	5 (21.7)	4 (23.5)	9 (22.5)
>59	10 (43.5)	8 (47.1)	18 (45.0)
Not assessed	1 (4.3)	1 (5.9)	2 (5.0)
Hematuria, n (%)			
<10 RBC/hpf	5 (21.7)	3 (17.6)	8 (20.0)
>=10 RBC/hpf	16 (69.6)	11 (64.7)	27 (67.5)
Not assessed	2 (8.7)	3 (17.6)	5 (12.5)

Note 1: ANCA=Anti-Neutrophil Cytoplasmic Antibody, AAV=ANCA-Associated Vasculitis, MPO=myeloperoxidase, PR3=proteinase-3, BMI=Body Mass Index, BVAS=Birmingham Vasculitis Activity Score, VDI=Vasculitis Damage Index, SF-36 v2=Short Form-36 version 2, EQ-5D-5L=EuroQOL-5D-5L Health Scale, eGFR=estimated glomerular filtration rate, UACR=urinary albumin:creatinine ratio, MCP-1=monoctye chemoattractant protein-1, RBC=Red Blood Cell, IVRS=Interactive Voice Response System. %=100*n/N
[1] Subjects can appear in more than one category

Program name: baseln.sas Run date: 23NOV2021 15:48 Database last modified: 27JAN2020 11:32

Summary of Baseline Characteristics
(UK Patients Only in the Intent-to-Treat Population)

Baseline Characteristic Statistic/Category	Prednisone + Standard of Care (N=23)	Avacopan + Standard of Care (N=17)	Total (N=40)
UACR (mg/g)			
N	21	15	36
Mean	504.333	572.933	532.917
SD	809.1367	853.5271	816.5142
Minimum	4.00	3.00	3.00
Median	194.000	233.000	211.000
Maximum	3516.00	2800.00	3516.00
UACR (mg/g), n (%)			
<10	4 (17.4)	3 (17.6)	7 (17.5)
10-300	8 (34.8)	5 (29.4)	13 (32.5)
>300	9 (39.1)	7 (41.2)	16 (40.0)
Not assessed	2 (8.7)	2 (11.8)	4 (10.0)
Urinary MCP-1:creatinine ratio (pg/mg creatinine)			
N	22	15	37
Mean	1178.25	1253.43	1208.72
SD	946.666	1341.582	1106.394
Minimum	182.0	124.4	124.4
Median	866.95	647.10	764.20
Maximum	3151.1	3949.8	3949.8

Note 1: ANCA=Anti-Neutrophil Cytoplasmic Antibody, AAV=ANCA-Associated Vasculitis, MPO=myeloperoxidase, PR3=proteinase-3, BMI=Body Mass Index, BVAS=Birmingham Vasculitis Activity Score, VDI=Vasculitis Damage Index, SF-36 v2=Short Form-36 version 2, EQ-5D-5L=EuroQOL-5D-5L Health Scale, eGFR=estimated glomerular filtration rate, UACR=urinary albumin:creatinine ratio, MCP-1=monoctye chemoattractant protein-1, RBC=Red Blood Cell, IVRS=Interactive Voice Response System. %=100*n/N
[1] Subjects can appear in more than one category

NICE National Institute for Health and Care Excellence

Patient organisation submission

Avacopan for maintenance treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Vasculitis UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Vasculitis UK is the recognised and CC registered patient support charity for UK vasculitis patients suffering from all 18 types of vasculitis. The charity has approx. 1500 subscribers to its postal mailing list but there are 2 online support groups on Facebook & HealthUnlocked platforms, each with 4-5000 subscribers. Obviously there will be some overlap in these numbers as some are members of all 3. However Vasculitis UK can fairly claim to be the Voice of the UK vasculitis community.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	No

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	**a)Vasculitis UK is a vasculitis patient support organisation for people with all forms of vasculitis so we have a telephone & email support service so we have daily interaction with patients.** **b) We run & monitor 2 online peer support discussion groups, each with 4-5000 members, where people can vent their woes & experiences. Side effects of steroids are a very frequent cause of discussion. For this appraisal we invited those in the groups to offer their positive & negative experiences of glucocorticoid medication – prednisolone.** **c) I contracted ANCA vasculitis in 2001 and was given standard of care treatment, which involved induction with high dose prednisolone & cyclophosphamide infusions, followed by maintenance over about 8-10 years with gradually reducing prednisolone dose + immune suppressing drugs. Some of the undesirable side effects of that long exposure to glucocorticoids are with me still!**
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	ANCA associated vasculitis(AAV) comes in different forms according to the type (there are 3 distinct variations), the degree of aggression of the disease, the organs affected and the delay to diagnosis.In some cases, where it is not diagnosed promptly, and treated appropriately, it can progress rapidly to multiple organ failure & death – sometimes the definitive diagnosis is only made post mortem. Treatment almost always entails the use of high dose glucocorticoids, for rapid suppression of inflammation, in conjuction with powerful immune suppressing drugs such as cyclophosphamide or, more recently,rituximab. AAV is commonly recognised as a relapsing disease, resulting in intermittent “flares”, where the symptoms return with varying degrees of severity. Clinicians typically use a temporary increase in the prednisolone dose as a “quick-fix” for the duration of the flare.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients given glucocorticoids are very keen to be given an alternative drug, due to the side effects. Increased appetite and consequent weight gain – with the resulting classic “moon face” is the most frequent complaint, but most patients are very conscious of the risks of diabetes, cataracts and osteoporosis.
8. Is there an unmet need for patients with this condition?	Treatment for AAV has improved dramatically since the introduction of rituximab, but as the recent OCTAVE trial has demonstrated. even targeted immune suppression can have serious negative effects.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients & carers currently know little about avacopan.Those AAV patients who do know have the hope/expectation that avacopan might have the potential to completely replace the use of prednisolone in AAV induction & maintenance, thereby leaving them without the unfortunate (& in many cases, irreversible) consequences of prolonged exposure to glucocorticoids**.** We (Vasculitis UK) have conducted a survey of vasculitis patients inviting them to comment on their experience of prednisolone. The results were generally very negative.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As there have, so far, not been any widespread “field” trials of avacopan, patients have not yet had the opportunity to experience either the benefits or downsides of treatment with avacopan.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Vasculitis comprises 18 types of vasculitis, most of which do not involve the complement channel, which is involved in ANCA vasculitis and is moderated by avacopan, thus unfortunately this group of Large Vessel Vasculitis (mainly elderly) patients, seem unlikely to benefit from Avacopan
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**None – unless cost becomes an issue.**

Other issues	
13. Are there any other issues that you would like the committee to consider?	We now know from the ADVOCATE trial that Avacopan is both safe and effective in controlling active AAV.However there is no widespread evidence to support the potential benefits or for anyone to experience the unforeseen undesirable side effects. As the potential health benefits for patients and financial benefits for the NHS are so great, there might be merit in NICE awarding temporary or restricted approval initially in order that the potential benefits and possible drawbacks of avacopan might be properly assessed.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Glucocorticoids, GCs) usually in the form of prednisolone are a frontline treatment in the management of the potentially fatal disease, ANCA vasculitis. The undesirable side-effects of prednisolone have been experienced and documented over many years.The hypothesis that avacopan disrupts the pathological process of AAV seems to be borne out in practise and trial evidence suggests that avacopan is both safe and effective for use in controlling this rare autoimmune disease.
- The direct costs to the NHS of dealing with the consequences of treating AAV with glucocorticoids are not easy to quantify, but must be significant. Diabetes and osteoporosis are difficult to control iatrogenic effects with expensive long-term consequences. Cataracts are relatively cheap to correct. Other issues such as cardiovascular complications are less well investigated.
- The personal cost of dependence on GCs in controlling AAV for patients can be high. For many, significant weight, gain which is difficult to reverse, results in a serious loss of self-esteem, impeding recovery from this devastating disease. This is coupled with loss of muscle mass. A significant number of AAV patients lose their mobility due to loss of digiits or limbs as a direct consequence of AAV but this is compounded by loss of mobility caused by diabetes as a consequence of GC treatment.
- Having established that Avacopan is both safe & effective in controlling AAV, the full potential benefits and possible drawbacks will only become apparent once there is widespread use. Thus some sort of restricted approval should be considered.

- With most diseases major breakthroughs occur only periodically. In the case of ANCA vasculitis, these were a) 1960s introduction of steroids b) 1970s use of chemo agent cyclophosphamide c) 2008 approval of rituximab. These 3 game-changers saved many lives, protected incalculable quality of life and made similarly incalculable savings for the NHS. Avacopan has the potential to be one of those game changers for people currently living with AAV and the curse of prednisolone.
-
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐**x Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Professional organisation submission

Avacopan for maintenance treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Association for Paediatric Nephrology (BAPN)**

3. Job title or position	**Guideline Lead (BAPN), Consultant Paediatric Nephrologist (Great Ormond Street Hospital)**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The BAPN is the professional organisation for clinicians working in paediatric nephrology, as part of the larger organisation – the UK Kidney Association (UKKA).**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To stop initial symptoms of vasculitis and prevent ongoing kidney damage, to prevent long-term complications such as chronic kidney disease.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Improvement in serum creatinine (if raised at baseline), improvement in other renal blood/urine tests Normalisation of ANCA Improvement in vasculitis disease activity scores

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is still a significant burden of disease in children with ANCA vasculitis and although there are successful treatments, they come with a significant side effect burden.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	The initial treatment of ANCA glomerulonephritis in children is with "induction" treatment which generally involves immunosuppressive medications, including corticosteroids, MMF, cyclophosphamide, rituximab and others less commonly.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no national guidelines on the treatment of ANCA glomerulonephritis (GN) in children, there are European and international guidelines but not focused on ANCA GN – the KDIGO GN guideline is probably the most widely used.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	There is some consistency but still variability remains given that this is an uncommon disorder in children, so each individual centre will only build up limited experience in this.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	If this were licensed for use in children, it may provide an alternative to corticosteroids for the induction treatment of ANCA vasculitis in children.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Paediatric data are required before any comment on that can be made.
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-	

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The main potential benefit is the reduction of side effect burden associated with corticosteroids, but until more paediatric data are available on Avacopan it will be difficult to comment in a meaningful evidence-based way.
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA308?	
21. How do data on real-world experience compare with the trial data?	I am not aware of any paediatric nephrology centre yet using Avacopan in clinical care of children with ANCA vasculitis.
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- There is an unmet need in the initial treatment of ANCA vasculitis in children, and many of these children end up with chronic kidney disease.
- Current treatment with immunosuppressive medications carries a significant side effect burden, particularly corticosteroids.
- Avacopan may offer the potential of reducing this side effect burden from current medications to treat ANCA vasculitis.
- Paediatric data are required before any evidence based comment can be made on the utility of this for children.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

NICE National Institute for Health and Care Excellence

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Avacopan for maintenance treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**UK Kidney Association**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**UK Kidney Association** We are the leading professional body for the UK renal community, dedicated to improving lives by supporting professionals in the delivery of kidney care and research. We have over 1,200 doctors, scientists and multi-professional team members. Funded by membership fees and corporate sponsorship
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	**No**

manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**NO**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To induce and maintain disease remission in anti-neutrophil cytoplasm antibody (ANCA) associated vasculitis- a set of multi-organ autoimmune diseases that can lead to significant morbidity and mortality, in combination with other immunosuppressive drugs.
7. What do you consider a clinically significant treatment response? (For example, a	Induction of remission – as defined by a clinical, biochemical and serologic response. A Birmingham vasculitis activity score(BVAS) of 0 is considered to effectively demonstrate remission, which is predominantly based on scoring clinical features

reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes; the issue at the moment is that there is considerable treatment related morbidity and mortality- due to infections
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Induction therapy with steroids (often a mixture of IV and oral) and immunosuppressive in the form of cyclophosphamide, rituximab or sometimes mycophenolate or methotrexate
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes many; eg EULAR guidelines: https://ard.bmj.com/content/75/9/1583; NICE guidance on rituximab https://www.nice.org.uk/guidance/ta308; American colleg of rheumatology guidelines https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Vasculitis
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals	Pathway generally well defined. There are variations in dosing of steroids and duration of therapy between centres in UK, but for the most part two years of treatment following induction therapy is considered to be usual

across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	It could allow for steroid avoidance which we believe contributes significantly to morbidity(infection predominantly, but new onset diabetes, hypertension and premature cardiovascular disease) and mortality
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes- but instead of using steroids ; in combination with immunosuppressives. No dat on whether it cols substitute for any other drug apart from steroids.
• How does healthcare resource use differ between the technology and current care?	Current regimen uses a starting dose of 1mg/kg of prednisolone, in addition to pulses of iv steroids if considered clinically important (eg severe disease). The new technology could avoid the use of the high dose oral steroids
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care and specialist clinics
• What investment is needed to introduce the technology? (For	None, except I presume this will need some sort of joint GP/specialists prescribing/monitoring agreement. It may that if restricted prescribing to secondary care/specialist centre agreement via MDT for a spoke and hub distribution may be needed.

example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, steroid avoidance should change the morbidities patient experience and significantly improved quality of life. However, he data from the trial do not suggest a reduction in infections or other serious side effects
• Do you expect the technology to increase length of life more than current care?	Probably not, but better quality.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, as seen in trial and experience of patients off or avoiding steroids
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Most benefit for those at greatest risk of steroid induced side effects – eg borderline diabetes, poorly controlled diabetes, obese, history of steroid intolerance, elderly and those with more advanced kidney disease(at greatest risk of infections).

The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No different- oral medication as with prednisolone; Monitoring will need to be considered and possibly shared care model could be develoed with primary care
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Usual testing will be required No rues to stop beyond the usual intolerance or adverse reactions

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, there has been a reliance on the use of steroids for the treatment of ANCA associated vasculitis for a number of years. This is the first opportunity to move away from this. Alternative strategies to achieve this aim would be to stop/reduce steroids and we have attempted to get trials sponsored to this end from HTA with no success. So without trial data this remains the only steroid sparing/avoiding strategy we have
• Is the technology a 'step-change' in the management of the condition?	Yes, See above
• Does the use of the technology address any	Again see above- steroid avoidance is a clear important unmet need

particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The reported side effects are no different to steroid treated patients as far as the only trial shows us, with the exception of steroid related adverse effects which were significantly improved.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, and many patients were enrolled from UK centres. The only main difference was the way the rituximab was administered which was weekly x4 rather than 2 doses 2 weeks apart. However, we know that there is little or no difference in outcomes based on these two protocols
• If not, how could the results be extrapolated to the UK setting?	N/A as the trial reflects the way care is provided in UK- wit the exception of the rituximab dosing
• What, in your view, are the most important outcomes, and were they measured in the trials?	Remission and relapse. In trial- Remission rates, Quality of life, steroid related side effects; the trial was fair in comparing the first six months of treatment of avacopan vs steroids. At this stage the drug was non inferior. From month 6 to 12, the interventions were not completely comparable(steroid arm had no maintenance steroids) while the avacopan limb continued with avacopan. As such its not clear what to make of the claims of superiority at 12 months and reduced rates of relapse.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No surrogates were used
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not as far as I am aware
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There are only two trials- a small phase II(67 patients) and the phase III. Total of just under 400 patients. As such I do not think a systemic review will help.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA308?	No, but the comparator is not really Rituximab it's the steroid arm which was also in theTA308. The pexivas trial examined two different steroid doses and showed that the lower of the doses was associated with fewer infections and could be used safely, making the point that steroid reduction was feasible.

21. How do data on real-world experience compare with the trial data?	I have had a total of three patients take the compound (as part of the trial) and they were OK. Beyond this I am not aware of any other real world experience
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None
22b. Consider whether these issues are different from issues with current care and why.	N/A
Key messages	
23. In up to 5 bullet points, please summarise the key messages of your submission. • Allows steroid avoidance which is good for quality of life and morbidity • Did not show a real difference in infections • Was tolerated and efficacious in inducing remisison • The duration of treatment was not considered- beyond the year used in the trial	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Professional organisation submission

Avacopan for maintenance treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	Renal Pharmacy Group

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	√☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? √☐ other (please specify): A member of a professional body
5a. Brief description of the organisation (including who funds it).	The UK Renal Pharmacy Group (UKRPG) represents the interests of renal pharmacists and renal pharmacy technicians across the UK and other countries. It provides a clinical network for members along with education and training activities, including an annual conference and clinical webinars. The UKRPG also provides expert pharmaceutical advice on matters relating to renal therapeutics, and authors the Renal Drug Handbook and Renal Drug Database - which provide healthcare professionals with a single reference of practical information relating to drug use in renally impaired patients, sourced from the practical experience of renal units throughout the UK. The UKRPG is funded by members' subscriptions and royalties from the Renal Drug Handbook and Renal Drug Database. Educational activities are funded by corporate sponsorship. The RPG is a non-profit organisation.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	The RPG has not received any funding from Vifor in the past 12 months

manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of the treatment is initiation of remission and then prevention of relapse.
7. What do you consider a clinically significant treatment response? (For example, a	Prevention of relapse and prevention of progression to end stage kidney disease.

reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The medications available at the moment have a burden on the patient in terms of side effects and treatment toxicity. A medication that prevents relapse and enables reduction in the amount of steroid without other toxicity would benefit patients. So yes there is a need for a medication which allows reduction in the use of steroids.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are KDIGO guidelines and there is a NHSE commissioning policy on the use of rituximab in vasculitis.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals	There are differences in opinion on when to use cyclophosphamide or rituximab as the trials have extended evidence beyond the NHSE commissioning document. Trials have furthered experience. This paper has reviewed the therapeutic options. HDJRE_5534851 1..14 (nih.gov)

across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Avacopan may enable reduction in the use of corticosteroids with the resultant reduction in treatment toxicity
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	If approved and funded, current care would change. Avacopan is currently unlicensed so only used within trials.
• How does healthcare resource use differ between the technology and current care?	At the moment cyclophosphamide is within tarif as is prednisolone and azathioprine. Depending on the cost of avacopan this would probably be funded separately.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This should be started in secondary care but could be continued in primary care dependant on monitoring requirements within the license.
• What investment is needed to introduce the technology? (For	Investment would be in the drug cost and perhaps in training.

example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes, if reduction in cardiovascular mortality and infection rates are shown in clinical practice this would extend patients life and time to dialysis.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes because patients would not have the toxicity they get at the moment from steroids.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I am not sure.

The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Not that I am aware of.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This depends on the license requirements.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Not sure.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	This is the first advance in many years and perhaps the first time a reduction in the use of steroids could be achieved.

• Does the use of the technology address any particular unmet need of the patient population?	For those patients at particular risk of steroid toxicity avacopan would be of great benefit, such as diabetes. Cardiovascular toxicity remains a problem for many patients taking steroids.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Monitoring of LFTs would be required regularly – exact timing will depend on the manufacturers licensing information.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	My worry from the Advocate study was the patient group who received rituximab didn't receive the usual maintenance therapy of azathioprine or further rituximab and it is unclear what effect that had on the outcomes.
• What, in your view, are the most important outcomes, and were they measured in the trials?	A reduction in the rate of relapse in the avacopan group, sustained remission, reduction in glucocorticoid toxic effect are all important and were looked at in the Advocate trial.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Longer term cardiovascular data.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA308?	Yes there have been trials showing that rituximab is superior to azathioprine in reducing relapse rates, and this drug has dropped in price since the 2014 appraisal and so is more cost effective now.

21. How do data on real-world experience compare with the trial data?	Real world data for longer use of rituximab is showing good effect as in the trials.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not that I am aware of.
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Reducing cardiovascular mortality in vasculitis is important as this is what many patients die from.
- Avacopan can reduce the amount of steroids that patients are required to take and this reduces the cardiovascular burden of therapy
- updating TA 308 is required with recent trial data
- From the Advocate study avacopan is non-inferior to steroids at reducing relapse rates but without the treatment toxicity burden
- Cost of the product is important and if it can be continued in primary care

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Avacopan for maintenance treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NHS England & Improvement Specialised Commissioning**

3. Job title or position	
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? ☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☒ an expert in treating the condition for which NICE is considering this technology? ☒ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NHS England Specialised Commissioning**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	**BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis (currently being revised but last published 2014)-** https://academic.oup.com/rheumatology/article/53/12/2306/1802843 **2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis** **EULAR/EUVAS 2015**
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway of care managed by specialised rheumatology in both children's and adult services. It is well - defined.
8. What impact would the technology have on the current pathway of care?	The marketing authorisation is for adjunctive treatment for adults with severe active ANCA autoantibody-associated vasculitis (GPA and MPA) to induce and maintain remission. Reduction in cumulative glucocorticoid doses required to achieve induction and maintain remission in ANCA associated vasculitis and thus reduce glucocorticoid burden/toxicity in the short term and long term. Access to treatment with avacopan would particularly enable patients with severe refractory/relapsing potentially organ-threatening disease, such as active renal disease, to try an effective therapeutic agent

	and reduce the glucocorticoid requirement so potentially reducing acute and long term glucocorticoid toxicity which can be a significant problem in these patients with this chronic, relapsing condition. By reducing flares because of sustained remission and reduced cumulative glucocorticoid dose, it will be an attractive option particularly for younger patients. It may be an option for patients with chronic opportunistic infection, particularly fungal infection, due to their high strength immunosuppression when they flare. It may reduce the risk of further complications by reducing the need for further IV and high dose oral glucocorticoids and/or reduce the need for bridging courses/maintenance courses of IVIg. However, avacopan was not evaluated in patients with pre-existing opportunistic infections in the clinical trial. Patients who received avacopan did not show a significant reduction in infectious episodes in general but they did experience fewer serious opportunistic infections.
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	Not available generally but occasionally on compassionate grounds
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Approval for treatment should be ratified at a regional specialised MDT meeting
• How does healthcare resource use differ	Avacopan is oral and replaces the need for long periods of high dose oral glucocorticoids. It is not clear whether it will reduce the need for any day case unit attendances for intravenous infusions of IV rituximab and/or cyclophosphamide. The trial did show longer sustained remission in the patients on avacopan at

between the technology and current care?	week 52 so there may potentially be fewer significant flares thus reducing the requirement for further treatment with IV cyclophosphamide and/or rituximab but this will need to be monitored.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	At specialised centres with experience in managing patients with vasculitis and their shared care partners/networks.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None in particular
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	No
11. What is the outcome of any evaluations or audits of the use of the technology?	Not aware of any that have been performed to date as this is a new therapy and very few patients living in England will have received the drug outside of the clinical trials.
Equality	

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	No equality issues known.
12b. Consider whether these issues are different from issues with current care and why.	N/A

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	**Sanjeev Patel**
2. Name of organisation	**NHSE**

3. Job title or position	**Clinical advisor : Commercial Medicines**
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? ☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**General taxation**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
Topic specific questions	

6. Do the 2019/20 NHS reference costs include costs for excess bed days?	**Yes. These reference costs include the cost of all bed days including excess bed days**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Avacopan for maintenance treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. Your response should not be longer than 10 pages.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	**Dr Peter Lanyon**
2. Name of organisation	**NHS England Specialised Rheumatology Clinical Reference Group**

3. Job title or position	
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? **x**☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? **x**☐ an expert in treating the condition for which NICE is considering this technology? **x**☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it **x**☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick	☐

here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Current treatment of the condition in the NHS	
8. Are any clinical guidelines used in the treatment of the condition, and if so, which?	BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis (currently being revised but last published 2014) https://academic.oup.com/rheumatology/article/53/12/2306/1802843 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis https://www.rheumatology.org/Portals/0/Files/Guideline-Management-ANCA-Associated-Vasculitis-2021.pdf Rituximab for maintenance of remission in ANCA-associated vasculitis: expert consensus guidelines https://doi.org/10.1093/rheumatology/kez632

9. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathways are in general well defined and facilitated by previous NHS England commissioning policies related to the treatment of ANCA-associated vasculitis. There will be some variation in care pathways according to both the presenting (organ) features of the disease and according to which specialties leads on the management of these condition in each NHS Trust. For example, in HES data (Hospital Episode Statistics), the specialty treatment function codes (TFC) that associate with an ICD code for ANCA-associated vasculitis combined with an OPCS code for an intravenous cytokine inhibitors band 1 (which includes rituximab) are predominately rheumatology and nephrology, indicative of the main specialties involved in the pathway of care (source: GIRFT National Specialty Report for rheumatology) There may also be variation in access to specialised MDT care when needed, and in whether an NHS Trust needs to seek external approval for the use of rituximab as maintenance therapy depending on whether that Trust is a recognised specialised centre on the Provider Eligibility List. These arrangements have been facilitated by the development of NHS England regional networks for autoimmune diseases/specialised rheumatology and the existence of informally recognised major tertiary/national centres of expertise for complex or refractory cases.
10. What impact would the technology have on the current pathway of care?	There is likely to be no significant increase in resources required for current pathways of care. The ability to reduce steroid use and steroid associated toxicity and hence adverse events has been demonstrated and this is likely to lead to less healthcare interaction related to assessing and treating these events. The ability to reduce relapse risk to week 52 (e.g., increase in sustained remission) would also be anticipated to lead to a reduction in the healthcare usage related to relapse.
The use of the technology	
11. To what extent and in which population(s) is the	I am not aware of any data on current use

technology being used in your local health economy?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	In terms of resource use associated with serious adverse events, comparison between the avacopan and steroid groups indicates higher risk in the in the prednisone group than in the avacopan group. There were more deaths, life-threatening or serious adverse events, and infections in the prednisone group than in the avacopan group. This is consistent with the higher glucocorticoid exposure. The resource use associated with this would therefore be anticipated to be lower with avacopan use. It is worth noting that although the Advocate trial did not include maintenance rituximab after the initial treatment course, at week 52 the magnitude of the treatment difference between avacopan and prednisolone arms is greater for the patients who receive rituximab induction as single dose compared to cyclophosphamide and azathioprine. This is an important consideration and should be interpreted in light of the current NHS landscape that the clinical community is trying where possible and clinicall appropriate to reduce exposure to rituximab during the COVID-10 pandemic. This is because ongoing B cell depletion risks a poor response to vaccination, leading to this exposure being included as a high priority group in the community roll-out of nMABs and antivirals for people with COVID-19 who remain vulnerable to infection. In other words, a drug that may have any rituximab-sparing potential or a relapse-prevention potential may have additional beneficial implications for the NHS that might not be captured in existing economic models.
• In what clinical setting should the technology be used? (For example,	There is likely to be discussion about implementation models for this treatment and whether this technology will require to be given at or in discussion with a specialised centre. However, it will be important to note that patients with this condition are likely to present acutely for remission induction treatment to any NHS Trust, and for example, the NHS England Commissioning Policy for use of rituximab in ANCA-associated

primary or secondary care, specialist clinics.)	vasculitis does not mandate specialised centre involvement for initiation of treatment, to avoid delays. Given that the most important aspect of care is rapid initiation of the best treatment, and given that the comparative mortality risks are highest in the early months from diagnosis, it may be more appropriate not to limit initiation by requiring involvement of a specialised centre MDT, as the frequency of these varies (e.g., monthly in some situations)
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Education for health professionals and patient education resources. Strengthening of regional networks if this is the route being considered.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	I anticipate stopping criteria for adverse events would follow current close monitoring arrangements for this existing patient group
13. What is the outcome of any evaluations or audits of the use of the technology?	Not aware of any evaluations and audits other than the clinical trial papers
Equality	
14a. Are there any potential equality issues that should be	None that I am aware of

taken into account when considering this treatment?	
14b. Consider whether these issues are different from issues with current care and why.	NA
Topic-specific questions	
15. In the ADVOCATE clinical trial, the comparator arm was prednisone in combination with cyclophosphamide followed by azathioprine or prednisone in combination with rituximab. How common is the use of prednisone for treating anti-neutrophil cytoplasmic antibody-associated vasculitis in the NHS in England? Please also comment on the use of	Prednisolone use is universal for remission induction in this condition, and also for maintenance at lower doses in some situations and is associated with infection and other related toxicity, and concerns related to outcome from COVID-19. There is significant literature on steroid toxicity and the central importance to patients and clinicians of trying to reduce this whilst maintaining treatment efficacy and response.

prednisolone in the NHS in England.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Avacopan for treating anti-neutrophil cytoplasmic autoantibody-associated vasculitis [ID1581]

Produced by Kleijnen Systematic Reviews (KSR) Ltd, United Kingdom (UK) in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University, the Netherlands

Authors
Jeremy Howick, Reviews Manager, KSR Ltd, UK
Maiwenn Al, Health Economic Researcher, Erasmus School of Health Policy & Management (ESHPM), EUR, the Netherlands
Nigel Armstrong, Health Economics Manager, KSR Ltd, UK
Charlotte Ahmadu, Health Economist, KSR Ltd, UK
Pim Wetzelaer, Health Economic Researcher, ESHPM, EUR, the Netherlands
Pawel Posadzki, Reviews Manager, KSR Ltd, UK
Hannah Penton, Health Economist, ESHPM, EUR, the Netherlands
Lisa Stirk, Information Specialist, KSR Ltd, UK
Robert Wolff, Managing Director, KSR Ltd, UK
Jos Kleijnen, Founder and Owner, KSR Ltd, UK

Correspondence to
Jeremy Howick, Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, YO19 6FD
United Kingdom

Date completed 14//01/2022

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number STA 13/53/71.

Declared competing interests of the authors

None.

Acknowledgements

None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Howick J, Al M, Armstrong N, Ahmadu C, Wetzelaer P, Posadski P, Penton H, Stirk L, Wolff R, Kleijnen J. Avacopan for treating anti-neutrophil cytoplasmic autoantibody-associated vasculitis [ID1581]: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2022.

Contributions of authors

Jeremy Howick acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Maiwenn Al acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Nigel Armstrong, Hannah Penton, and Pim Wetzelaer acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Charlotte Ahmadu and Pawel Posadzki acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence, and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Robert Wolff and Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report, and supervised the project.

Abbreviations

AAV	Anti-neutrophil cytoplasmic autoantibody–associated vasculitis
AE	Adverse event
AiC	Academic in confidence
AIS	Aggregate Improvement Score
ANCA	Anti-neutrophil cytoplasmic autoantibody
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
AZA	Azathioprine
BHPR	British Health Professionals in Rheumatolog
BMI	Body mass index
BSR	British Society of Rheumatology
BVAS	Birmingham Vasculitis Activity Score
CADTH	Canadian Agency for Drugs and Technologies in Health
C-ANCA	Cytoplasmic anti-neutrophil cytoplasmic autoantibody
CD19	Cluster of differentiation 19
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CiC	Commercial in confidence
CPRD	Clinical Practise Research Datalink
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
CS	Company submission
CSR	Clinical study report
CT	Computed tomography
CV	Cardiovascular
CWS	Cumulative Worsening Score
CYC	Cyclophosphamide
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EGPA	Eosinophilic granulomatosis with polyangiitis
ELISA	Enzyme-linked immunosorbent assay
ERG	Evidence Review Group
ESHPM	Erasmus School of Health Policy & Management
ESRD	End-stage renal disease
EUR	Erasmus University Rotterdam
FDA	Food and Drug Administration
GC	Glucocorticoid
GPA	Granulomatosis with polyangiitis
GTI	Glucocorticoid Toxicity Index
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
hpf	High-power field
HRQoL	Health-related quality of life
hsCRP	High-sensitivity C-reactive protein
IGRA	Interferon-gamma release assay
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
KSR	Kleijnen Systematic Reviews
LFT	Liver function test

LSM	Least squares mean
LY	Life year
MCP-1	Monocyte chemoattractant protein-1
MDRD	Modification of Diet in Renal Disease
MMF	Mycophenolate mofetil
MPA	Microscopic polyangiitis
MPO	Myeloperoxidase
MTX	Methotrexate
NA	Not applicable
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported
OR	Odds ratio
P-ANCA	Perinuclear anti-neutrophil cytoplasmic autoantibody
PD	Pharmacodynamics
PK	Pharmacokinetics
PPD	Purified protein derivative
PR3	Proteinase 3
PRESS	Peer Review of Electronic Search Strategies
QALY	Quality-adjusted life year
QoL	Quality of life
QTcF	Fridericia's correction formula
RBC	Red blood cell
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
ROB	Risk of bias
RTX	Rituximab
SAE	Serious adverse event
SD	Standard deviation
SEM	Standard error of measurement
SF-36v2	36-Item Short Form Health Survey version 2
SMC	Scottish Medicines Consortium
SoC	Standard of care
STA	Single Technology Appraisal
TEAE	Treatment-emergent adverse event
THIN	The Health Improvement Network
TNF	Tumour necrosis factor
UACR	Urinary albumin-to-creatinine ratio
UK	United Kingdom
VDI	Vasculitis Damage Index
WHO	World Health Organization

Table of Contents

Table of Tables

Table of Figures

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. If possible, it also includes the ERG's preferred assumptions and the resulting incremental cost effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues related to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness. Other key issues are discussed in Section 1.6 while a summary in presented in Section 1.7.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main ERG report, see Section 2 (decision problem), Section 3 (clinical effectiveness) and Section 4 (cost effectiveness) for more details.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1 provides a summary of the key issues identified by the ERG.

Table 1.1: Summary of key issues

ID1581	Summary of issue	Report Sections
1	The narrower population in the CS may impact generalisability of the findings.	2.1
2	The inclusion of glucocorticoids in the intervention group may have generated biased effect estimates of the intervention.	2, 3.2
3	The list of comparators differs from the list in the final scope issued by NICE, potentially affecting the relative apparent efficacy, safety, and cost of avacopan.	2
4	The model assumes only azathioprine is used during the maintenance phase of the treatment. However, BSR/BHPR guidelines specify that RTX may be used for maintenance treatment for patients achieving remission after RTX induction.	4.2.4
5	The estimated hazard ratio (pooled estimate versus single study) of developing ESRD has a large impact on the cost effectiveness results.	4.2.6.3
6	The company explored two different approaches to estimate the probability to transition the ESRD leading to very different results.	4.2.6.3
7	Validity of costing approach used for hospitalisation costs	4.2.8.3
8	Representativeness of modelled annual health care costs	4.2.8.6

BHPR = British Health Professionals in Rheumatology; BSR = British Society of Rheumatology; CS = company submission; ESRD = end-stage renal disease; ITT = intention to treat; NICE = National Institute for Health and Care Excellence; RTX = rituximab

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are related to using Clinical Practise Research Datalink (CPRD) data rather than literature to estimate the probability of developing end-stage renal disease (ESRD), using a pooled estimate rather than one based on single study for the hazard ratio of developing ESRD, excluding excess bed days

from the calculation of hospitalisation costs, and using an estimate from a United Kingdom (UK) study instead of a South Korean study for the relative risk of mortality due to ESRD.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life (QoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing remission rates
- Decreasing relapse rates
- Reducing ESRD and associated mortality

Overall, the technology is modelled to affect costs by:

- Its higher unit price than current treatments
- Reducing costs for treatment of ESRD
- Reducing hospitalisation costs

The modelling assumptions that have the greatest effect on the ICER are:

- The source of the transition probabilities to ESRD
- The hazard ratio of developing ESRD, which is adjusted based on changes in the estimated glomerular filtration rate (eGFR) following relapse/remission
- Excluding excess bed days in the calculation of hospitalisation costs
- The estimated relative risk of mortality due to ESRD

1.3 The decision problem: summary of the ERG's key issues

With a few exceptions, the decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, the population studied by the company is a bit narrower (Table 1.2), the inclusion of glucocorticoids in the intervention group may have generated biased effect estimates of the intervention (Table 1.3) and the comparators are not in line with those listed in the NICE scope (Table 1.4).

Table 1.2: Key issue 1: Narrower population in the company submission

Report Section	**2.1**
Description of issue and why the ERG has identified it as important	The population defined in the NICE scope is people with newly diagnosed or relapsed anti-neutrophil cytoplasmic autoantibody-associated vasculitis (AAV). The population studied by the company is people with severe microscopic polyangiitis (MPA) or granulomatosis with polyangiitis (GPA) variant of newly diagnosed or relapsed AAV. The population studied by the company is therefore narrower than the population defined in the final NICE scope.
What alternative approach has the ERG suggested?	Inclusion of all people with newly diagnosed or relapsed AAV regardless of disease severity and clinicopathologic variants.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is unclear.
What additional evidence or analyses might help to resolve this key issue?	Inclusion of all eligible people in line with the final NICE scope.

Report Section	2.1
AAV = Anti-neutrophil cytoplasmic autoantibody–associated vasculitis; ERG = Evidence review group; GPA = Granulomatosis with polyangiitis; MPA= Microscopic polyangiitis = NICE = National Institute for Health and Care Excellence	

Table 1.3: Key issue 2: The inclusion of glucocorticoids in the intervention group may have generated biased effect estimates of the intervention

Report Section	2, 3.2
Description of issue and why the ERG has identified it as important	The intervention is described as avacopan in contrast to the comparator, which is described as the "prednisone-based regimen" in the clinical effectiveness section and "glucocorticoid" (GC) in the cost effectiveness section. This is potentially misleading given that GCs were given in addition to avacopan, and GCs given in addition to the randomised dose of prednisolone as required during the trial would form part of standard of care (SoC) on this basis. Whether the level prescribed is as would be expected in clinical practice is uncertain.
What alternative approach has the ERG suggested?	GC as required needs to be added to the description of both the intervention and comparator.
What is the expected effect on the cost effectiveness estimates?	None as long as the cost and adverse event consequences of GCs are included for both intervention and comparator.
What additional evidence or analyses might help to resolve this key issue?	GC as required needs to be added to the description of both the intervention and comparator. At least for the comparator, the level prescribed in clinical practice could be informed by evidence and/or clinical expert opinion.
ERG = Evidence review group; GC = Glucocorticoid; SoC = Standard of care	

Table 1.4: Key issue 3: The comparators are not in line with the final NICE scope

Report Section	2
Description of issue and why the ERG has identified it as important	Whereas the company considers treatment including azathioprine (AZA) as a comparator treatment for inducing remission, the final NICE scope does not. Also, the company uses methotrexate (MTX) and MMR as alternatives to cyclophosphamide (CYC), whereas the final NICE scope does not. The different comparators could have affected the relative apparent efficacy, safety, and cost of avacopan.
What alternative approach has the ERG suggested?	The ERG recommends focusing on the comparators listed in the final NICE scope.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is unclear.
What additional evidence or analyses might help to resolve this key issue?	The company could exclude the analyses with the additional outcomes or add outcomes which are less likely to bias the detection of harms in the control groups.
AZA = Azathioprine; ERG = Evidence review group; NICE = National Institute for Health and Care Excellence	

1.4 Clinical effectiveness evidence: summary of the ERG's key issues

There were no key issues related to clinical effectiveness.

1.5 Cost effectiveness evidence: summary of the ERG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the ERG's summary and detailed critique in Section 4, and the ERG's amendments to the company's model and results are presented in Section 6. The main ERG results are reproduced using confidential prices for comparator drugs in a confidential Appendix. The key issues in the cost effectiveness evidence are discussed in Tables 1.5 to 1.9.

Table 1.5: Key issue 4: Rituximab should be included for maintenance therapy

Report Section	**4.2.4**
Description of issue and why the ERG has identified it as important	The model assumes that only azathioprine is used during the maintenance phase of the treatment. However, British Society of Rheumatology/British Health Professionals in Rheumatology guidelines specify that rituximab may be used for maintenance treatment for patients achieving remission after rituximab induction. The company included (as exploratory analysis) the option to model rituximab as maintenance treatment (in line with the) instead of azathioprine but had to use a non-adjusted naïve comparison to do so.
What alternative approach has the ERG suggested?	No alternative approach was suggested by the ERG. In the ERG base case, the same approach was selected as in the company base case. The impact of the alternative approach was assessed through a scenario analysis.
What is the expected effect on the cost effectiveness estimates?	The explorative analysis when rituximab is given during the maintenance phase leads to a much higher ICER, almost double that of the ERG base case.
What additional evidence or analyses might help to resolve this key issue?	The company explored, without success, randomised controlled trials to create a network including RTX maintenance. Observational data may be available for this purpose.
ERG = Evidence review group; ICER = Incremental cost-effectiveness ratio; RTX = ritixumab	

Table 1.6: Key issue 5: Not all evidence was used to estimate the hazard ratio of developing ESRD

Report Section	**4.2.6.3**
Description of issue and why the ERG has identified it as important	The estimated hazard ratio (pooled estimate versus single study) of developing ESRD has a large impact on the cost effectiveness results.
What alternative approach has the ERG suggested?	Instead of using an estimate based on a single study, the ERG prefers to use a pooled estimate based on the studies identified by the company.

Report Section	4.2.6.3
What is the expected effect on the cost effectiveness estimates?	When applied in isolation of other ERG changes, the use of a pooled estimate increased the ICER by approximately £12,000.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence is required.
ERG = Evidence review group; ICER = Incremental cost-effectiveness ratio	

Table 1.7: Key issue 6: Choosing between two methods to estimate the probability of developing ESRD

Report Section	4.2.6.3
Description of issue and why the ERG has identified it as important	The company explored two different approaches to estimate the probability of transition to ESRD. Both these approaches have merit but lead to very different results. When the transition probabilities are based on literature and ADVOCATE, they are about six times higher than when they are based on CPRD data.
What alternative approach has the ERG suggested?	In the ERG base case the approach using CPRD data was selected.
What is the expected effect on the cost effectiveness estimates?	The ERG preferred base case in which the probability of transitioning to ESRD is based on CPRD data rather than literature and ADVOCATE leads to an ICER above £100,000 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	The ERG has tried to validate the choice by looking at the ESRD incidence rate observed and the rate predicted by the model. It might be good to see if there is other observational data against which the two approaches may be compared.
CRPD = Clinical Practise Research Datalink; ERG = Evidence review group; ESRD = End-stage renal disease; ICER = Incremental cost-effectiveness ratio; QALY = Quality-adjusted life year	

Table 1.8: Key issue 8: Validity of costing approach used for hospitalisation costs

Report Section	4.2.8.3
Description of issue and why the ERG has identified it as important	The ERG has concerns regarding the validity of including costs for excess bed days, which were sourced from the 2017/2018 NHS Reference costs, in combination with unit costs for hospitalisations from the NHS Reference costs 2019/2020.
What alternative approach has the ERG suggested?	The ERG prefers to use the unit cost for hospitalisations from the NHS Reference costs 2019/2020 as such, without additional costs for excess bed days.
What is the expected effect on the cost effectiveness estimates?	The exclusion of excess bed day costs increased the ICER by about £5,000 when applied in isolation of other ERG changes.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence is required.
ERG = Evidence review group; ICER = Incremental cost-effectiveness ratio; NHS = National Health Service	

Table 1.9: Key issue 9: Representativeness of modelled annual health care costs

Report Section	**4.2.8.6**
Description of issue and why the ERG has identified it as important	The modelled annual health care costs (approximately £13,400 for CYC/RTX+GC) were considerably lower than those that were estimated in the CPRD study (approximately £25,000).
What alternative approach has the ERG suggested?	No alternative approach was suggested by the ERG.
What is the expected effect on the cost effectiveness estimates?	The expected impact of using an alternative approach is unknown.
What additional evidence or analyses might help to resolve this key issue?	To be able to use cost estimates from the CPRD study to inform health state costs in the model, information on disease state from the CPRD would be required to allow stratification. If data from patients treated with avacopan were available in the CPRD, this would allow an estimation of changes in resource use due to the use of avacopan.
CPRD = Clinical Practise Research Datalink; CYC = Cyclophosphamide; ERG = Evidence review group; GC = Glucocorticoid; RTX = Ritixumab	

1.6 Summary of the ERG's view

Table 1.10 shows the step-by-step changes made by the ERG to the company base-case. The change with the largest impact on the results was changing the hazard ratio of developing ESRD per unit change in eGFR. This change leads to slightly higher incremental costs and a smaller QALY gain, leading to an increase in the ICER of over 50%. The impact of changing to hospitalisation costs is smaller but still substantial, with an increase in ICER of around 25%. The change in the relative risk for mortality due to ESRD actually lowers the ICER by 25%, both through a reduction in incremental costs and a decrease in the number of QALYs gained.

Table 1.10: Incremental impact of ERG preferred assumptions

Preferred assumption	**AVA + CYC/RTX**		**CYC/RTX + GC**		**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£/QALY)**
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**			
Company base-case (original)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,537
Company base-case (after clarification)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,492
Company base-case (errors corrected by ERG)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,513
Corrected Company BC + ESRD HR for mortality of 6.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,174

Preferred assumption	AVA + CYC/RTX		CYC/RTX + GC		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
Corrected Company BC + Exclude excess bed days for hospitalisation costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,519
Corrected Company BC + CPRD as source for ESRD transition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,746
Corrected Company BC + HR eGFR based on pooled estimate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,519
Corrected Company BC + treatment independent HSUV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,537
ERG BC (including all ERG changes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	102,973

Based on the ERG preferred version of the electronic model
AVA = avacopan; CYC = cyclophosphamide; GC = glucocorticoid; Incr. = incremental; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years; RTX = rituximab; HSUV = health state utility values

2 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	People with newly diagnosed or relapsed anti-neutrophil cytoplasmic autoantibody-associated vasculitis (AAV).	People with severe microscopic polyangiitis (MPA) or granulomatosis with polyangiitis (GPA) variant of newly diagnosed or relapsed AAV.	In their response to clarification, the company stated: "*AAVs [anti-neutrophil cytoplasmic autoantibody–associated vasculitis'] are a collection of relatively rare autoimmune diseases characterised by inflammatory cell infiltration causing necrosis of blood vessels. GPA and MPA are the main forms of the disease that also carry the most severe complications, with EGPA the rarer variant, having a distinctive clinical phenotype and treatment pathway*"[1] and "*The use of avacopan, in combination with a CYC or RTX regimen, is indicated for severe, active GPA or MPA. As such, the population in the decision problem did not include patients with localised disease at low risk of suffering organ damage, and MTX and MMF were not considered as relevant comparator treatments.*"[1]	The population studied by the company (people with severe MPA or GPA variant of newly diagnosed or relapsed AAV). The population defined in the NICE scope (People with newly diagnosed or relapsed AAV). The population studied by the company is therefore narrower than the population studied in the final NICE scope.
Intervention	Avacopan	Avacopan in combination with standard of care (SoC) (i.e., cyclophosphamide	In their response to clarification questions, the company stated: "*Combination therapy with*	The intervention studied by the company differs from

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
		(CYC), followed by AZA/mycophenolate mofetil (MMF), or rituximab (RTX))	*glucocorticoids (GCs) and cyclophosphamide (CYC) is currently standard therapy for remission induction[2 3]. NHS England will routinely fund the use of rituximab (RTX) for the treatment of AAV as an option for inducing remission in adults, if:* *The disease has remained active or progressed, or has relapsed, despite a course of CYC lasting 3-6 months, OR* *CYC is contraindicated (as defined in the summary of product characteristics) or not tolerated, OR* *The person has not completed their family and treatment with CYC may materially affect their fertility, OR* *The person has had uroepithelial malignancy* *Where RTX is used instead of CYC, GCs are still used at standard doses but should also be used as pre-medication for RTX[2 3].* *Long-term therapy with CYC has been used to maintain remission, but the toxicity associated with this makes it an unattractive option and is not common clinical practice in the UK. As such, following*	the intervention specified in the final NICE scope, notably in that it includes treatment with glucocorticoids (GCs). The inclusion of GCs in the intervention group risks confounding the results.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			induction of remission, azathioprine (AZA) or methotrexate (*MTX) can be used as maintenance therapy*[2]*. MTX should not be used in those with organ-threatening or renal disease. Mycophenolate mofetil (MMF) may be used for remission maintenance if there is intolerance to AZA*[2]*. In addition, in patients with RTX-induced remission, remission maintenance with RTX is an option*[2]*.* *The British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) in 2014* [4] *have published consensus recommendations based on varying levels of evidence to try and harmonise therapy and refine treatment strategies. These guidelines are developed using processes which NICE have accredited and are also closely aligned with guidelines from the European League Against Rheumatism (EULAR), published in 2016*[5]*.* *Avacopan, in combination with a RTX or CYC regimen, is indicated*	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			for the treatment of adult patients with severe, active GPA or MPA. In line with its indication, avacopan was administered in combination with RTX or CYC, with/without GCs, in all three trials. *To ensure SoC was similar within the intervention and control groups, patients were stratified by RTX/CYC use prior to randomisation in the ADVOCATE, CLEAR and CLASSIC studies*" Also, in their response to clarification questions, the company stated that glucocorticoids were anticipated to be used in both groups.	
Comparator(s)	**To induce remission:** Established clinical management without avacopan including corticosteroids (GCs) and RTX, CYC, MTX or MMF **Maintenance treatment:** Established clinical management without avacopan including low dose corticosteroids (GCs) and RTX (in line with the NHS England commissioning policy), azathioprine, methotrexate, or MMF	**Remission induction** • GCs in combination with CYC, followed by AZA/MMF • GCs in combination with RTX **Maintenance treatment** • Low-dose GCs in combination with AZA/MMF • RTX in combination with low-dose GCs	Current SoC for induction of remission in adult AAV patients includes GCs in combination with either CYC, followed by AZA/MMF, or RTX. The standard GC regimen involves a high dose tapering as remission is achieved but is often then continued at low dose to sustain remission. MTX and MMF are recommended as alternatives to CYC (followed by AZA/MMF) or RTX for remission induction in patients with localised disease at low risk of	The extent to which the deviation from the final NICE scope is justified by current treatment guidelines remains unclear to the ERG.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	Low dose GCs and rituximab, AZA, methotrexate or MMF		suffering organ damage. These patients were not studied in the key avacopan clinical trials and so, in this setting, they are not relevant comparators for avacopan.	
Outcomes	The outcome measures to be considered include: • Mortality • morbidity including damage to organs • remission rate and duration of remission • change in renal function • use of immunosuppressants and corticosteroids (including corticosteroid toxicity) • adverse effects of treatment (including infection rates) • HRQoL	The outcome measures to be considered include the following: • Mortality • Morbidity, including damage to organs • Remission rate and duration of remission • GC toxicity (measured with an objective score) • GC-related AEs • Sustained GC-free vasculitis remission • Change in renal function • Use of immuno-suppressants and GCs • AEs of treatment • Risk of infection • HRQoL	Avacopan is a targeted therapy, the use of which aims to reduce/replace GCs and avoid associated serious toxicity. Therefore, the following outcomes were considered to be relevant in addition to the proposed outcomes: • GC toxicity (measured with an objective score) • GC-related AEs • Sustained GC-free vasculitis remission Because infection is such a clinical challenge in AAV, risk of infection was examined separately from overall AEs	The additional outcomes could increase the risk of false positive results. They are also potentially biased in the absence of measuring avacopan-related AEs.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from a National Health Service (NHS) and Personal Social Services (PSS) perspective.			The economic analysis follows on all elements included in the final NICE scope reference case.
Subgroups to be considered	None specified.			In the economic analysis the company has included subgroups that were pre-specified and for which the ADVOCATE trial was stratified.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Special considerations including issues related to equity or equality	None identified.			

Based on Table 1 and pages 10 to 12 of the CS[6]

AE = adverse effects; AZA = Azathioprine; CS = company submission; CYC = Cyclophosphamide; DCIS = ductal carcinoma in situ; eBC = early breast cancer; HER2 = human epidermal growth factor receptor 2; GC = Glucocorticoid; GPA = Granulomatosis with polyangiitis; HRQoL = health-related quality of life; IDFS = invasive disease-free survival; MMF = Mycophenolate mofetil; MPA = Microscopic polyangiitis; MTX = Methotrexate; N/A = not applicable; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; PAS = patient access scheme; pCR = pathological complete response; RID = residual invasive disease; RTX = Rituximab; SoC = Standard of Care; QALY = quality-adjusted life year

2.1 Population

The population defined in the scope is: People with newly diagnosed or relapsed anti-neutrophil cytoplasmic autoantibody-associated vasculitis (AAV).[7]

There are three major clinicopathologic variants of AAVs, namely: microscopic polyangiitis (MPA); granulomatosis with polyangiitis (GPA); and eosinophilic granulomatosis with polyangiitis (EGPA). The NICE final scope does not specify MPA and GPA as the population's variants of interest. The company submission (CS) states that avacopan was only studied (within the ADVOCATE[8], CLASSIC[9, 10] AND CLEAR[11] trials) in patients with active GPA or MPA.[6]

In their response to clarification questions, the company stated:

- *"AAVs are a collection of relatively rare autoimmune diseases characterised by inflammatory cell infiltration causing necrosis of blood vessels. GPA and MPA are the main forms of the disease that also carry the most severe complications, with EGPA the rarer variant, having a distinctive clinical phenotype and treatment pathway"*[1]
- *"EGPA is not part of the marketing authorisation for Avacopan".*[1]
- *"The use of avacopan, in combination with a CYC or RTX regimen, is indicated for severe, active GPA or MPA. As such, the population in the decision problem did not include patients with localised disease at low risk of suffering organ damage, and MTX and MMF were not considered as relevant comparator treatments."*[1]

This suggests that the population is restricted to those with severe disease and without the EGPA variant.

ERG comment: The population studied by the company is people with severe MPA or GPA variant of newly diagnosed or relapsed anti-neutrophil cytoplasmic autoantibody-associated vasculitis. The population specified in the final NICE scope is people with newly diagnosed or relapsed anti-neutrophil cytoplasmic autoantibody-associated vasculitis. The population studied by the company is therefore narrower than the population defined in the final NICE scope which the ERG wanted to highlight the committee.

2.2 Intervention

The intervention described in the final NICE scope is avacopan (as an add-on to SoC). Table 1 of the CS states that the intervention is avacopan in combination with SoC (i.e., CYC, followed by AZA/MMF, or RTX).[6]

Avacopan is taken orally (30 mg: three hard capsules of 10 mg each) twice per day with food. Avacopan is intended for use to induce and maintain remission in people with newly diagnosed AAV or people with AAV who are undergoing a significant relapse. It is to be used concomitantly with immunosuppressant drugs, CYC or RTX, and it reduces or replaces the need for adjunctive glucocorticoids (GC). Once remission is achieved, avacopan treatment can be continued during the maintenance phase.

In the request for clarification, the ERG noted that GCs were included in both the intervention and control group. In their response to clarification questions, the company stated: "*Combination therapy with glucocorticoids (GCs) and cyclophosphamide (CYC) is currently standard therapy for remission induction*[2, 3]*. NHS England will routinely fund the use of rituximab (RTX) for the treatment of AAV as an option for inducing remission in adults, if:*

- *The disease has remained active or progressed, or has relapsed, despite a course of CYC lasting 3-6 months, OR*
- *CYC is contraindicated (as defined in the summary of product characteristics) or not tolerated, OR*
- *The person has not completed their family and treatment with CYC may materially affect their fertility, OR*
- *The person has had uroepithelial malignancy*

Where RTX is used instead of CYC, GCs are still used at standard doses but should also be used as pre-medication for RTX.[2, 3]

Long-term therapy with CYC has been used to maintain remission, but the toxicity associated with this makes it an unattractive option and is not common clinical practice in the UK. As such, following induction of remission, azathioprine (AZA) or methotrexate (MTX) can be used as maintenance therapy AZA[2]*. MTX should not be used in those with organ-threatening or renal disease. Mycophenolate mofetil (MMF) may be used for remission maintenance if there is intolerance to AZA* [2]*. In addition, in patients with RTX-induced remission, remission maintenance with RTX is an option* [2]*.*

The British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) in 2014[4] *have published consensus recommendations based on varying levels of evidence to try and harmonise therapy and refine treatment strategies. These guidelines are developed using processes which NICE have accredited and are also closely aligned with guidelines from the European League Against Rheumatism (EULAR), published in 2016* [5]*.*

Avacopan, in combination with a RTX or CYC regimen, is indicated for the treatment of adult patients with severe, active GPA or MPA. In line with its indication, avacopan was administered in combination with RTX or CYC, with/without GCs, in all three trials (…) To ensure SoC was similar within the intervention and control groups, patients were stratified by RTX/CYC use prior to randomisation in the ADVOCATE, CLEAR and CLASSIC studies"[1]*.*

Also, in their response to clarification questions, the company stated that GCs were anticipated to be used in both groups.[1]

ERG comment: Given that GCs as required are part of SoC in both the intervention and the control groups, the use of GCs as part of the intervention, even at a reduced dose, should be explicitly acknowledged. Whether the level prescribed is as would be expected in clinical practice is uncertain.

2.3 Comparators

The description of the comparators in the NICE scope for induction of remission is as follows: "*Established clinical management without avacopan, including GCs and either RTX, CYC, MTX, or MMF*".[7] The description of the comparators in the NICE scope for maintenance treatment is as follow: "*Established clinical management without avacopan, including low-dose GCs and either RTX (in line with the NHSE commissioning policy), AZA, MTX, or MMF*".[7]

The description of the comparators in the CS for induction of remission is as follows: "*GCs in combination with CYC, followed by AZA/MMF, GCs in combination with RT*".[6]The description of the comparators in the CS for maintenance treatment is as follows: "*Low-dose GCs in combination with AZA/MMF, RTX in combination with low-dose GCs*".[6]

There are a few differences between the comparators studied by the company and the comparators suggested in the final NICE Scope document (see Table 2.1).

1. Whereas the company considers treatment including azathioprine (AZA) as a comparator treatment for inducing remission, the final NICE scope does not. In the CS (page 12), it is stated that the reason for this is that "*[c]urrent SoC for induction of remission in adult AAV patients includes GCs in combination with either CYC, followed by AZA/MMF, or RTX. The standard GC regimen involves a high-dose tapering as remission is achieved but is often then continued at low dose to sustain remission.*"[6] NICE Guideline 308 does not mention the use of azathioprine in their "key conclusions",[3] and the other guideline cited by the company in their response to clarification questions does not mention AZA for inducing remission.[2]
2. The company uses MTX and MMR as alternatives to CYC, stating in their submission (page 12) that "*MTX and MMF are recommended as alternatives to CYC (followed by AZA/MMF) or RTX for remission induction in patients with localised disease at low risk of suffering organ damage. These patients were not studied in the key avacopan clinical trials and so, in this setting, they are not relevant comparators for Avacopan.*"

The comparators section of Table 1 of the CS has a separate heading of maintenance treatment, suggesting that this is a subgroup of the relevant population for which avacopan is being evaluated.[6]

In their response to clarification, the company stated that "*[m]aintenance treatment is warranted following induction of remission to prevent relapse (as per the NHS, BSR/BHPR and EULAR guidelines).*[2-5]*, and is, therefore, not considered as a separate subgroup*."

ERG comment:

- The ERG does not fully understand the rationale or consequences of including AZA as a comparator treatment and notes that the final NICE scope does not include this comparator.

- As stated in Section 2.2, GC as required should also be acknowledged as part of the comparator. Whether the level prescribed is as would be expected in clinical practice is uncertain: this could be informed by evidence and/or clinical expert opinion.

2.4 Outcomes

The NICE final scope lists the following outcome measures:

- Mortality
- Morbidity, including damage to organs
- Remission rate and duration of remission
- Change in renal function
- Use of immunosuppressants and corticosteroids
- Adverse effects of treatment (including infection rates)
- HRQoL

In addition to those listed in the final NICE scope, the company also measured:

- GC toxicity
- GC-related AEs
- Sustained GC-free vasculitis remission

In the CS (page 12), the company states that the rationale for these additional outcomes was: "*Avacopan is a targeted therapy, the use of which aims to reduce/replace GCs and avoid associated serious toxicity. Therefore, the following outcomes [those listed above] were considered to be relevant.*"[6]

ERG comments:

- Measuring AEs related to GCs may have led to bias in the absence of corresponding measurement of similar avacopan-related AEs.
- The most widely used generic tool to quantify the primary outcome of remission i.e., the Birmingham Vasculitis Activity Score (BVAS) was operationalised differently within the different included trials (see Section 3.2.1).

2.5 Other relevant factors

According to the company, avacopan is a first-in-class innovative technology that (a) improves remission rates compared to established therapy, and (b) reduces the AEs related to GC use in current established therapy. By selectively inhibiting C5aR1, *"avacopan permits otherwise normal functioning of the complement cascade and preserves important immune defence processes such as the membrane attack complex (C5b-9) and C3a [12], a major advantage with regards to vulnerability for major infections"*.[6]

This appraisal does not fulfil the end-of-life criteria as specified by NICE because the average life expectancy of people eligible for avacopan exceeds 24 months (see Section 7).

According to the company, there are no known equality issues relating to the use of avacopan in patients with AAV (CS, Section B.1.4).[6]

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

A systematic literature review (SLR) was performed to identify all studies that provided information on the clinical efficacy, safety, and tolerability of avacopan in combination with CYC or RTX (with or without GCs) compared with relevant comparator therapies for adult patients with GPA or MPA. However, the ERG required further clarification regarding the language restrictions, the selection of specific databases, the application of eligibility criteria, quality assessments performed, as well as details regarding the data extraction process.

3.1.1 Searches

The following paragraphs contain summaries and critiques of all searches related to clinical effectiveness presented in the company submission. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[13, 14] The submission was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[15] The ERG has presented only the major limitations of each search strategy in the report.

Appendix D of the CS details the SLR undertaken to identify all studies that provide information on the clinical efficacy, safety, and tolerability of avacopan in combination with CYC or RTX (with or without GCs) compared with relevant comparator therapies for adult patients with GPA or MPA. The SLR was conducted in three stages: an initial SLR on 4 June 2018 and updates on 16 June 2020 and 18 June 2021. The same search strategies were used in the original SLR and updates.

A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

	Resource	Host/Source	Date Ranges	Dates searched
Electronic Databases	MEDLINE (MEDLINE; Epub Ahead of Print; In-Process, and Other Non-Indexed Citations; MEDLINE Daily)	Ovid	1946-04/06/18 1946-15/06/20 1946-15/06/21	04/06/18 16/06/20 16/06/21
	Embase	Ovid	1974-2018 Wk23 1974-2020 Wk24 1974-2021 Wk23	04/06/18 16/06/20 16/06/21
	CDSR CENTRAL	Wiley	to 04/06/18 to 16/06/20 to 16/06/21	04/06/18 16/06/20 16/06/21
	HTA Database DARE	Wiley	to 04/06/18	04/06/18
	Epistemonikos	Internet	to 16/06/20 to 16/06/21	16/06/20 16/06/21
Additional resources	ClinicalTrials.gov	Internet	to 04/06/18 to 16/06/20 to 16/06/21	04/06/18 16/06/20 16/06/21

	Resource	Host/Source	Date Ranges	Dates searched
	ICTRP		to 04/06/18 to 16/06/21	04/06/18 16/06/21
CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; HTA Database = Health Technology Assessment Database; DARE = Database of Abstracts of Reviews of Effects; ICTRP = International Clinical Trials Registry Platform; WHO = World Health Organization				

ERG comment:

- Searches were undertaken to identify data published on the clinical efficacy, safety, and tolerability of avacopan compared with relevant comparator therapies for adult patients with GPA or MPA. The CS and response to clarification provided sufficient details for the ERG to appraise the literature searches.
- A good range of databases and clinical trials registers were searched. Supplementary searches of conference proceedings, and specialist and organisational websites could have been undertaken to further improve recall.
- Searches were well structured, although there were issues with documentation where the search strategies had been copied into a tabular format, and the field names listed in a 'Facet' column. The Cochrane Manual recommends that *"... bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy. The search strategies should not be re-typed, because this can introduce errors."*[16]
- The search strategies contained only a population facet, which was then limited to randomised controlled trials (RCTs). They included a good range of terms for anti-neutrophil associated vasculitis (AAV), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), using both free-text and subject indexing terms. Additional free-text terms could also have been added to the strategies in order to improve recall, such as: (Wegener$ adj3 (syndrome or disease or morbus or granuloma$)).ti,ab.; (ANCA adj2 (vasculitis or vasculitide$)).ti,ab.; or (necroti?ing respiratory granulomatos$ or pneumogenic granulomatos$).ti,ab. It may also have been helpful to include search terms for avacopan and its relevant synonyms.
- Results were limited by study design to RCTs. Although the study design filters used are not cited in the CS, they appear to be filters designed to optimise sensitivity and specificity[17, 18]. More sensitive strategies may have been useful to retrieve additional RCTs for potential inclusion in this SLR.
- Separate adverse events searches were not performed. The clinical effectiveness searches incorporated a methodological filter intended to limit the search to RCTs. Guidance by the Centre for Reviews and Dissemination (CRD)[19] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare, or unanticipated are not missed. It is possible that some relevant adverse event evidence may not have been identified as a consequence of the study design limits used.

3.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for RCTs and non-RCTs is presented in Table 3.2.

Table 3.2: Eligibility criteria used in search strategy for RCT evidence

Criterion/parameter	Inclusion	Exclusion
Population	Patients aged ≥18 years with GPA or MPA and renal-limited vasculitis	Paediatric patients Patients without GPA or MPA

Criterion/parameter	Inclusion	Exclusion
Interventions	Avacopan, in combination with cyclophosphamide or rituximab, with or without steroids, used for the induction of response/remission and maintenance of remission	Any intervention not listed in the inclusion criteria
Comparators	In combination with or without steroids: • Cyclophosphamide • Rituximab • Methotrexate • Azathioprine • Mycophenolate mofetil • Abatacept • Anti-tumour necrosis factor drugs (e.g., infliximab, etanercept) • Plasma exchange • Placebo	Any comparator not listed in the inclusion criteria
Outcomes	• Mortality • Remission rate and duration of remission • Number and severity of relapses • Change in renal function • Cumulative dose of steroids and steroid toxicity • Cumulative dose of immunosuppressants • AE associated with treatment • Vasculitis damage • Patient-reported outcomes • Healthcare resource • Infections • Disease progression (end-stage renal disease) • Dialysis • Renal replacement therapy • Cardiovascular outcomes	Any outcome not listed in the inclusion criteria

Criterion/parameter	Inclusion	Exclusion
Study type	Randomised controlled trials	• Non-randomised studies (including single-arm trials) • Pharmacokinetic studies and proof-of-concept studies • Case reports, case series, editorials, and letters • Reviews/systematic reviews/pooled trial analyses • Conference abstracts • Non-human studies
Language restrictions	English language only	Non-English language at full text
Based on Table 66 of the CS[6] Please note the CS refers to these criteria to retrieve cost-effectiveness studies rather than clinical effectiveness. Please also refer to the clarification question A:19.[1, 20] AE = adverse event; CS = company submission; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis.		

ERG comment: The ERG noted that the list of comparators (as per Table 66 of the Appendix D) differs from the list in the final scope issued by NICE.[21] In their clarification response, the company explained that a broad scope, aiming to determine the clinical efficacy and tolerability of all commonly used treatments for MPA and GPA had been adopted.[1] Hence, the ERG believes that MTX and MMF are considered as relevant comparator treatments. The existence of some inconsistencies in Figure 2 of the clarification response has been noted. These include the exclusion of 206 titles and abstracts and full text screening of 22 papers should give 20.

3.1.3 Critique of data extraction

Information provided in the CS regarding the data extraction process was scarce.

ERG comment: The ERG requested further clarification from the company regarding data extraction.[20] In their clarification response, the company noted that one reviewer extracted the data, and this was validated by the second reviewer.[1] This could potentially introduce bias into the extraction process (typically two reviewers independently of each other perform this exercise); and it is unclear whether a third researcher was involved in case of any disagreements in the extracted data.

3.1.4 Quality assessment

Information provided in the CS regarding the quality assessment was incomplete.

ERG comment:

- The ERG requested further clarification from the company regarding quality assessments performed. As per Table 69 of Appendix D 1.4 (subsequently replicated in Table 8 of the clarification response), the company claims that the Cochrane Collaboration's Risk of Bias 2 (ROB2) tool was used to perform quality assessment of the clinical evidence.[22]
- The ERG believes that some key domains of that assessment tool were not utilised. For instance, baseline differences between intervention groups suggesting a problem with the randomisation process; and risk of bias due to deviations from the intended interventions; and risk of bias in measurement of the outcome were not critically evaluated.

3.1.5 Evidence synthesis

As per the section B.2.8 of the CS, no meta-analyses were carried out by the company. The ERG carried out an evidence synthesis using RevMan (version 5.4)[16] for some of the main outcomes for the ADVOCATE [8], and CLEAR[12] trials (see Table 3.3). The ERG deemed it to be unsuitable to include the CLASSIC[10] trial in the meta-analysis due to differences (see section 3.2.1). Meta-analysis of the two trials showed that avacopan had little effect on eGFR when compared with prednisone (MD = 2.84, 95% CI -2.21, 7.89) at 12- and 52-weeks follow-up. There was no evidence of heterogeneity (Tau^2 = 0.00; Chi^2 = 0.01, df = 1 (P = 0.91); I^2 = 0%). Meta-analysis of two trials showed that avacopan had little effect on remission when compared with prednisone (OR = 1.06, 95% CI 0.68, 1.66) at 12- and 26-weeks follow-up. There was no evidence of heterogeneity (Tau^2 = 0.00; Chi^2 = 0.32, df = 1 (P = 0.57); I^2 = 0%). Meta-analysis of two trials showed that avacopan had little effect on the Vasculitis Damage Index (VDI) when compared with prednisone (SMD = -0.20, 95% CI -0.77, 0.37) at 12- and 52-weeks follow-up. There was evidence of significant heterogeneity (Tau^2 = 0.12; Chi^2 = 3.18, df = 1 (P = 0.07); I^2 = 69%). Meta-analysis of two trials showed that avacopan had little effect on quality of life (measured with EQ-5D) when compared with prednisone (SMD = 2.85, 95% CI -2.51, 8.21) at 12- and 52-weeks follow-up. There was evidence of considerable heterogeneity (Tau^2 = 13.41; Chi^2 = 8.72, df = 1 (P = 0.003); I^2 = 89%).

ERG comment:

- None of the included studies were synthesised quantitatively by the company.
- When the ERG synthesised the results and found that the results were broadly comparable to the results presented by the company for the main trial (ADVOCATE),and none of the pooled analyses showed difference between avacopan and prednisone. . Relatedly, the effect sizes were small and had wide confidence intervals. In short, the results of the ERG's evidence synthesis did not support the superiority of avacopan.

Table 3.3. Pooled data for the ADVOCATE and CLEAR, trials

Outcome	No. studies	No. participants	Statistical method	Effect estimate
eGFR (pooled)	2	306	MD* (IV, 95% CI)	2.84 [-2.21, 7.89]
eGFR at 12 weeks	1	41	MD* (IV, 95% CI)	3.48 [-8.47, 15.43]
eGFR at 52 weeks	1	265	MD* (IV, 95% CI)	2.70 [-2.87, 8.27]
Remission (pooled)	2	371	OR* (M-H, 95% CI)	1.06 [0.68, 1.66]
Remission at 12 weeks	1	41	OR* (M-H, 95% CI)	0.75 [0.21, 2.68]
Remission at 26 weeks	1	330	OR* (M-H, 95% CI)	1.11 [0.69, 1.79]
Vasculitis damage index (pooled)	2	371	SMD* (IV, 95% CI)	-0.20 [-0.77, 0.37]
Vasculitis damage index at 12 weeks	1	41	SMD* (IV, 95% CI)	-0.58 [-1.20, 0.05]
Vasculitis damage index at 52 weeks	1	330	SMD* (IV, 95% CI)	0.03 [-0.19, 0.24]

Outcome	No. studies	No. participants	Statistical method	Effect estimate
Quality of life (EQ-5D) pooled	2	336	SMD* (IV, 95% CI)	2.85 [-2.51, 8.21]
Quality of life at 12 weeks	1	41	SMD* (IV, 95% CI)	0.40 [-0.22, 1.01]
Quality of life at 52 weeks	1	295	SMD* (IV,95% CI)	5.90 [2.30, 9.50]

Based on ERG analysis
*Random effects model
CI = Confidence interval; eGFR = Estimated glomerular filtration rate; EQ-5D = European Quality of Life Five Dimension; I-V = inverse variance; MD = mean difference; M-H = Mantel-Haenszel; OR= Odd ratio, SMD = standardised mean difference

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The CS identified three trials investigating the efficacy and safety of avacopan in MPA and GPA AAV, as being relevant to this submission - the Phase III RCTs - ADVOCATE (NCT02994927)[23], and two Phase II RCTs - CLEAR (NCT01363388)[11] and CLASSIC (NCT02222155)[10]. The main evidence for the clinical effectiveness of avacopan was from the ADVOCATE trial (NCT02994927) due to the avacopan dosage in the CLEAR and CLASSIC trials not being in line with the anticipated license dosing regimen and the treatment duration of both trials being too short to inform the economic model.[6] However, information from both additional trials were used to support the efficacy and safety evidence of avacopan, presented in this section of the report. The study methodologies of all three trials have been summarised in Table 3.4.

3.2.1 Details of the included trials: ADVOCATE, CLEAR, and CLASSIC

ADVOCATE was a Phase III randomised, double-blinded, active-controlled, multicentre international trial where patients with a clinical diagnosis of GPA or MPA were randomised in a 1:1 ratio to either avacopan 30 mg twice daily plus cyclophosphamide (CYC) followed by azathioprine (AZA) or prednisone-matching placebo plus rituximab (RTX), or a 20-week tapering oral regimen of prednisone plus CYC followed by AZA or avacopan-matching placebo plus RTX, for 52 weeks of treatment with an 8 week follow-up.[6] The study consisted of three periods: screening (up to 2 weeks), treatment (52 weeks), and follow-up (8 weeks).[23] The primary outcomes were remission (defined as achieving a BVAS of zero and not taking GCs for AAV within 4 weeks prior to week 26) and sustained remission (defined as remission at week 26 and remission at week 52, without having a relapse between week 26 and week 52) (see Table 3.4).

The CLEAR trial was a Phase II randomised, double-blinded, double-dummy, placebo-controlled, multicentre study which enrolled subjects with a clinical diagnosis of GPA, MPA, or renal limited vasculitis, and consisted of three steps.[6, 11] In Step 1, AAV patients with renal disease involvement were stratified into newly diagnosed versus relapsed AAV with renal involvement, and randomised to receive avacopan plus a two-thirds reduced starting dose of oral GCs or placebo plus a full starting dose of oral GCs in a 2:1 ratio, while receiving intravenous (IV) CYC background treatment.[11] In Step 2, oral GCs were no longer given to patients on the avacopan arm while patients on the placebo arm continued with their full dose of oral GCs. IV CYC treatment continued at this step.[11] In Step 3, 41 AAV patients with or without renal disease involvement (stratified according to i) newly diagnosed versus relapsed AAV; ii) proteinase 3 (PR3) versus myeloperoxidase (MPO), anti-neutrophil cytoplasmic autoantibody–associated vasculitis (ANCA) positivity; iii) CYC versus RTX standard of care) were randomised in a

1:1:1 ratio to receive avacopan plus CYC/RTX and no oral GCs, placebo plus CYC/RTX with a full starting dose of oral GCs, or avacopan plus CYC/RTX with a two-thirds reduced starting dose of oral GCs.[11] The primary outcome was clinical response, defined as a decrease from baseline to week 12 in BVAS of at least 50%, with no worsening in any body system (see Table 3.4).

CLASSIC was a Phase II randomised, double-blind, placebo-controlled clinical trial where patients with new or relapsed AAV on background CYC/RTX plus GC treatment were stratified according to newly diagnosed or relapsed AAV, MPO or PR3 ANCA positivity, and CYC/RTX SoC treatment and randomised 1:1:1 to receive avacopan 10mg twice daily (bid) plus CYC/RTX plus GCs, avacopan 30 mg bid plus CYC/RTX plus GCs, or placebo bid plus CYC/RTX plus GCs. [10] The primary outcome was 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 (see Table 3.3).

ERG comment: The BVAS was operationalised differently across these trials. A decrease from baseline to week 12 of at least 50%, with no worsening in any body system in CLASSIC and CLEAR; and a BVAS of zero and not taking GCs within 4 weeks prior to week 26 in ADVOCATE.

Table 3.4: Summary of study methodologies of ADVOCATE, CLEAR, and CLASSIC trials

Study methodology	ADVOCATE (NCT02994927)	CLEAR (NCT01363388)	CLASSIC (NCT02222155)
Trial design	Phase 3, randomised, double-blind, double-dummy, active-controlled, multicentre international clinical study.	Phase 2, randomised, double-blind, double-dummy, placebo-controlled clinical study.	Phase 2, randomised, double-blind, double-dummy, placebo-controlled clinical study.
Participant eligibility criteria	Patients aged at least 18 years, with newly diagnosed or relapsed AAV for which treatment with CYC or RTX was needed, with a clinical diagnosis of GPA or MPA, consistent with Chapel Hill Consensus Conference definitions. Adolescents (12 to 17 years old) may have been enrolled.	Male and female subjects aged at least 18 years with new (typically within 4 weeks prior to screening) or relapsed AAV for which treatment with CYC or RTX would be required, with a clinical diagnosis of GPA, MPA, or renal-limited vasculitis, consistent with Chapel Hill Consensus Conference definitions.	Male and female subjects aged at least 18 years with new (typically within 4 weeks prior to screening) or relapsed AAV for which treatment with CYC or RTX would be required, with a clinical diagnosis of GPA, MPA, or renal-limited vasculitis, consistent with Chapel Hill Consensus Conference definitions.
Settings and locations	143 study centres in North America, Europe, Australia, New Zealand, and Japan, including 31 centres in the UK and three in the Republic of Ireland.	60 sites in Austria, Belgium, Czech Republic, Hungary, France, Germany, Ireland, The Netherlands, Poland, Sweden, and the UK.	47 sites in the United States and Canada.
Trial drugs	Patients were randomised in a 1:1 ratio to either of two study treatment groups: • 30 mg twice daily avacopan plus CYC (followed by AZA) or RTX plus prednisone-matching placebo (N=166) • Tapering oral regimen of prednisone plus CYC (followed by AZA) or RTX plus avacopan-matching placebo (N=165)	Patients were randomised in a 1:1:1 ratio to one of three treatment groups: • Avacopan plus CYC or RTX plus no oral GCs (N=22) • Avacopan plus CYC or RTX plus a two-thirds reduced starting dose of oral GCs (N=22) • Placebo plus CYC or RTX plus a full starting dose of oral GCs (N=23)	Patients were randomised in a 1:1:1 ratio to one of three study treatment groups: • Avacopan 10 mg twice daily plus CYC or RTX plus GCs (N=13) • Avacopan 30 mg twice daily plus CYC or RTX plus GCs (N=16) • Placebo twice daily plus CYC or RTX plus GCs (N=13)

Study methodology	ADVOCATE (NCT02994927)	CLEAR (NCT01363388)	CLASSIC (NCT02222155)
	Avacopan (30 mg twice daily) or matching placebo was given for 52 weeks, with 8 weeks of follow-up. Prednisone or a matched placebo was given on a tapering schedule for 20 weeks (60 mg per day tapered to discontinuation by week 21).	The avacopan/placebo treatment period was 84 days (12 weeks), followed by an 84-day (12 weeks) follow-up period. All subjects were to visit the study centre during the screening period, and on days 1, 2, 8, 15, 22, 29, 43, 57, 71, 85, 99, 113, 141, and 169.	All subjects received prednisone 60 mg orally per day starting on day 1 with a tapered dose, per protocol-specified schedule. Twice-daily dosing of avacopan or placebo continued for 84 days (12 weeks).
Primary outcome(s)	• Remission, defined as achieving a BVAS of zero and not taking GCs for AAV within 4 weeks prior to week 26 • Sustained remission, defined as remission at week 26 and remission at week 52, without having a relapse between week 26 and week 52. Remission at week 52 was defined as having a BVAS of 0 and not taking GCs for AAV for 4 weeks prior to week 52	Clinical response, defined as a decrease from baseline to week 12 in BVAS of at least 50%, with no worsening in any body system.	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.
Secondary outcomes	• Rapidity of response, based on BVAS of 0 at week 4 (regardless of GC use) • GC-induced toxicity, assessed using GTI • Changes in parameters of renal disease in subjects with active renal disease at baseline, including: eGFR, UACR, and urinary MCP-1:creatinine ratio	• In subjects with haematuria and albuminuria at baseline, the proportion of subjects achieving renal response at day 85 • Proportion of subjects achieving disease remission at day 85 defined as BVAS of zero or one plus no worsening in eGFR and urinary RBC count <10/hpf • Percent change from baseline to day 85 in BVAS	• In subjects with haematuria and albuminuria at baseline, the proportion of subjects achieving renal response at day 85 • Proportion of subjects achieving disease remission at day 85 defined as BVAS of zero • Proportion of subjects achieving early disease remission (BVAS of zero) at days 29 and 85

Study methodology	ADVOCATE (NCT02994927)	CLEAR (NCT01363388)	CLASSIC (NCT02222155)
	• Changes in cumulative organ damage based on VDI) • HRQoL changes, assessed using SF-36v2 and EQ-5D-5L • Incidence of AEs	• Change and percent change from baseline to day 85 in eGFR • In subjects with baseline haematuria >5 RBCs/hpf, the proportion of subjects and time to first achieving urinary RBC count ≤5/hpf at any time during the 84-day treatment period • In subjects with baseline haematuria ≥30 RBCs/hpf, the proportion of subjects and time to first achieving urinary RBC count <30/hpf at any time during the 84-day treatment period • In subjects with haematuria at baseline, the percent change from baseline to day 85 in urinary RBC count • In subjects with albuminuria at baseline, the percent change from baseline to day 85 in UACR • Percent change from baseline to day 85 in urinary MCP-1:creatinine ratio • Proportion of subjects requiring rescue IV or oral GC treatment • Change from baseline to day 85 in the VDI • Change from baseline to day 85 in HRQoL, as measured by the SF-36 v2 and EQ-5D-5L	• Percent change from baseline to day 85 in BVAS • Change and percent change from baseline to day 85 in eGFR • In subjects with haematuria at baseline, the percent change from baseline to day 85 in urinary RBC count • In subjects with albuminuria at baseline, the percent change from baseline to day 85 in UACR • Percent change from baseline to day 85 in urinary MCP-1:creatinine ratio • Proportion of subjects requiring rescue GC treatment • Change from baseline to day 85 in the VDI • Change from baseline to day 85 in HRQoL as measured by the SF-36v2 and EQ-5D • Total cumulative study-supplied prednisone dose and duration of dosing during the 84-day treatment period • Total cumulative systemic GC dose (any use) and duration of dosing during the 84-day treatment period

Study methodology	ADVOCATE (NCT02994927)	CLEAR (NCT01363388)	CLASSIC (NCT02222155)
		• Total cumulative study-supplied prednisone dose and duration of dosing during the 84-day treatment period • Total cumulative systemic GC dose (any use) and duration of dosing during the 84-day treatment period • Total cumulative CYC or RTX dose and duration of dosing during the 84-day treatment period • Percent change from baseline in hsCRP • Percent change from baseline in ANCA (anti-PR3 and anti-MPO) at day 85 • Proportion of subjects becoming ANCA-negative at day 85 • Change and percent change from baseline in plasma and urine biomarkers • PK/PD endpoints	• Total cumulative CYC or RTX dose and duration of dosing during the 84-day treatment period • Percent change from baseline in hsCRP • Percent change from baseline in ANCA (anti-PR3 and anti-MPO) at day 85 • Proportion of subjects becoming ANCA negative at day 85 • Change and percent change from baseline in plasma and urine biomarkers All stated efficacy endpoints were assessed through the end of the follow-up period, day 169.
Pre-planned subgroups	• Subjects with renal disease at baseline (based on BVAS renal component) • Subjects without active renal disease at baseline • Subjects with GPA • Subjects with MPA • IV RTX	• Subjects with renal disease at baseline (defined as subjects with BVAS items scored in the renal organ system) • Subjects without renal disease at baseline (defined as subjects with no BVAS items scored in the renal organ system)	• Subjects with renal disease at baseline (defined as subjects with BVAS items scored in the renal organ system) • Subjects without renal disease at baseline (defined as subjects with no BVAS items scored in the renal organ system)

Study methodology	ADVOCATE (NCT02994927)	CLEAR (NCT01363388)	CLASSIC (NCT02222155)
	• IV CYC • Oral CYC • Anti-PR3 ANCA • Anti-MPO ANCA • Newly diagnosed AAV • Relapsed AAV	• Subjects who received CYC background treatment • Subjects who received RTX background treatment • Subjects with newly diagnosed disease • Subjects with relapsed disease • Subjects with MPO+ disease • Subjects with PR3+ disease • Subjects with GPA • Subjects with MPA	• Subjects receiving CYC background treatment • Subjects receiving RTX background treatment • Subjects with newly diagnosed disease • Subjects with relapsed disease • Subjects with MPO+ disease • Subjects with PR3+ disease • Subjects with GPA • Subjects with MPA

Based on Tables 5, 6, and 7 of the CS[6]

AAV = anti-neutrophil cytoplasmic autoantibody–associated vasculitis; AE = adverse event; ANCA = anti-neutrophil cytoplasmic autoantibody; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate aminotransferase; AZA = azathioprine; BMI = body mass index; BVAS = Birmingham Vasculitis Activity Score; CD19 = cluster of differentiation 19; CT = computed tomography; CYC = cyclophosphamide; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EGPA = eosinophilic granulomatosis with polyangiitis; GC = glucocorticoid; GPA = granulomatosis with polyangiitis; GTI = Glucocorticoid Toxicity Index; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hpf = high-power field; HRQoL = health-related quality of life; IGRA = interferon gamma release assay; IV = intravenous; MCP-1 = monocyte chemoattractant protein-1; MDRD = Modification of Diet in Renal Disease; MPA = microscopic polyangiitis; MPO = myeloperoxidase; PPD = purified protein derivative; PR3 = proteinase 3; RBC = red blood cell; RTX = rituximab; SF-36v2 = 36-Item Short Form Health Survey version 2; TNF = tumour necrosis factor; UACR = urinary albumin-to-creatinine ratio; VDI = Vasculitis Damage Index

3.2.2 Statistical analyses of the included trials: ADVOCATE, CLEAR, and CLASSIC

In the ADVOCATE trial, non-inferiority and superiority tests were carried out for the primary efficacy endpoints (the proportion of patients achieving disease remission at week 26, and sustained remission at week 52). A sample size of 150 patients per treatment arm was estimated to provide more than 90% power for the non-inferiority (NI) test.[23] The company states that this sample size would:

- provide 90% power to detect approximately 18% superiority in the proportion of patients achieving remission at week 26 if the control group remission rate is 60% or,
- provide 85% power to detect approximately 18% superiority in the proportion of patients achieving sustained remission at week 52 if the control group sustained remission rate is 45%.[6]

The ADVOCATE trial CSR (page 68) states that, *"a non-inferiority margin of -20 percentage points was derived for the difference between avacopan and prednisone groups, and a one-sided alpha level of 0.025. This non-inferiority margin was based on a thorough review and meta-analysis of all previous clinical studies conducted in subjects with ANCA-associated vasculitis, as well as precedent."*[23]

Regarding the methods used by the company to propose the non-inferiority margin, the Food and Drug Administration (FDA) was critical.[24] As there are no historical placebo-controlled trials that evaluate the efficacy of GCs as an add-on therapy to CYC or RTX, single arm results from various studies were used. Yet, the relevance of these historical studies is questionable due to the potential differences in factors such as patient population, standard of care, treatment regimen, endpoint definitions, etc. Moreover, the extent to which GCs have contributed to the historical estimated remission rate on GCs + CYC/RTX are based on implausible and unverifiable assumptions as it is unlikely that the efficacy of GCs alone is similar to that of GCs + CYC/RTX.[24] The FDA concludes by stating: *"with the proposed NI margin of -20%, it would be very difficult to determine if a finding of similar remission rates on the proposed comparator arms was due to the efficacy of avacopan due to the fact that the remission rates on both arms were primarily driven by the induction treatment with cyclophosphamide of rituximab (with little or no benefit provided from avacopan)"* (page 36).[24]

Subsequently, 166 patients were randomised on the intervention arm to receive avacopan, and 165 were randomised to receive the control treatment.[6] All 166 patients were included in end-point analyses at both week 26 and week 52. However, on the comparator arm, although 165 patients were randomised to receive prednisone, 164 patients were included in end-point analyses at weeks 26 and 52 (as seen in Figure 22 of the CS Appendix D).[21] The one subject who did not receive at least one dose of the study medication was withdrawn from the study by the investigator upon re-review of renal biopsy for the presence of vasculitis.[23] Patients were stratified according to three standard of care immunosuppressant treatment regimes, a PR3 or MPO positive test at diagnosis, and newly-diagnosed versus relapsed ANCA-associated vasculitis (AAV).[23] The participant flow for the CLEAR and CLASSIC trials can be seen in Figures 23 and 24 of Appendix D in the CS, and patient stratification prior to randomisation in these trials was based on similar stratification factors (as detailed in Section 3.2.1).[21] The statistical analyses of all three trials have been summarised in Table 3.5.

ERG comment: The ADVOCATE trial non-inferiority margin chosen does not rule out with sufficient rigour that avacopan differs from placebo. However, the results from the ADVOCATE trial demonstrate that an avacopan-based regimen is not inferior and may be interpreted as being superior to a prednisone-based regimen (see Section 3.2.5) and therefore this is probably not a key issue.

Table 3.5: Summary of the statistical analyses of the ADVOCATE, CLEAR, and CLASSIC trials

Trial	ADVOCATE (NCT02994927)	CLEAR (NCT01363388)	CLASSIC (NCT02222155)
Hypothesis objective	To evaluate the efficacy of avacopan to induce and sustain remission in subjects with active AAV, when used with CYC followed by AZA, or with RTX	To determine whether avacopan could replace oral GCs in the treatment of AAV without compromising efficacy	To determine the safety, tolerability, and efficacy of avacopan in subjects with MPA or GPA, on SoC CYC or RTX plus GC treatment
Statistical analysis	For the purposes of data analysis, the intention to treat (ITT) population included all patients who had provided written informed consent and were randomised in the study. The safety population included all patients who were randomised and had received at least 1 dose of study drug. The primary analysis was conducted when all randomised subjects completed at least the week 52 study visit. The database was locked on 20 November 2019 to conduct this analysis. The week 60 follow-up analysis results were subsequently summarised. The database lock date for the follow-up analysis was 27 January 2020. No inferential statistical analyses were conducted on the follow-up period data.	For the purposes of data analysis, the ITT population included all subjects who were randomised, had received at least 1 dose of study medication, and had at least 1 post-baseline, on-treatment BVAS assessment. The safety population included all subjects who were randomised and had received at least 1 dose of study medication. Data for subjects from steps 1, 2, and 3 treated with placebo were combined for summary and analyses purposes. Data were presented separately for the CYC and RTX strata.	The safety population included all subjects who were randomised and received at least 1 dose of study medication. The ITT population comprised all subjects who were randomised, received at least 1 dose of study medication and had at least 1 post-baseline, on-treatment BVAS assessment. The main efficacy analysis was in the ITT population. If deemed appropriate, sensitivity analyses also could have been performed on all randomised subjects and a per protocol population, excluding subjects with major protocol deviations.
Sample size, power calculation	A sample size of 150 patients per group (300 in total) was estimated to provide more than 90% power for the non-inferiority test. This sample size provides 90% power to detect approximately 18% superiority in the	The planned study size was 60 patients. Assuming a control group BVAS response of 44% at day 85 and an avacopan group response of 86%, a sample size of 20 in each group provided ~90% power for the	The sample size was based on practical rather than statistical considerations, considering AAV is an orphan disease.

Trial	ADVOCATE (NCT02994927)	CLEAR (NCT01363388)	CLASSIC (NCT02222155)
	proportion of patients achieving clinical remission at week 26 if the control group remission rate is 60%. A sample size of 150 patients per group (300 in total) is estimated to provide 85% power to detect approximately 18% superiority if the control group sustained remission rate at week 52 is 45%.	primary efficacy analysis.	
Data management, patient withdrawals	Investigators were to clearly distinguish between study drug treatment discontinuation and study withdrawal. Patients who discontinued study drug treatment or who initiated medication changes (including those prohibited by the protocol) were to be automatically withdrawn from the study, but all efforts were made to continue to follow the patients for all regularly scheduled visits. Patients were to be withdrawn from the study for only one of the following 2 reasons: patient withdrawal of consent to contribute additional outcome information and loss to follow-up.	In the event of withdrawal from the study prior to the day 85 visit, the tests and evaluations listed for study day 85 were to be carried out as part of the early termination visit, whenever possible. For subjects who withdrew after day 85, the day 169 study tests and evaluations were to be performed. In the event of treatment failure where rescue GC therapy was needed, the study medication (avacopan or placebo) and study-supplied prednisone were discontinued, and appropriate open-label SoC measures were taken. However, the subject was asked to remain in the study and complete all remaining study visits.	In the event of withdrawal from the study prior to the day 85 visit, the tests and evaluations listed for study day 85 were to be carried out as part of the early termination visit, whenever possible. For subjects who withdrew after day 85, the day 169 study tests and evaluations were to be performed. In the event of treatment failure where rescue GC therapy was needed, the study medication (avacopan or placebo) and study-supplied prednisone were discontinued, and appropriate open-label SoC measures were taken. However, the subject was asked to remain in the study and complete all remaining study visits.

Based on Table 11 of the CS[6]
AAV = anti-neutrophil cytoplasmic autoantibody–associated vasculitis; AZA = azathioprine; BVAS = Birmingham Vasculitis Activity Score; CYC = cyclophosphamide; GC = glucocorticoid; GPA = granulomatosis with polyangiitis; hsCRP = high-sensitivity C-reactive protein; ITT = intention to treat; MCP 1 = monocyte chemoattractant protein-1; MPA = microscopic polyangiitis; RBC = red blood cell; RTX = rituximab; SoC = standard of care; UACR = urinary albumin-to-creatinine ratio

3.2.3 Participant characteristics of the included trials: ADVOCATE, CLEAR, and CLASSIC

The key baseline and demographic characteristics of randomised patients in the ADVOCATE trial have been summarised in Table 3.6. At screening, the age of randomised subjects ranged from 13 to 88 years old with 3 (0.9%) patients being between 12-17 years while the ages of the majority of patients-224 (67.7%), fell between 51 and 75 years old.[6, 23] The majority of randomised patients were male (56.5%), White (84.3%), and enrolled at sites in Europe (70.1%).[23]Most patients in the intention-to-treat (ITT) population had been newly diagnosed with ANCA-associated vasculitis (AAV) (69.45%), had renal disease at baseline (81.2%) and were taking IV RTX (64.8%) or IV CYC (30.9%) as standard of care (SoC) treatment, with a range of duration of AAV from 0 months to 362.3 months.

In the CLEAR trial, patients were randomised 1:1:1 into one of three treatment arms: avacopan plus CYC/RTX with no oral GCs, placebo plus CYC/RTX with a full starting dose of GCs; or avacopan plus CYC/RTX plus a two-thirds reduced starting dose of oral GCs.[11] The baseline and baseline patient characteristics have summarised in Table 3.7. Most randomised patients were male (70.1%), White (100%), newly diagnosed with ANCA disease status (73.1%), and were taking CYC (80.6%) as background treatment, with a range of 0-162 months of duration of AAV disease at screening.[11]

Table 3.8 outlines a concise summary of the baseline characteristics of patients in the CLASSIC trial. Most patients were female (54.8%), White (90.5%), obese- mean body mass index (BMI) (kg/m^2) = 30.2, newly diagnosed with ANCA disease status (64.3%), and were taking RTX (92.9%) as background treatment, with a range of 0-347 months of duration of AAV at screening.[10]

ERG comment: Overall, patient baseline and demographic characteristics were generally balanced for avacopan, prednisone and placebo treatment arms across all three trials. However, it should be noted that the range for duration of ANCA-associated vasculitis on all three trials is wide, and as patients were not stratified by shorter duration versus longer of ANCA-associated vasculitis, it is unclear if there has been equal distribution across active and control arms.

3.2.3.1 ADVOCATE trial concomitant medications

The ERG in its clarification letter asked the company to provide a list of both protocol and non-protocol specified concomitant medications administered to patients during the ADVOCATE trial. The company in its response indicated that a combination of sulphonamides and trimethoprim was the most common protocol-specified concomitant medication administered to 91.6% of patients on the avacopan-based regimen arm, and 92.7% of patients on the prednisone-based regimen arm.[1] In addition, [redacted] on the prednisone-based regimen arm received co-trimoxazole compared to [redacted] on the avacopan arm.[25] The company also stated that the non-protocol administered medications during the trial were: RTX, AZA, CYC, mycophenolate, MTX, methotrexate sodium, cyclosporine, tacrolimus, alemtuzumab, belimumab, abatacept or other immunosuppressants.[1]

The use of non-protocol allowed immunosuppressants or other treatments for AAV in the ADVOCATE trial was relatively low (as can be seen in Table 14.1.9 of the ADVOCATE clinical study report (CSR)[25]). The use of non-protocol allowed GCs has been discussed in Section 3.2.5.6's ERG comment.

3.2.3.2 ADVOCATE trial UK generalisability

The ERG in its clarification letter asked the company to provide more information on the 12.1% of patients in the ADVOCATE trial who were enrolled in UK study sites, and to discuss the generalisability of the participants in the ADVOCATE trial to the general UK AAV population. The company stated that, *"a total of 40 UK patients were included in the ADVOCATE study, of which 17*

received an avacopan-based regimen and 13 received a prednisone-based regimen".[1] The mean age of ITT UK patients on the trial at baseline was comparable to the trial population, 57.9 years versus 60.9 years, with most patients between ages 51 and 75 years, 75% versus 67.7%.[1] The majority of randomised patients were male (60%), White (95%), newly diagnosed with AAV (72.5%), anti-MPO positive (52.5%), had renal disease at baseline (77.5%) and were taking IV RTX (50%) or IV CYC (42.5%) as SoC treatment, with a range of duration of AAV from 0 months to 64.7 months.[1] The ERG notes that although the median duration of AAV for ITT patients enrolled in UK study sites is comparable to the ADVOCATE trial ITT population (both 0.23 months), the mean duration of AAV is much shorter in this sub-population (Mean [SD] = 8.18 [16.71] months, n = 40) when compared to the trial population (Mean [SD] = 21.54 [46.84] months, n = 330).[1] The baseline mean ± SD Birmingham Vasculitis Activity Score (BVAS) and Vasculitis Damage Index (VDI) scores for the ADVOCATE trial UK sub-population and whole ITT population was also generally comparable across both avacopan and prednisone arms. To provide assurance that the findings of the ADVOCATE trial are generalisable to the treatment of people with AAV in the UK, the company stated that, "*the findings of the Clinical Practice Research Datalink (CPRD) study that we conducted indicate that the baseline demographics and characteristics of the population included in the ADVOCATE trial are generalisable to the UK AAV population."*[1] They also emphasised that, *"in addition, a retrospective clinical audit of healthcare records of 300 UK AAV patients indicates a higher proportion receive CYC induction therapy but otherwise the demographic and clinical characteristics of the patients are similar to those in the ADVOCATE study."*[1] The ERG accedes to the company's statement on the ADVOCATE trial population being comparable to the general UK AAV population.

Table 3.6: Baseline and demographic characteristics of patients in ADVOCATE trial

Baseline characteristic	Avacopan	Prednisone
Number of patients, N	166	164
Mean age at screening ± SD, years	61.2±14.6	60.5±14.5
Male, n (%)	98 (59.0)	88 (53.7)
Race		
White, n (%)	138 (83.1)	140 (85.4)
Asian, n (%)	17 (10.2)	15 (9.1)
Black, n (%)	3 (1.8)	2 (1.2)
Other, n (%)	8 (4.8)	7 (4.3)
Mean BMI ± SD, kg/m^2	26.7±6.0	26.8±5.2
Newly diagnosed, n (%)	115 (69.3)	114 (69.5)
Median duration of ANCA-associated vasculitis, months (range)	0.23 (0-362.3)	0.25 (0-212.5)
ANCA status		
Anti-PR3 positive, n (%)	72 (43.4)	70 (42.7)
Anti-MPO positive, n (%)	94 (56.6)	94 (57.3)
Type of vasculitis		
GPA, n (%)	91 (54.8)	90 (54.9)
MPA, n (%)	75 (45.2)	74 (45.1)
Mean BVAS ± SD	16.3±5.9	16.2±5.7
Mean VDI ± SD	0.7±1.5	0.7±1.4

Baseline characteristic	Avacopan	Prednisone
Immunosuppressant induction treatment		
Intravenous RTX, n (%)	107 (64.5)	107 (65.2)
Intravenous CYC, n (%)	51 (30.7)	51 (31.1)
Oral CYC, n (%)	8 (4.8)	6 (3.7)
GC use during screening period		
Use of any GCs, n (%)	125 (75.3)	135 (82.3)
Intravenous use, n (%)	63 (38.0)	73 (44.5)
Oral use, n (%)	99 (59.6)	113 (68.9)
Total prednisone-equivalent dose ± SD, mg	654.0±744.4	727.8±787.8
Daily prednisone-equivalent dose ± SD, mg	46.7±53.2	52.0±56.3
Previous immunosuppressant use		
CYC, n (%)	4 (2.4)	2 (1.2)
RTX, n (%)	1 (0.6)	4 (2.4)
Renal disease at baseline		
Yes	134 (80.7)	134 (81.7)
No	32 (19.3)	30 (18.3)

Based on Table 8 of the CS[6] and Table 14.1.5.1 of ADVOCATE CSR[25]
ANCA = anti-neutrophil cytoplasmic autoantibody; BMI = body mass index; BVAS = Birmingham Vasculitis Activity Score; CS = company submission; CSR = clinical study report; CYC = cyclophosphamide; GC = glucocorticoid; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; MPO = myeloperoxidase; N = number of subjects in the intention-to-treat population; PR3 = proteinase 3; RTX = rituximab; SD = standard deviation; VDI = Vasculitis Damage Index

Table 3.7: Baseline and demographic characteristics of patients in CLEAR (NCT01363388) trial

Baseline characteristic	Avacopan + 20 mg prednisone	Avacopan + no prednisone	Placebo + 60 mg prednisone
Number of patients, N	22	22	23
Mean age at screening ± SD, years	57.0±14.2	57.4±14.0	59.1±14.0
Male, n (%)	14 (63.6)	16 (72.7)	17 (73.9)
White, n (%)	22 (100.0)	22 (100.0)	23 (100.0)
Mean BMI ± SD, kg/m^2	24.9±4.0	26.5±4.7	27.3±7.1
Newly diagnosed, n (%)	15 (68)	16 (73)	18 (78)
Median duration of ANCA-associated vasculitis, months (range)	0.0 (0-61)	1.0 (0-108)	0.0 (0-162)
ANCA status			
Anti-PR3 positive, n (%)	10 (45)	8 (36)	11 (48)
Anti-MPO positive, n (%)	12 (55)	13 (59)	10 (43)
Both PR3- and MPO-positive	0 (0.0)	0 (0.0)	1 (4)
ANCA equivocal or negative	0 (0.0)	1 (5)	1 (4)
Type of vasculitis			
GPA, n (%)	11 (50)	12 (55)	10 (44)
MPA, n (%)	11 (50)	10 (45)	12 (52)

Baseline characteristic	Avacopan + 20 mg prednisone	Avacopan + no prednisone	Placebo + 60 mg prednisone
Renal-limited vasculitis	2 (9.1)	1 (4.5)	2 (8.7)
Unknown	0 (0.0)	0 (0.0)	1 (4.3)
Mean BVAS ± SD	14.3±6.0	13.8±6.4	13.2±5.8
Mean VDI ± SD	0.9±1.5	0.5±1.2	1.2±1.4
Mean eGFR ± SD, ml/min/1.73 m^2	52.5±26.7	54.7±19.6	47.6±15.1
Mean UACR, mg/g	279 (24-2459)	283 (25-3051)	354 (28-5962)
Prior GC use			
Use of any GCs, n (%)	14 (64)	11 (50)	11 (48)
Intravenous use, n (%)	9 (41)	5 (23)	5 (25)
Total prednisone-equivalent dose, mg	49	44	53
Prior immunosuppressant use			
Immunosuppressants, including AZA, MTX or mycophenolate mofetil, n (%)	4 (18)	3 (14)	2 (9)
CYC or RTX, n (%)	0 (0.0)	0 (0.0)	0 (0.0)

Based on Table 9 of the CS[6] and Table 14.1.5.1 of ADVOCATE CSR[25]
ANCA = anti-neutrophil cytoplasmic autoantibody; AZA = azathioprine; BMI = body mass index; BVAS = Birmingham Vasculitis Activity Score; CS = company submission; CSR = clinical study report; CYC = cyclophosphamide; eGFR = estimated glomerular filtration rate; GC = glucocorticoid; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; MPO = myeloperoxidase; MTX = methotrexate; N = number of subjects in the intent-to-treat population; PR3 = proteinase 3; RTX = rituximab; SD = standard deviation; UACR = urinary albumin-to-creatinine ratio; VDI = Vasculitis Damage Index

Table 3.8: Baseline characteristics of patients in CLASSIC (NCT02222155) trial

Baseline characteristic	Avacopan 10 mg + SoC	Avacopan 30 mg + SoC	Placebo + SoC
Number of patients, N	13	16	13
Mean age at screening ± SD, years	60.0±10.17	55.3±13.81	58.5±15.42
Male, n (%)	4 (30.8)	8 (61.5)	7 (43.8)
Race			
White, n (%)	11 (84.6)	14 (87.5)	13 (100)
Black, n (%)	2 (15.4)	1 (6.3)	0 (0.0)
Other, n (%)	0 (0.0)	1 (6.3)	0 (0.0)
Mean BMI ± SD, kg/m^2	27.6±8.91	31.5±7.59	31.0±12.51
Newly diagnosed, n (%)	10 (76.9)	9 (56.3)	8 (61.5)
Median duration of ANCA-associated vasculitis, months (range)	1.0 (0-347)	2.5 (0-170)	1.0 (0 -95)
ANCA status			
Anti-PR3 positive, n (%)	7 (53.8)	8 (50.0)	6 (46.2)
Anti-MPO positive, n (%)	6 (46.2)	8 (50.0)	7 (53.8)
Type of vasculitis			
GPA, n (%)	8 (61.5)	12 (75.0)	9 (69.2)

Baseline characteristic	Avacopan 10 mg + SoC	Avacopan 30 mg + SoC	Placebo + SoC
MPA, n (%)	4 (30.8)	4 (25.0)	3 (23.1)
Renal-limited vasculitis, n (%)	1 (7.7)	0 (0.0)	1 (7.7)
Mean BVAS ± SD	15.8±8.84	15.1±6.43	15.0±4.45
Mean VDI ± SD	0.8±2.49	0.6±1.15	1.2±1.77
Mean eGFR ± SD, ml/min/1.73 m^2	56.4±26.75	61.4±31.09	60.1±24.25
Mean UACR, mg/g	499 (103-3466)	464 (98-2693)	652 (163-7291)
Prior GC use			
Systemic GCs, n (%)	12 (92.3)	13 (81.3)	9 (69.2)
Prior immunosuppressant use			
CYC, n (%)	0 (0.0)	2 (12.5)	1 (7.7)
RTX, n (%)	13 (100.0)	14 (87.5)	12 (92.3)

Based on Table 10 of the CS[6] and Table 14.1.5.1 of ADVOCATE CSR[25]
ANCA = anti-neutrophil cytoplasmic autoantibody; BMI = body mass index; BVAS = Birmingham Vasculitis Activity Score; CS = company submission; CSR = clinical study report; CYC = cyclophosphamide; eGFR = estimated glomerular filtration rate; GC = glucocorticoid; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; MPO = myeloperoxidase; N = number of subjects in the intention-to-treat population; PR3 = proteinase 3; RTX = rituximab; SD = standard deviation; SoC = standard of care; UACR = urinary albumin-to-creatinine ratio; VDI = Vasculitis Damage Index

3.2.4 Quality assessments of the included trials: ADVOCATE, CLEAR, and CLASSIC

The company assessed the quality of the ADVOCATE, CLEAR, and CLASSIC trials using the Cochrane Risk of Bias 2 (ROB2) tool.[22] The ERG asked the company to clarify the number of reviewers involved in the assessment of the risk of bias of these trials and the company stated that, "*the quality assessment process was carried out by a single analyst who was required to answer specific questions for each study regarding selection, performance, attrition, and detection bias. A second analyst checked and validated the findings regarding the study quality; if a consensus could not be achieved, a third reviewer was consulted*."[1] Concerning the result of the assessment, the company concluded that the quality of the three avacopan trials was found to be high and that"the risk of bias on all domains was low for all 3 trials."[21] Table 3.9 details the results of the RoB assessment included in the CS and CL response.

Table 3.9: Quality assessment of ADVOCATE, CLEAR, and CLASSIC trials

Trial name		ADVOCATE		CLEAR		CLASSIC	
		CS	**CL response**	**CS**	**CL response**	**CS**	**CL response**
Selection bias (systematic differences between the comparison groups)	Was an appropriate method of randomisation used to allocate participants to treatment groups?	Yes	Yes	Yes	Yes	Not clear	Yes
	Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes	Yes	Yes
	Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes	Yes	Yes
	Risk of selection bias	Low risk	Low risk	Low risk	Low risk	Unclear/ unknown risk	Low risk
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)	Did the comparison groups receive the same care apart from the intervention(s) studied?	No	Yes	No	Yes	Yes	Yes
	Were participants receiving care kept “blind” to treatment allocation?	Yes	Yes	Yes	Yes	Yes	Yes
	Were individuals administering care kept “blind” to treatment allocation?	Yes	Yes	Yes	Yes	Yes	Yes
	Risk of performance bias	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Trial name		ADVOCATE		CLEAR		CLASSIC	
		CS	CL response	CS	CL response	CS	CL response
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)	Were all groups were followed up for an equal length of time?	No	Yes	Yes	Yes	Yes	Yes
	Were there any unexpected imbalances in dropouts between groups?	No	No	No	No	Not clear	No
	Did the analysis include an intention to treat analysis?	No	Yes	Yes	Yes	No	No
	Risk of attrition bias	Unclear/ unknown risk of bias	Low risk	Low risk	Low risk	Low risk	Low risk
Detection bias (bias in how outcomes are ascertained, diagnosed, or verified)	Were investigators kept 'blind' to participants' exposure to the intervention?	Yes	Yes	Yes	Yes	Yes	Yes
	Risk of detection bias	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Reporting bias (bias in how outcomes are ascertained, diagnosed, or verified)	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes	No	No	No	Not clear	No
	Risk of reporting bias	Unclear/ unknown risk	Low risk	Low risk	Low risk	Unclear/ unknown risk	Low risk

Based on Table 69 in Appendix D of CS [21] and Table 8 in the response to request for clarification[1]
CL = response to clarification questions; CS = company submission

ERG comment:

- To avoid bias and error, it is normally recommended that two reviewers independently assess the methodological quality of included studies.[16]
- The results of the company's initial risk of bias assessment (included in Appendix D) and that of Table 8 in the CL response differ across four of the five RoB domains. As there were no changes in the ADVOCATE, CLEAR, and CLASSIC trial methodologies between the submission of evidence from the company and submission of response to clarification, the ERG queries the discrepancies in the methodological quality results.

3.2.5 Efficacy results of the included trials: ADVOCATE, CLEAR, and CLASSIC

The CS reported on nine clinical effectiveness outcomes: remission, sustained remission, early remission (BVAS of zero at week 4), relapses, glucocorticoid-induced toxicity, estimated glomerular filtration rate (eGFR), urinary albumin-to-creatinine ratio (UACR), urinary monocyte chemoattractant protein 1 (MCP-1):creatinine ratio, and vasculitis damage index (VDI).

ERG comment: These outcomes adequately cover the NICE final scope outcomes of morbidity (including damage of organs), remission rate, change in renal function, and use of corticosteroids. HRQoL results were not included in the CS, but as they were published in the trial CSRs, have been reported in this section. As multiple study endpoints have been reported for secondary outcomes, the ERG urges caution in that the evaluation of multiple hypotheses does not prelude to inflation of the probability of Type I error.

3.2.5.1 Remission

In the ADVOCATE trial, remission was defined as achieving a Birmingham Vasculitis Activity Score (BVAS) of 0 at week 26, no administration of GCs for treatment of AAV within 4 weeks prior to week 26 and no BVAS >0 during the 4 weeks prior to week 26.[6] At week 26, 72.3% of patients on the avacopan arm compared to 70.1% on the prednisone arm, had achieved remission in the intention-to-treat (ITT) population. In the per-protocol (PP) population, [redacted] patients on the avacopan arm, and [redacted] patients on the prednisone arm had achieved disease remission at week 26, showing consistent results with the ITT population.[23] The ITT population consisted of all subjects who were randomised in the study and had received at least one dose of the blinded study drug while the PP population consisted of all subjects in the ITT population who were compliant with taking avacopan/ placebo and who did not have major protocol deviations that could have significantly affected the interpretation of results.[23]

In the CLEAR trial, clinical remission in the post-hoc analysis was defined as a BVAS score of zero at Day 85.[11] 45.5% of patients in the avacopan + low-dose prednisone group, 33.3% of patients in the avacopan + no prednisone group, and 40% of patients in the placebo + full-dose prednisone group achieved clinical remission.[6, 11]

In the CLASSIC trial, clinical remission was defined as achieving BVAS score of zero at Day 85.[10] 66.7% of patients in the avacopan 10 mg + standard of care (SoC) group, 46.7% of patients in the avacopan 30 mg + SoC group, and 53.8% of patients in the placebo + SoC group achieved clinical remission.[6, 10]

These results have been summarised in Table 3.10.

ERG comment: Results across all three trials demonstrate that although the treatment effect of avacopan is not superior to that of a prednisone-based regimen, an avacopan-based regimen is non-

inferior to a prednisone-based regimen in inducing remission in patients with AAV after 26 weeks of treatment. In the ADVOCATE trial, the interpretation of avacopan's non-inferiority to prednisone in inducing remission in patients with AAV is not an avacopan versus prednisone comparison, but rather an avacopan + lower dose glucocorticoids versus higher dose glucocorticoids (See Section 3.2.5.6 for further arguments on GC use in the trial). As a non-inferiority comparison might be insufficient to isolate the effect of avacopan from that of RTX/CYC as the primary driver of efficacy, the ERG thus expresses its concern on the meaningfulness of this comparison.

The ERG in its clarification letter asked the company to shed more light on the reliable measurement tools or biomarkers used to validate the measurement of remission across the avacopan trials. The company explained that although testing for the presence of ANCA antibodies, along with clinical assessments and other blood tests for inflammatory markers, kidney function, and urine measurements for blood and protein, support an AAV diagnosis, as the utility of these clinical assessments alone as an indicator of disease activity or as a predictor of relapse is inconsistent, the BVAS tool (a composite score which evaluates 56 clinical features from 9 organ systems that are attributed to active vasculitis where each item is weighted according to the severity, with a score of 0 often being adopted as the definition of disease remission in studies) was used for assessing remission.[1]

3.2.5.2 Sustained remission

The results on the effects of avacopan in inducing sustained remission in AAV patients from the ADVOCATE, CLEAR, and CLASSIC trials have been summarised in Table 3.10.

In the ADVOCATE trial's ITT population, 65.7% of patients achieved sustained disease remission at week 52 compared to 54.9% of patients on the prednisone arm.[6, 23] These results were consistent with the PP population where [redacted] on the avacopan arm, and [redacted] on the prednisone arm achieved sustained disease remission at week 52.[23] Sustained disease remission at week 52 was defined as a BVAS of 0 as determined by the adjudication committee (AC) and no administration of GCs for AAV within 4 weeks prior to week 52.[23]

In the CLEAR trial, the post-hoc analysis of sustained remission defined it as achieving remission at week 4 (based on a BVAS of 0) which was sustained at week 12.[6] 3/22 patients in the avacopan + low-dose prednisone arm, 6/21 patients in the avacopan + no prednisone arm, and 1/20 patients in the placebo + full-dose prednisone arm achieved sustained clinical remission at week 12.[6]

The CLASSIC trial also defined sustained remission as remission at week 4 (BVAS of 0) which was sustained at week 12.[6] 1/12 patients in the avacopan 10mg + SoC group, 3/15 patients in the avacopan 30mg + SoC group, and 2/13 of patients in the placebo + SoC group achieved sustained remission at week 12.[6]

ERG comment: At 52 weeks of treatment, results from the ADVOCATE trial demonstrate that an avacopan-based regimen is not inferior and may be interpreted as being superior to a prednisone-based regimen in sustaining disease remission in patients with AAV.

Table 3.10: Effect of avacopan on remission and sustained remission

Trial	ADVOCATE		CLEAR			CLASSIC		
Treatment arm	Avacopan-based regimen (N = 166)	Prednisone-based regimen (N = 164)	Avacopan + 20 mg prednisone (N = 22)	Avacopan + no prednisone (N = 21)	Placebo + 60 mg prednisone (N = 20)	Avacopan 10 mg + Soc (N = 12)	Avacopan 30 mg + SoC (N = 15)	Placebo + SoC (N = 13)
Remission								
Follow-up	26 weeks	26 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks
n/N (%)	120/166 (72.3)	115/164 (70.1)	10/22 (45.5)	7/21 (33.3)	8/20 (40.0)	8/12 (66.7)	7/15 (46.7)	7/13 (53.8)
95% CI[a]	64.8 to 78.9	62.5 to 77.0	-	-	-	-	-	-
Difference in %[b]	3.4		5.5	6.7	-	12.8	-7.2	-
95% CI for difference in %[c]	-6.0, 12.8		-19.6, 30.5	-31.4, 18.1	-	-19.09, 44.73	-38.26, 23.90	-
Non-inferior P value	<0.0001		0.0476	0.1875	-	-	-	-
Superior P value	0.2387		-	-	-	-	-	-
Sustained remission								
Follow-up	52 weeks	52 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks
n/N (%)	109/166 (65.7)	90/164 (54.9)	3/22 (13.6)	6/21 (28.6)	1/20 (5.0)	1/12 (8.3)	3/15 (20.0)	2/13 (15.4)
95% CI[a]	57.9, 72.8	46.9, 62.6	-	-	-	-	-	-
Difference in %[b]	12.5		-	-	-	-	-	-
95% CI for difference in %[c]	2.6, 22.3		8.6	23.6	-	7.1	4.6	-
Non-inferior P value	<0.001		-5.8, 23.1	5.5, 41.7	-	-28.10, 14.00	-19.04, 28.27	-
Superior P value	0.0066		-	-	-	-	-	-

Based on Tables 13 and 14 of the CS[6]

Trial	ADVOCATE		CLEAR			CLASSIC		
Treatment arm	Avacopan-based regimen (N = 166)	Prednisone-based regimen (N = 164)	Avacopan + 20 mg prednisone (N = 22)	Avacopan + no prednisone (N = 21)	Placebo + 60 mg prednisone (N = 20)	Avacopan 10 mg + Soc (N = 12)	Avacopan 30 mg + SoC (N = 15)	Placebo + SoC (N = 13)
[a]Clopper and Pearson exact CI; [b]Summary score estimate of the common difference in remission rates by using inverse-variance stratum weights; [c]Miettinen-Nurminen (score) confidence limits for the common difference in remission rates CI = confidence interval; N = number of subjects in the intention-to-treat population; n = number of patients achieving remission; SoC = standard of care								

3.2.5.3 Early remission

Early remission in both ADVOCATE and CLASSIC trials was defined as a BVAS of 0 at week 4.[6] In the ADVOCATE trial, 68.9% of patients on the prednisone arm achieved early remission when compared to 62.7% of patients on the avacopan arm.[6] While in the CLASSIC trial, five out of 15 patients on the avacopan 30mg + SoC arm achieved early remission when compared to 1/12 patient on the avacopan 10mg + SoC arm and 2/13 patients on placebo + SoC arm.[6] These results have been summarised in Table 3.11.

Table 3.11: Effect of avacopan on early remission at 4 weeks

Trial	ADVOCATE		CLASSIC		
Treatment arm	Avacopan-based regimen (N = 166)	Prednisone-based regimen (N = 164)	Avacopan 10 mg + Soc (N = 12)	Avacopan 30 mg + SoC (N = 15)	Placebo + SoC (N = 13)
Mean ± SD at baseline	16.3±5.87	16.2±5.69	15.8±8.84	15.1±6.43	15.0±4.45
n/N (%)	104/166 (62.7)	113/164 (68.9)	1/12 (8.3)	5/15 (33.3)	2/13 (15.4)
95% CI[a]	54.8, 70.0	61.2, 75.9	-	-	-
Estimate of common difference in %[b]	-5.6		-	-	-
Two-sided 95% CI for difference in %[c]	-15.4, 4.2		-	-	-
Superior P-value	0.8695		-	-	-
Based on Table 14 of CS[6] [a]Clopper and Pearson exact CI; [b]Summary score estimate of the common difference in remission rates by using inverse-variance stratum weights; [c]Miettinen-Nurminen (score) confidence limits for the common difference in remission rates CI = confidence interval; N = number of subjects in the intention-to-treat population; n = number of patients achieving BVAS of 0 at week 4; SD = standard deviation; SoC = standard of care					

3.2.5.4 Relapses

In the ADVOCATE trial, relapse was defined as return of at least one major item, or three or more minor items, or one or two minor items in the BVAS recorded at two consecutive visits, after disease remission has been achieved previously (BVAS=0).[23] 9 (7.5%) patients on the avacopan arm

experienced relapses after achieving remission at week 26, compared to 14 (12.2%) patients on the prednisone arm (see Table 3.12).

Table 3.12: Effect of avacopan on relapses following previous remission in ADVOCATE trial ITT population

Treatment arm	Avacopan-based regimen (N= 166)	Prednisone-based regimen (N=164)
Follow-up	52 weeks	52 weeks
Number of patients achieving previous remission at week 26, N'	120	115
Patients experiencing a relapse following previous remission at week 26, n/N' (%)	9/120 (7.5)	14/115 (12.2)
95% CI[a]	3.5, 13.8	6.8, 19.6
Difference in %	-4.7	
Estimate common difference in %[b]	-6.0	
Two-sided 95% CI for difference in %[c]	-14.4, 2.4	
Superiority P-value	0.0810	

Based on Table 15 in CS[6]
[a]Clopper and Pearson exact CI; [b]Summary score estimate of the common difference in remission rates by using inverse-variance stratum weights; [c]Miettinen-Nurminen (score) confidence limits for the common difference in remission rates
Note: Disease remission at Week 26 was assessed by the adjudication committee
CI = confidence interval; ITT = intention to treat; N = number of subjects in the intention-to-treat population; n = number of subjects relapsing following disease remission at week 26; N = number of subjects achieving disease remission (BVAS=0) at week 26

3.2.5.4.1 Exploratory analyses

The ADVOCATE study pre-specified an exploratory analysis of time to relapse from the first time point when BVAS of 0 would be achieved.[23] Results show that the rate of relapse at any time during the study after BVAS=0 had been achieved was 10.1% in the avacopan group and 21.0% in the prednisone SoC group with the hazard ratio of the time to relapse in the two arms being 0.46, 95%Cl (0.25, 0.84). Rate of relapse exploratory analyses results have been summarised in Table 3.13. The median time to relapse and its associated 95%Cl could not be estimated due to there being a small number of relapsed patients.[23] However, a plot of Kaplan-Meier estimates showing the probability of remaining relapse-free after induction of remission has been demonstrated in Figure 3.1.

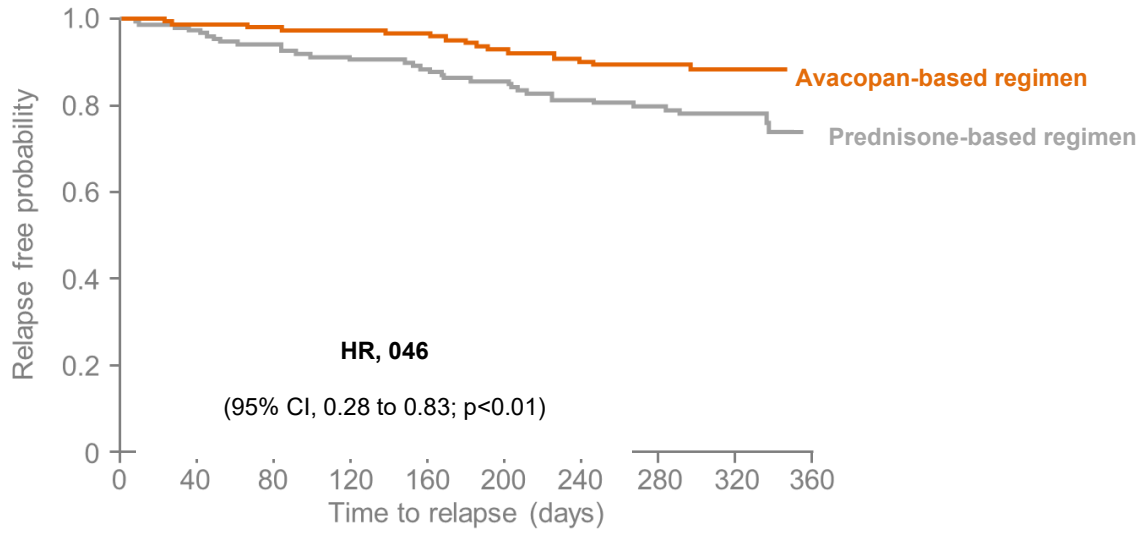
Table 3.13 Exploratory analyses of relapse in ADVOCATE trial ITT population

Treatment arm	Avacopan-based regimen (N = 166)	Prednisone-based regimen (N = 164)
Patients who achieved BVAS=0, N'	158	157
Patients experiencing relapse after BVAS=0 was achieved, n/N' (%)[a]	16/158 (10.1)	22/157 (21.0)
Patients censored, n (%)	142 (89.9)	124 (79.0)
Treatment comparison vs SoC		

Hazard ratio	NA	0.461
95% CI for hazard ratio	NA	0.254 to 0.838
P value	NA	0.0091

Based on Table 16 of CS[6]
[a]As assessed by the Adjudication Committee; based on the Investigators' assessment, a relapse was defined as worsening of disease, after previous achievement of a BVAS of 0 (on a scale from 0 to 63, with higher scores indicating greater disease activity), that involved 1 or more major items in the BVAS, three or more minor items in the BVAS, or 1 or 2 minor items in the BVAS recorded at 2 consecutive trial visits
Note: The median time to relapse was not estimable because of small number of relapsed subjects. Therefore, the Kaplan-Meier estimates were not calculated. The P values are from the log-rank test to compare the treatment groups.
BVAS = Birmingham Vasculitis Activity Score; CI = confidence interval; ITT = intention to treat; N = number of subjects in the intention-to-treat population; n/N' = number of subjects in the specified category/number of subjects who achieved BVAS=0 during the 52-week treatment period and is used as the denominator for percentage calculations; NA = not applicable; SoC = standard of care

Figure 3.1: Kaplan-Meier plot of time-to-relapse in ADVOCATE trial



Based on Figure 4 in CS[6]
Note: Relapse was defined as the absence of worsening disease, as measured by BVAS, with no involvement of major items in the BVAS, <3 minor items in the BVAS, and no minor items in the BVAS recorded at 2 consecutive trial visits.
CI = confidence interval; HR = hazard ratio

3.2.5.5 Glucocorticoid-induced toxicity

In the ADVOCATE trial, the use of an avacopan-based regimen, relative to prednisone SoC, was associated with statistically less GC-induced toxicity at weeks 13 and 26, for both glucocorticoid toxicity index (GTI) scores.[6] At week 13, the least squares mean (LSM) of the GTI-Cumulative Worsening Score (GTI-CWS) for the avacopan arm was 25.7 compared to 36.6 on the prednisone arm, and 39.7 against 56.6 at week 26. Similarly, for the GTI-Aggregate Improvement Score (GTI-AIS), at week 13 the LSM for avacopan was 9.9 compared to 23.2 on the prednisone arm, and 11.2 against 23.4 at week 26. Results have been summarised in Table 3.14.

Table 3.14 Effect of avacopan on glucocorticoid-induced toxicity in the ADVOCATE trial

Treatment arm	Avacopan-based regimen	Prednisone-based regimen	Avacopan-based regimen	Prednisone-based regimen
Follow-up	13 weeks	13 weeks	26 weeks	26 weeks
Number of patients, N	166	164	166	164
GTI-CWS				
Mean ± SD at baseline	NA	NA	NA	NA
LSM ± SEM	25.7±3.40	36.6±3.41	39.7±3.43	56.6±3.45
P value	0.014		0.0002	
GTI-AIS				
Mean ± SD at baseline	NA	NA	NA	NA
LSM ± SEM	9.9±3.45	23.2±3.46	11.2±3.48	23.4±3.50
P value	0.003		0.008	

Based on Table 17 of CS[6]
AIS = Aggregate Improvement Score; CWS = Cumulative Worsening Score; GTI = Glucocorticoid Toxicity Index; ITT = intention-to-treat; LSM = least squares mean; N = number of subjects in the intention-to-treat population; NA = not applicable; SD = standard deviation; SEM = standard error of measurement

ERG comment: As more patients on the prednisone arm received GCs during the screening period when compared to patients on the avacopan arm (see Table 3.6 for baseline characteristics), the ERG asked the company to clarify how this sticking point would impact this outcome (which has been employed to express the steroid-sparing effect of avacopan). The company in its response to clarification stated that, "*The incidence of prior GCs use was numerically higher in the prednisone group, but the difference between groups was not statistically different (p=0.119, chi-squared test)" and that, "in patients receiving oral GCs during the screening period, the dose needed to be tapered to a dose that did not exceed 20 mg prednisone equivalent on day 1 (first dosing day) of the study and to be tapered to zero over a 4-week period after day 1. The GTI measures change in GC toxicity rather than absolute GC toxicity to account for the effects of prior GC therapy and background rate of AEs. As the GTI measured CWS and AIS over the first and subsequent 13 weeks of the study, prior GC use is unlikely to have had a meaningful impact on the outcomes observed*."[1] The ERG also notes that GC dosing for patients on the prednisone-regimen based arm was specified and not based on investigator assessment of active AAV.

Due to the high proportion of patients that received non-study supplied GCs on the avacopan arm (see ERG comment in Section 3.2.5.6), the ERG has some concern on the meaningfulness of what appears to be a comparison of GTI scores between avacopan + non-study supplied GCs (lower dose GCs) versus study GCs + non-study supplied GCs (higher dose GCs) arms.

3.2.5.6 Use of immunosuppressants and corticosteroids

In the ADVOCATE trial, from day 1 to end of treatment (Day 365 or early termination visit), 87.3% (145/166) of patients on the avacopan arm and 90.9% (149/164) of patients on the prednisone arm utilised concomitant non-study GCs.[23] Likewise, 17.5% (29/166) of patients on the avacopan arm and 22.0% (36/164) of patients on the prednisone arm utilised concomitant non-protocol specified immunosuppressant drugs or other treatments for AAV from day 1 to end of treatment.[23] The mean

cumulative total GC dose (study supplied and non-study supplied) of patients on avacopan during the 52-week treatment period was 1348.9mg compared to 3654.5mg on the prednisone arm. These results have been summarised in Table 3.15.

The ERG asked the company in its clarification letter to discuss the results of this outcome in the ADVOCATE trial. The company in its response to clarification stated that, *"sources of additional, non–study-supplied GCs in both groups were tapered in the first 4 weeks from pre-randomisation GC dosing, GC from co-administration with RTX (65% of all subjects) over first 4 weeks, and off-protocol GC use (for AAV relapse or no improvement in major BVAS item in the first 4 weeks) as prescribed by clinician. During the last 26 weeks of the treatment period, 39.0% of the prednisone group and 27.1% of the avacopan group received non-study supplied GCs; GC exposure was 40% lower in the avacopan-based regimen group, with a mean cumulative GC dose during the treatment period of 295.6 mg for the avacopan group vs 489.0 mg for the prednisone group.*" (See Figure 3.2 for the mean cumulative dose over time in the ADVOCATE ITT population)[1] And that, "the difference in GC use between the treatment arms in the ADVOCATE trial corresponds to the potential steroid-sparing effect of avacopan."[1] They also stated that, "*the incidence of use of concomitant other non-protocol specified immunosuppressant drugs or other treatments for AAV was also lower in the avacopan-based regimen group (range: 8.4-27.1%) compared to the prednisone- based regimen group (range: 9.8-33.5%) across all study periods.*"[1]

ERG comment:

- The ERG in its clarification letter asked the company to clarify if the extra oral/IV non-study GC treatment administered to patients during the ADVOCATE trial was given as rescue medication. The company in its response stated that, *"treatment that was not provided as prednisone study medication was avoided as much as possible"* and that, *"the protocol allowed subjects who experienced a relapse of their AAV during the study to be treated with IV GCs and/or oral GCs, tapered according to the subject's condition"*.[1]
- The ERG expresses concern on the high proportion of patients on the avacopan arm supplied with non-study GCs during the treatment period in the ADVOCATE trial.
- The ERG also emphasises that the mean dose of non-study supplied GCs used as rescue medication for AAV relapse was higher on the avacopan arm when compared to the prednisone arm, despite the company's attempts to highlight that the total (study + non-study) supplied GC mean dose was higher for the GC-based regimen arm when compared to the avacopan-based regimen arm. The use of non-protocol specified immunosuppressant drugs or other treatments during the ADVOCATE trial has been discussed in the ERG comment in Section 3.2.3 of this report.

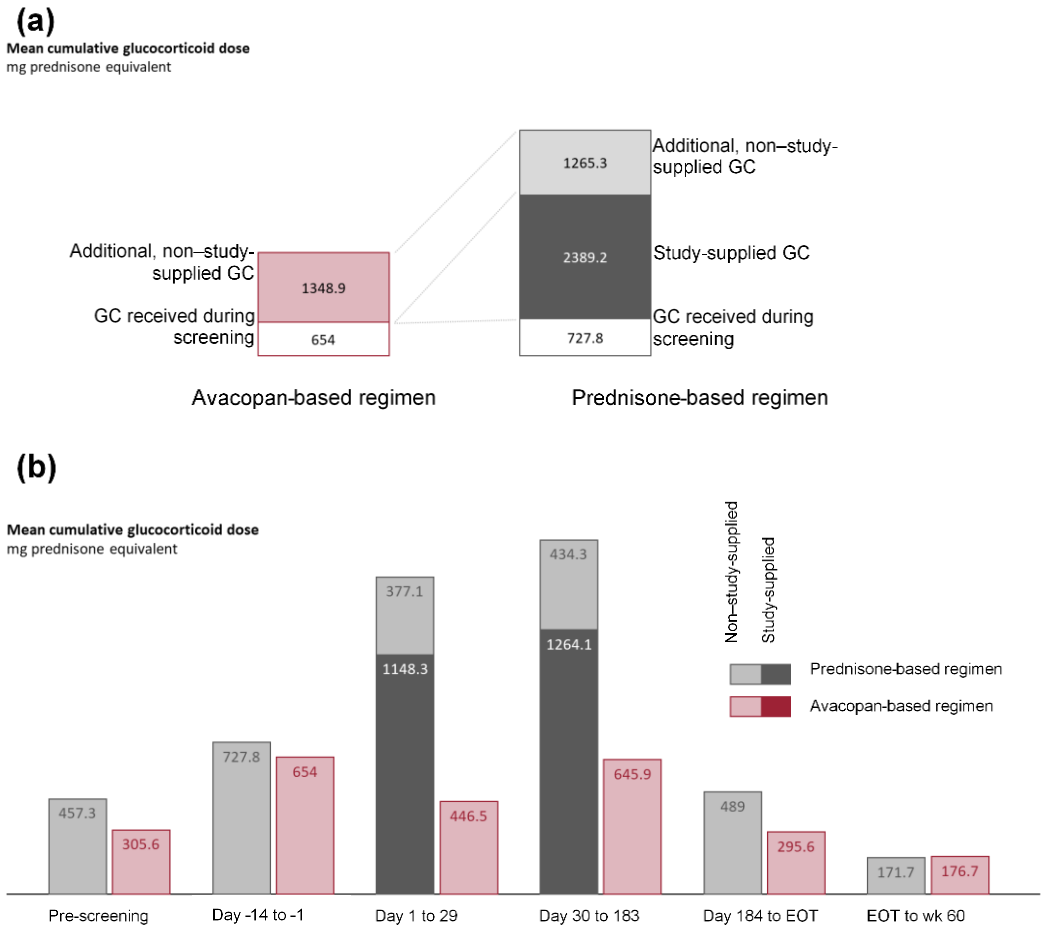
Table 3.15: Summary of GC use and other non-protocol specified treatments in ADVOCATE trial ITT population

Treatment arm	Avacopan-based regime (N = 166)	Prednisone-based regime (N = 164)
Concomitant non-study GC use* , n (%)		
Day 1 to 183	143 (86.1)	149 (90.9)
Day 1 to End of Treatment**	145 (87.3)	149 (90.9)
Day 1 to End of 60-week Study Period	146 (88.0)	151 (92.1)

Treatment arm	Avacopan-based regime (N = 166)	Prednisone-based regime (N = 164)
Concomitant other non-protocol specified immunosuppressant drugs or other treatments for ANCA-associated vasculitis* , n (%)**		
Day 1 to 183	14 (8.4)	16 (9.8)
Day 1 to End of Treatment	29 (17.5)	36 (22.0)
Day 1 to End of 60-week Study Period	45 (27.1)	55 (33.5)
Non-study supplied oral or IV GCs Day 1 to End of Treatment, mg		
Mean (SD)	1348.9 (2040.29)	1265.3 (1650.64)
Total (study supplied and non-study supplied) GCs Day 1 to End of Treatment, mg		
Mean (SD)	1348.9 (2040.29)	3654.5 (1709.83)

Based on Tables 11 and 12 in ADVOCATE CSR[23]
* Concomitant IV or oral glucocorticoids other than the prednisone study medication
** End of Treatment is Day 365 or Early Termination visit
*** Includes non-protocol specified rituximab, azathioprine, cyclophosphamide, mycophenolate, methotrexate, methotrexate sodium, cyclosporine, tacrolimus, alemtuzumab, belimumab, abatacept or other Immunosuppressants
ANCA = anti-neutrophil cytoplasmic autoantibodies; CSR = clinical study report; GC = Glucocorticoids; IV = Intravenous; N = number of subjects randomized to treatment group in the Safety Population; n = number of subjects in specified category

Figure 3.2: Mean cumulative glucocorticoid dose over time in the ADVOCATE trial (ITT population)



Based on Figure 4 of the response to the request for clarification[1]
(a) Overall and (b) by time period
EOT = end of treatment; GC = glucocorticoid; wk = week

3.2.5.7 Estimated glomerular filtration rate (eGFR)

In the ADVOCATE trial, change from baseline in kidney function in patients with renal disease (based on the BVAS renal component) was measured by estimated glomerular filtration rate (eGFR) (based on the Modified Diet in Renal Response (MDRD) formula).[23] At week 26, the LSM change in eGFR of patients with renal disease at baseline in the avacopan and prednisone arms was 5.8 and 2.9 ml/min/1.73m^2, respectively.[23] Similarly, at week 52, LSM change in the avacopan and prednisone arms was 7.3 and 4.1 ml/min/1.73m^2, respectively.[6] Table 3.17 details the change from baseline in eGFR in the ADVOCATE trial patients with renal disease at baseline, stratified by renal disease severity. In the CLEAR trial, the mean eGFR (based on MDRD formula using serum creatinine) following the 84-day treatment period for patients with renal disease at baseline was higher for the avacopan + low-dose GC group and avacopan + no GC group, when compared to the placebo + full-dose GC.[11] In the CLASSIC trial, the MMRM analysis of the mean eGFR (based on the MDRD formula using serum creatinine) in patients with baseline renal disease resulted in the avacopan 10mg + SoC arm being 49.1 ml/min/1.73m^2, 64.0 ml/min/1.73m^2 in the avacopan 30mg + SoC arm, and 59.2 ml/min/1.73m^2 in the placebo + SoC arm.[10] Results for all three trials have been summarised in Table 3.16.

ERG comment:

- The CS presented change in eGFR results from the CLEAR trial in the ITT population: Table 14.2.5.1.1 in CLEAR CSR, rather than all patients with renal disease at baseline in the ITT population. The ERG has presented the baseline and Day 85 results for ITT population - all patients with renal disease at baseline for the CLEAR trial (Table 14.2.5.1.2 in CLEAR CSR) to ensure that all trial results are comparable.
- The ERG notes that overall, [redacted] on the prednisone-based regimen group compared to [redacted] on the avacopan-based regimen group required dialysis, either temporarily or permanently.[23]

Table 3.16: Effect of avacopan on eGFR in ITT population – renal disease at baseline

Trial	ADVOCATE [8, 23]		CLEAR [10, 12]			CLASSIC[9, 10]		
Treatment arm	Avacopan-based regimen	Prednisone-based regimen	Avacopan + 20 mg prednisone	Avacopan + no prednisone	Placebo + 60 mg prednisone	Avacopan 10 mg + Soc	Avacopan 30 mg + SoC	Placebo + SoC
Population (N'/N)	119/134	125/134	[redacted]	[redacted]	[redacted]	8/12	10/15	9/13
Follow-up (weeks)	52	52	12	12	12	12	12	12
Mean + SD at baseline	44.6±27.67	45.6±27.27	[redacted]	[redacted]	[redacted]	47.9±6.97	57.8±11.71	57.2±8.55
Mean ± SD following treatment	53.2±24.09	50.5±22.09	[redacted]	[redacted]	[redacted]	49.1±6.66	64.0±11.16	59.2±8.02
LSM ± SEM	7.3±1.05	4.1±1.03	[redacted]	[redacted]	[redacted]	9.6±13.03	18.3±10.66	13.4±11.44
95% CI	5.2 to 9.4	2.1 to 6.1	[redacted]	[redacted]	[redacted]	-17.09 to 36.37	-3.73 to 40.29	-10.21 to 36.96
P value	0.0294		[redacted]	[redacted]	[redacted]	0.8132	0.7400	NA

Based on Table 19 of the CS[6] and CLEAR CSR[11]

* Statistics for differences between specified treatment groups and placebo are from a MMRM model with treatment group, visit, treatment-by visit interaction, AAV disease status (new or relapsed), and ANCA positivity (MPO of PR3) as factors and the baseline value as a covariate

CI = confidence interval; CS = company submission; CSR = clinical study report; eGFR = estimated glomerular filtration rate; LSM = least squares mean; N = number of subjects in the analysis population for the specified treatment group; N'/N = subjects with data at baseline and specified visit/number of subjects in the analysis population for the specified treatment group; NA = not applicable; NR = not reported; SD = standard deviation; SEM = standard error of measurement; SoC = standard of care

Table 3.17: Effect of avacopan on eGFR in ADVOCATE trial stratified by renal disease severity

Treatment	N	Week 26			Week 52		
		N'	LSM change in eGFR	P value	N'	LSM change in eGFR	P value
Subjects with baseline eGFR <30 ml/min/1.73 m^2							
Prednisone-based regimen	48	42	6.4	0.0361	42	8.2	0.005
Avacopan-based regimen	52	46	10.5		45	13.7	
Subjects with baseline eGFR 30 to 59 ml/min/1.73 m^2							
Prednisone-based regimen	51	51	5.4	0.3535	50	7.8	0.2115
Avacopan-based regimen	46	44	7.3		43	10.5	
Subjects with baseline eGFR >59 ml/min/1.73 m^2							
Prednisone-based regimen	35	34	-6.0	0.3640	33	-7.5	0.6721
Avacopan-based regimen	33	31	-2.6		31	-5.9	

Based on Table 20 of CS[6]
CS = company submission; eGFR = estimated glomerular filtration rate; LSM = least squares mean; N = number of subjects in the analysis population for the specified treatment group; N' = number of subjects with data at baseline and the specified visit

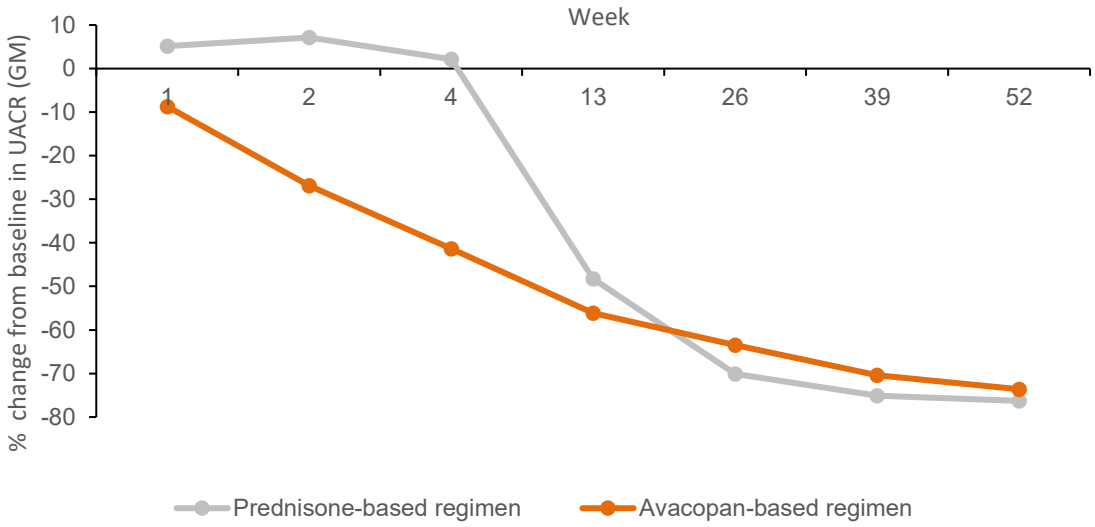
3.2.5.8 Urinary albumin-to-creatinine ratio (UACR)

The effects of avacopan on urinary albumin-to-creatinine ratio (UACR) in patients with albuminuria at baseline in the ADVOCATE, CLEAR, and CLASSIC trials have been summarised in Table 3.18. In the ADVOCATE trial, the UACR of patients with albuminuria at baseline on the avacopan arm improved more rapidly than those on the prednisone arm, as demonstrated in Figure 3.3. Although there was a statistically significant difference in UACR between the two arms at week 4, by week 52, the difference in overall improvement in UACR between the two arms was not statistically significant.

In the CLEAR trial, the geometric mean (GM) in first morning UACR at Day 85 (following the treatment period for steps 1 through 3 combined) in the avacopan + low-dose GC arm was 126.96 (Geometric mean ratio [GMR] (Day 85/baseline: 0.438), 158.41 (GMR: 0.569) in the avacopan + no GC arm, and 252.1 (GMR: 0.794) in the placebo + full-dose GC arm, in patients with albuminuria at baseline.

In the CLASSIC trial, the geometric mean (GM) in first morning UACR at Day 85 (following the treatment period) in the avacopan 10mg + SoC arm was 88.18 (mean decrease from baseline: 51%), 98.95 (mean decrease from baseline: 68%) in the avacopan 30mg + SoC arm, and 85.01 (mean decrease from baseline: 73%) in the placebo + SoC arm, in patients with albuminuria at baseline.

Figure 3.3: UACR percent change from baseline in patients with renal disease and albuminuria at baseline in ADVOCATE trial



Based on Figure 7 in the CS[6]
Renal disease was based on BVAS, and albuminuria was based on UACR ≥10 mg/g creatinine at baseline.
BVAS = Birmingham Vasculitis Activity Score; CS = company submission; ITT = intent-to-treat; GM = geometric mean; UACR = urinary albumin-to-creatinine ratio

Table 3.18: Effect of avacopan on UACR in ITT population – albuminuria at baseline

Trial	ADVOCATE				CLEAR*			CLASSIC*		
Treatment arm	Avacopan-based regimen		Prednisone-based regimen		Avacopan + 20 mg prednisone	Avacopan + no prednisone	Placebo + 60 mg prednisone	Avacopan 10 mg + SoC	Avacopan 30 mg + SoC	Placebo + SoC
Population (N'/N)	109/125		114/128		20/22	18/21	20/20	[redacted]	[redacted]	[redacted]
Follow-up (weeks)	4	52	4	52	12	12	12	12	12	12
GM at baseline	432.87		312.16		278.60	279.76	317.64	181.92	287.04	311.59
GM following treatment	254.95	285.31	310.36	276.28	126.96	158.41	[redacted]	88.18	98.95	85.01
GMR	0.59	0.26	1.02	0.24	0.438	0.569	0.794	0.485	0.317	0.273
LSM ratio ± SEM	0.60± 1.136	1.12± 1.141	NA	NA	0.49	0.72	NA	1.597±1.699	1.123±1.575	NA
LSM ratio 95% CI	0.47 to 0.78	0.86 to 1.45	NA	NA	0.31 to 0.76	0.46 to 1.14	NA	0.532 to 4.792	0.438 to 2.880	NA
P value	<0.0001	0.3991	NA	NA	0.0016	0.1627	NA	0.3869	0.8006	NA

Based on Table 21 of the CS[6], CLEAR CSR[11], and CLASSIC CSR[10]

*Statistics for differences between specified treatment groups and placebo are from a MMRM model with treatment group, visit, treatment-by visit interaction, AAV disease status (new or relapsed), and ANCA positivity (MPO or PR3) as factors and the baseline value as covariate. Logarithmic transformations were applied to the data before fitting the MMRM model. In CLEAR trial, the 95% confidence interval was transformed back to the original scale. In CLASSIC trial, the LS means, LSM ratios, and associated 95% Cl's were transformed back to the original scale.

CI = confidence interval; CS = company submission; CSR = clinical study report; GM = geometric mean; GMR = geometric mean ratio; LSM = least squares mean; N'/N = subjects with data at baseline and specified visit/number of subjects in the analysis population for the specified treatment group; NA = not applicable; NR = not reported; SD = standard deviation; SEM = standard error of measurement; SoC = standard of care; UACR = urinary albumin-to-creatinine ratio

3.2.5.9 Urinary monocyte chemoattractant protein 1 (MCP-1):creatinine ratio

The effects of avacopan on urinary monocyte chemoattractant protein 1 (MCP-1):creatinine ratio in patients with renal disease at baseline in the ADVOCATE, CLEAR, and CLASSIC trials have been summarised in Table 3.19. In the ADVOCATE trial, there was a slightly higher decrease in urinary MCP-1:creatinine ratio for patients on the avacopan arm (GMR: 0.27; 73% change from baseline) when compared to patients on the prednisone arm (GMR: 0.3; 70% change from baseline) by week 52 in patients with baseline renal disease.

In the CLEAR trial, the GMR for the first morning urinary MCP-1:creatinine ratio for patients with baseline renal disease on the avacopan + low-dose GC arm was 0.3 (GMR decrease from baseline: 70%), 0.49 (GMR decrease from baseline: 51%) in the avacopan + no GC arm, and 0.55 (GMR decrease from baseline: 45%) in the placebo + full-dose GC arm, following an 84-day treatment period.

In the CLASSIC trial, the GMR for the first morning urinary MCP-1:creatinine ratio for patients with baseline renal disease on the avacopan 10mg + SoC arm was 0.49 (GMR decrease from baseline: 51%), 0.49 (GMR decrease from baseline: 51%) for the avacopan 30mg + SoC arm, and 0.5 (GMR decrease from baseline: 50%) for patients on the placebo + SoC arm, following the 84-day treatment period.

ERG comment: The CS presented change in MCP-1:creatinine ratio results from CLEAR and CLASSIC trials in the ITT population- Table 14.2.10.1.1 in CLEAR CSR and Table 14.2.9.1 in CLASSIC CSR rather than all patients with renal disease at baseline in the ITT population. The ERG has presented the baseline and Day 85 results for ITT population - all patients with renal disease at baseline for the CLEAR trial (Table 14.2.10.1.2) in CLEAR CSR) and CLASSIC trial (Table 14.2.9.2) to ensure that the results presented are comparable with the ADVOCATE trial results which are for ITT patients with renal disease at baseline.

Table 3.19: Effect of avacopan on urinary MCP-1:creatinine ratio in ITT population – renal disease at baseline

Trial	ADVOCATE		CLEAR			CLASSIC		
Treatment arm	**Avacopan-based regimen**	**Prednisone-based regimen**	**Avacopan + 20 mg prednisone**	**Avacopan + no prednisone**	**Placebo + 60 mg prednisone**	**Avacopan 10 mg + Soc**	**Avacopan 30 mg + SoC**	**Placebo + SoC**
Population (N'/N)	67/81	67/82	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up (weeks)	52	52	12	12	12	12	12	12
GM at baseline	983.84	947.76	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GM at follow-up	252.10	274.64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMR	0.27	0.30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM ratio ± SEM	0.90±1.086	NA	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA
LSM ratio 95% CI	0.77 to 1.06	NA	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA
P value	0.2223		[redacted]	[redacted]	NA	[redacted]	[redacted]	NA

Based on Table 22 of CS[6], CLEAR CSR[11], CLASSIC CSR[10]

*Statistics for differences between specified treatment groups and placebo are from a MMRM model with treatment group, visit, treatment-by visit interaction, AAV disease status (new or relapsed), and ANCA positivity (MPO or PR3) as factors and the baseline value as a covariate. Logarithmic transformations were applied to the data before fitting the MMRM model. The 95% confidence interval was transformed back to the original scale.

CI = confidence interval; CS = company submission; CSR = clinical study report; GM = geometric mean; GMR = geometric mean ratio; LSM = least squares mean; MCP 1 = monocyte chemoattractant protein 1; N'/N = subjects with data at baseline and specified visit/number of subjects in the analysis population for the specified treatment group; NA = not applicable; NR = not reported; SEM = standard error of measurement; SoC = standard of care

3.2.5.10 Vasculitis Damage Index (VDI)

The effects of avacopan on Vasculitis Damage Index (VDI) in the ITT population of the ADVOCATE, CLEAR, and CLASSIC trials, have been summarised in Table 3.20. In the ADVOCATE trial, there was no statistical difference in LSM change from baseline (at week 52) in VDI between the two treatment arms, as assessed by the AC. In the CLEAR trial, at week 12, the mean change in VDI in the avacopan + low-dose GC arm was 0.3 (mean change from baseline: 37.5%), 0.2 (mean change from baseline: 45%) on the avacopan + no GC arm, and 0.7 (mean change from baseline: 41.11%) on the placebo + full-dose GC arm. In the CLASSIC trial, at week 12, the mean change in VDI in the avacopan 10mg + SoC arm was 1.00 (mean change from baseline: 0.09), 0.86 (mean change from baseline: 0.14) in the avacopan 30mg + SoC arm, and 1.46 (mean change from baseline: 0.31) in the placebo + SoC arm..

Table 3.20: Effect of avacopan on VDI in ITT population

Trial	ADVOCATE		CLEAR			CLASSIC		
Treatment arm	**Avacopan-based regimen**	**Prednisone-based regimen**	**Avacopan + 20 mg prednisone**	**Avacopan + no prednisone**	**Placebo + 60 mg prednisone**	**Avacopan 10 mg + Soc**	**Avacopan 30 mg + SoC**	**Placebo + SoC**
Population (N'/N)	151/166	150/164	20/22	19/21	20/20	[redacted]	[redacted]	[redacted]
Follow-up (weeks)	52	52	12	12	12	12	12	12
Mean + SD at baseline	0.66±1.544	0.72±1.393	0.9±1.46	0.5±1.21	1.2±1.35	0.83±2.588	0.67±1.175	1.15±1.772
Mean ± SD at follow-up	1.99±1.711	1.95±1.368	1.2±1.53	0.8±1.51	1.8±1.88	1.00±2.720	0.86±1.292	1.46±2.295
LSM difference ± SEM	0.03 ± 0.118	NA	-0.32*	-0.37*	NA	-0.20 ±0.209	-0.15 ±0.199	NA
LSM difference 95% CI	-0.20, 0.26	NA	-0.74, 0.10*	-0.80, 0.06*	NA	-0.625 to 0.228	-0.557 to 0.253	NA
LSM difference P value	0.7868	NA	[redacted]	[redacted]	[redacted]	0.3492	0.4490	NA

Based on Table 23 of the CS[6], CLEAR CSR[11], and CLASSIC CSR[10]

*Statistics for differences between specified treatment groups and placebo are from ANCOVA models with treatment group, AAV disease status (new or relapsed) and ANCA positivity (MPO or PR3) as factors and the baseline value as a covariate.

CI = confidence interval; CS = company submission; CSR = clinical study report; LSM = least squares mean; N'/N = subjects with data at baseline and specified visit/number of subjects in the analysis population for the specified treatment group; NA = not applicable; NR = not reported; SD = standard deviation; SEM = standard error of measurement; SoC = standard of care; UACR = urinary albumin-to-creatinine ratio; VDI = Vasculitis Damage Index

3.2.5.11 HRQoL

The effects of avacopan on health-related quality of life (HRQoL) in the ITT population of the ADVOCATE, and CLASSIC trials, have been summarised in Table 3.21. Patients on the avacopan-based treatment arm in the ADVOCATE trial experienced a higher improvement in the physical component summary score when compared to patients on the prednisone-based arm.

Table 3.21: Effect of avacopan on SF36v2 in ITT population

Trial	ADVOCATE		CLASSIC		
Treatment arm	**Avacopan-based regimen (N = 166)**	**Prednisone-based regimen (N = 164)**	**Avacopan 10 mg + Soc (N = 12)**	**Avacopan 30 mg + SoC (N = 15)**	**Placebo + SoC (N = 13)**
SF-36 v2					
SF-36 Physical component summary, Mean±SEM					
N'/N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 Mental health summary, Mean±SEM					
N'/N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 14.2.5 ADVOCATE CSR[25] and Table 13 in CLASSIC CSR[10]
CS = company submission; CSR = clinical study report; N = number of subjects in the analysis population for the specified treatment group; N' = number of subjects with data at baseline; SEM = standard error of the mean; SF-36v2 = Short Form-36 version 2; ITT = Intent-to-Treat.

ERG comments: The ERG notes a very small HRQoL benefit in the avacopan group relative to the control group. However, it is unclear whether this benefit is clinically meaningful. Moreover, the HRQoL measures are general and not specific to vasculitis.

3.2.6 Subgroup analysis

As a significantly higher proportion of patients on the avacopan arm achieved sustained clinical remission, when compared to prednisone in the ADVOCATE trial, analyses of sustained remission at week 26 and 52 in subgroups of interest have been summarised in Table 3.22. The company noted the limitations of subgroup analyses in clinical trials being that the small sample size will increase the likelihood of false positive results, and the baseline investigator immunosuppressive therapies (CYC or RTX) being likely to introduce bias to subgroup analyses.[6] Figure 3.4 demonstrates sustained remission at week 52 in all subgroups of interest in the ADVOCATE trial.

At both weeks 26 and 52, more patients on the avacopan arm receiving either RTX (IV) or CYC (oral/ IV) experienced sustained remission following treatment, when compared to the prednisone arm.

However, greater efficacy in the RTX treatment subgroup at week 52 was noted on the avacopan arm when compared to prednisone (71.0% of patients versus 56.1% respectively).

There was not much difference in the number of patients with sustained remission of both treatment arms in the newly diagnosed patients subgroup at both weeks 26 and 52, however in the relapsed disease subgroup, more patients on the avacopan arm experienced sustained remission when compared to the prednisone arm, at both weeks 26 and 52. At week 52, greater efficacy in the relapsed disease subgroup on the avacopan arm when compared to the prednisone arm was noted (76.5% of patients versus 48.0% respectively).

At both weeks 26 and 52, more patients on the avacopan arm in either anti-PR3+ AAV or anti-MPO+ AAV subgroup, experienced sustained remission following treatment, when compared to the prednisone arm.

ERG comment: Despite efforts to balance the participants' characteristics in the subgroups, the ERG notes that these subgroup analyses were exploratory. As such, they are likely to have been underpowered and takes a cautionary stance on the interpretation of these results.

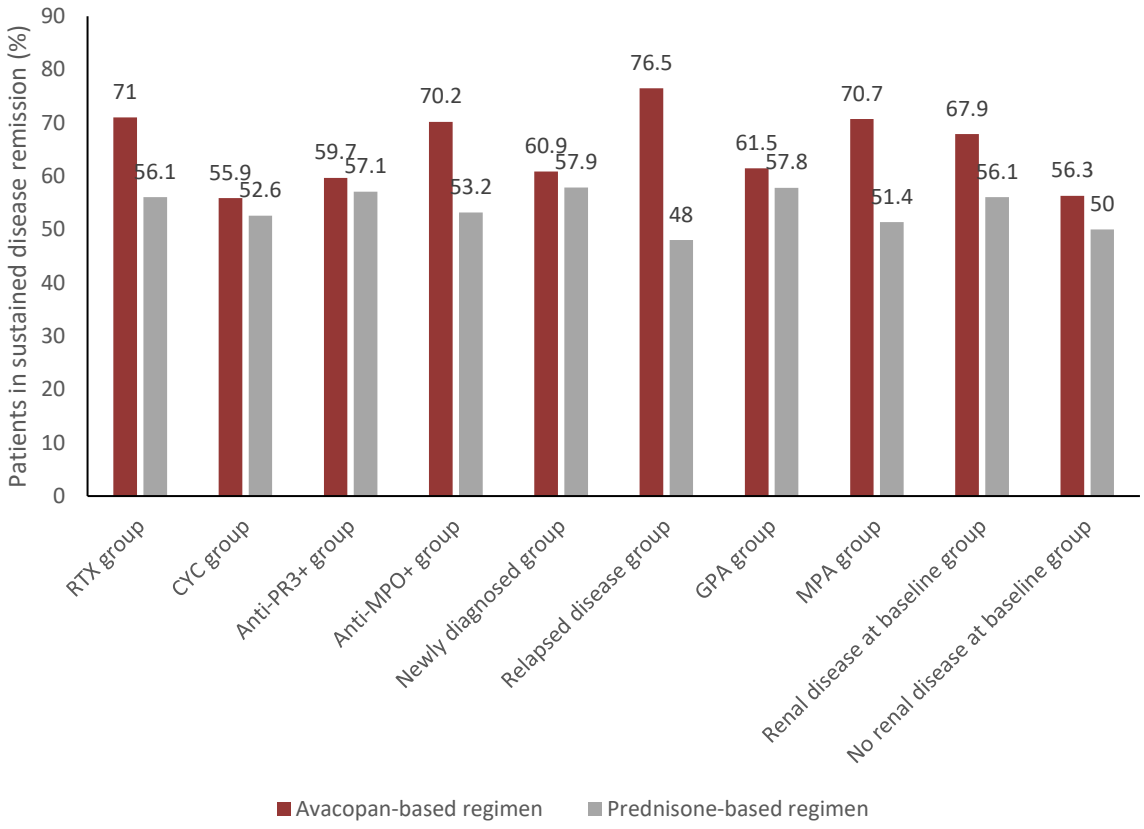
Table 3.22: Proportion of patients in sustained remission in ADVOCATE trial ITT population, stratified by subgroup

Treatment arm	Avacopan-based regimen (N=166)		Prednisone-based regimen (N=164)	
Patient subgroup	**Number of patients in the ITT population**	**Number of patients with sustained remission (%)**	**Number of patients in the ITT population**	**Number of patients with sustained remission (%)**
Patients receiving RTX (IV)				
Week 26	107	83 (77.6)	107	81 (75.7)
Week 52		76 (71.0)		60 (56.1)
Patients receiving CYC (oral/IV)				
Week 26	59	37 (62.7)	57	34 (59.6)
Week 52		33 (55.9)		30 (52.6)
Anti-PR3+ AAV patients				
Week 26	72	51(70.8)	70	50 (71.4)
Week 52		43 (59.7)		40 (57.1)
Anti-MPO+ AAV patients				
Week 26	94	69 (73.4)	94	65 (69.1)
Week 52		66 (70.2)		50 (53.2)
Newly diagnosed patients				
Week 26	115	76 (66.1)	114	76 (66.7)
Week 52		70 (60.9)		66 (57.9)
Patients with relapsing disease				
Week 26	51	44 (86.3)	50	39 (78.0)
Week 52		39 (76.5)		24 (48.0)
Patients with GPA				
Week 26	91	65 (71.4)	90	65 (72.2)
Week 52		56 (61.5)		52 (57.8)
Patients with MPA				
Week 26	75	55 (73.3)	74	50 (67.6)
Week 52		53 (70.7)		38 (51.4)
Patients with renal disease at baseline				
Week 52	134	91 (67.9)	132	74 (56.1)

Treatment arm	Avacopan-based regimen (N=166)		Prednisone-based regimen (N=164)	
Patients without renal disease at baseline				
Week 52	32	18 (56.3)	32	16 (50)

Based on Table 24 of CS[6]
AAV = anti-neutrophil cytoplasmic autoantibody–associated vasculitis; CS = company submission; CYC = cyclophosphamide; ITT = intention-to-treat; IV = intravenous; MPA = microscopic polyangiitis; MPO = myeloperoxidase; RTX = rituximab

Figure 3.4: Sustained remission at week 52 in subgroups in ADVOCATE trial



Based on Figure 8 of CS[6]
CS = company submission; CYC = cyclophosphamide; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; MPO = myeloperoxidase; PR3 = proteinase 3; RTX = rituximab

3.2.7 Adverse events

In this section, safety results from the ADVOCATE trial have been reported in the safety population. This included all subjects who were randomised and had received at least one dose of study drug in the Phase III ADVOCATE trial.[23] The company in its response to clarification on the follow-up period for adverse events reporting stated that, *"all AEs were monitored until resolution or, if the AE was determined to be chronic, until a cause was identified. The final scheduled AE assessment occurred at week 60, eight weeks after discontinuation of avacopan treatment."*[1]

3.2.7.1 Treatment-emergent adverse events

Overall, 1779 treatment-emergent adverse events (TEAEs) were observed in 164 patients (98.8%) on the avacopan-based regimen arm and 2139 TEAEs in 161 patients (98.2%) on the prednisone treatment arm, and the number of TEAEs on the prednisone arm was 20% higher when compared to the avacopan

arm.[23] Table 3.23 summarises the incidence of TEAEs in the safety population. The majority of TEAEs on avacopan and prednisone treatment arms were of moderate (49.4% versus 41.5%) or severe (23.5% versus 25.0%) severity. Deaths were rare, four subjects (2.4%) on the prednisone arm died compared to 2 subjects (1.2%) on the avacopan arm. In general, 116 serious adverse events (SAEs) were observed in 70 patients (42.2%) on the avacopan arm and 166 SAEs in 74 patients (45.1%) on the prednisone treatment, and a 43% higher number of SAEs were reported in the prednisone arm compared to the avacopan arm. The most common SAE by system organ class (SOC) was infections and infestations: 22 subjects (13.3%) on the avacopan arm and 25 subjects (15.2%) on the prednisone arm.[23] Adverse events reported in ≥5% of patients in either treatment arm has been summarised in Table 3.24. Nausea was the most frequently reported TEAE in the avacopan arm and peripheral oedema in the prednisone arm. TEAEs stratified by background treatment had been explored in Section 3.2.7.3.

Table 3.23: Summary of TEAEs in the ADVOCATE trial, safety population

Treatment arm	Avacopan-based regimen (N=166)	Prednisone-based regimen (N=164)
All TEAEs		
TEAEs, n	1779	2139
Patient incidence of TEAEs, n (%)	164 (98.8)	161 (98.2)
Maximum severity of TEAE, n (%)		
Mild	33 (19.9)	34 (20.7)
Moderate	82 (49.4)	68 (41.5)
Severe	39 (23.5)	41 (25.0)
Life-threatening	8 (4.8)	14 (8.5)
Death	2 (1.2)	4 (2.4)
Patient incidence of discontinuation due to AEs, n (%)	27 (16.3)	28 (17.1)
Serious TEAEs		
Number of serious TEAEs	116	166
Patient incident of serious TEAEs, n (%)	70 (42.2)	74 (45.1)
Patients with any serious infection, n (%)	22 (13.3)	25 (15.2)
Deaths due to infection, n (%)	1 (0.6)	2 (1.2)
Patients with any serious hepatic system AE, n (%)	9 (5.4)	6 (3.7)
GC-related AEs		
Patients with any AE potentially related to GCs*, n (%)	110 (66.3)	132 (80.5)

Based on Table 26 of the CS[6]
*Investigators blinded assessment; AEs were coded using Medical Dictionary for Regulatory Activities (version 19.1)
AE = adverse event; CS = company submission; GC = glucocorticoid; N = number of subjects randomised to treatment group in the safety population; n = number of subjects in specified category; TEAE = treatment-emergent adverse event (serious or non-serious events starting on or after the date/time of first dose of study medication)

Table 3.24: Summary of TEAEs by preferred term observed in ≥5% in either treatment arm of safety population

Preferred Term	Avacopan-based regimen (N=166)		Prednisone-based regimen (N=164)	
	Subjects, n (%)	Events, n	Subjects, n (%)	Events, n
Any TEAE	164 (98.8)	1,779	161 (98.2)	2,139
Nausea	39 (23.5)	54	34 (20.7)	46
Oedema peripheral	35 (21.1)	39	40 (24.4)	56
Headache	34 (20.5)	43	23 (14.0)	30
Arthralgia	31 (18.7)	42	36 (22.0)	48
Hypertension	30 (18.1)	36	29 (17.7)	31
Anti-neutrophil cytoplasmic antibody positive vasculitis	26 (15.7)	30	34 (20.7)	46
Cough	26 (15.7)	31	26 (15.9)	29
Diarrhoea	25 (15.1)	33	24 (14.6)	31
Nasopharyngitis	25 (15.1)	38	30 (18.3)	46
Vomiting	25 (15.1)	29	21 (12.8)	27
Upper respiratory tract infection	24 (14.5)	28	24 (14.6)	33
Rash	19 (11.4)	26	13 (7.9)	17
Muscle spasms	18 (10.8)	23	37 (22.6)	47
Fatigue	17 (10.2)	19	15 (9.1)	15
Back pain	16 (9.6)	16	22 (13.4)	22
Myalgia	16 (9.6)	17	22 (13.4)	25
Pyrexia	15 (9.0)	18	19 (11.6)	25
Epistaxis	14 (8.4)	21	21 (12.8)	30
Anaemia	13 (7.8)	13	18 (11.0)	19
Insomnia	13 (7.8)	13	25 (15.2)	27
Pain in extremity	13 (7.8)	13	13 (7.9)	13
Hypercholesterolaemia	12 (7.2)	13	20 (12.2)	21
Leukopenia	12 (7.2)	15	14 (8.5)	20
Urinary tract infection	12 (7.2)	19	23 (14.0)	33
Abdominal pain upper	11 (6.6)	12	10 (6.1)	13
Constipation	11 (6.6)	11	11 (6.7)	11
Dizziness	11 (6.6)	14	10 (6.1)	10
Pneumonia	11 (6.6)	12	11 (6.7)	11
Blood creatinine increased	10 (6.0)	10	8 (4.9)	10
Pruritus	10 (6.0)	15	10 (6.1)	11
Sinusitis	10 (6.0)	10	12 (7.3)	12
Paraesthesia	9 (5.4)	10	7 (4.3)	8
Dyspnoea	8 (4.8)	11	11 (6.7)	14
Alopecia	7 (4.2)	7	12 (7.3)	12
Increased tendency to bruise	7 (4.2)	7	10 (6.1)	11
Lymphopenia	6 (3.6)	7	18 (11.0)	27
Oropharyngeal pain	6 (3.6)	7	12 (7.3)	12

Preferred Term	Avacopan-based regimen (N=166)		Prednisone-based regimen (N=164)	
	Subjects, n (%)	Events, n	Subjects, n (%)	Events, n
Bronchitis	5 (3.0)	7	10 (6.1)	11
Dyspepsia	5 (3.0)	6	10 (6.1)	12
Cushingoid	3 (1.8)	3	9 (5.5)	9
Tremor	1 (1.2)	2	10 (6.1)	11
Weight increased	1 (0.6)	1	17 (10.4)	19

Based on Table 27 of CS[6]
An AE was considered treatment-emergent if the start date/time of the event was on or after the date/time of first dose of study medication. AEs were coded using Medical Dictionary for Regulatory Activities (version 19.1).
CS = company submission; N = number of subjects randomised to treatment group in the safety population; n = number of subjects in specified category; TEAE = treatment-emergent adverse event

ERG comment: The ERG asked the company to provide the metric used to classify the severity of TEASs. The company in its response to clarification clarified that *"an AE was considered treatment-emergent if the start date/time of the event was on or after the date/time of first dose of study medication."*[1] And that the severity of each AE was determined by the Investigator using the following scale:

- Mild (Grade 1): no limitation of usual activities
- Moderate (Grade 2): some limitation of usual activities
- Severe (Grade 3): inability to carry out usual activities
- Life-threatening (Grade 4): an immediate risk of death
- Death (Grade 5)

The ERG concurs that on the whole, treatment-emergent infections, serious infections, and opportunistic infections of patients in the avacopan-based regimen group was fewer than or similar to those of patients in the prednisone-based regimen group.

3.2.7.1.1 Moderate treatment-emergent adverse events

As Table 3.25 showed that patients on the avacopan-based regimen arm experienced more moderate-severity TEAEs, the ERG asked the company to provide more information on the incidence of moderate TEAEs across all three avacopan trials. These have been summarised in Tables 3.25, 3.26, and 3.27. As stated in Section 3.2.7.1, moderate TEAEs were determined by the investigator to be those that place some limitations on usual activities.

In the ADVOCATE trial, patients on the avacopan arm experienced more gastrointestinal, musculoskeletal, and connective tissue, nervous system, vascular, renal, and urinary, eye, ear, and labyrinth disorders, when compared to the prednisone arm.

Table 3.25: Summary of moderate TEAEs by system class in the ADVOCATE trial, safety population

Treatment arm	Prednisone-based regimen (N=164)	Avacopan-based regimen (N=166)
Any moderate TEAEs	68 (41.5)	82 (49.4)
Infections and infestations	49 (29.9)	39 (23.5)
Gastrointestinal disorders	29 (17.7)	31 (18.7)

Treatment arm	Prednisone-based regimen (N=164)	Avacopan-based regimen (N=166)
Musculoskeletal and connective tissue disorders	29 (17.7)	33 (19.9)
General disorders and administration site conditions	31 (18.9)	23 (13.9)
Skin and subcutaneous tissue disorders	21 (12.8)	15 (9.0)
Nervous system disorders	14 (8.5)	27 (16.3)
Investigations	19 (11.6)	26 (15.7)
Respiratory, thoracic, and mediastinal disorders	27 (16.5)	27 (16.3)
Metabolism and nutrition disorders	19 (11.6)	16 (9.6)
Vascular disorders	15 (9.1)	17 (10.2)
Blood and lymphatic system disorders	17 (10.4)	17 (10.2)
Injury, poisoning and procedural complications	15 (9.1)	9 (5.4)
Psychiatric disorders	12 (7.3)	8 (4.8)
Immune system disorders	16 (9.8)	15 (9.0)
Renal and urinary disorders	11 (6.7)	15 (9.0)
Cardiac disorders	7 (4.3)	13 (7.8)
Eye disorders	3 (1.8)	9 (5.4)
Ear and labyrinth disorders	3 (1.8)	4 (2.4)
Hepatobiliary disorders	0 (0.0)	3 (1.8)
Reproductive system and breast disorders	2 (1.2)	1 (0.6)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	6 (3.7)	2 (1.2)
Endocrine disorders	4 (2.4)	1 (0.6)

Based on Table 4 of the response to request for clarification[1]
TEAE = treatment-emergent adverse event

Table 3.26: Summary of TEAEs by system class in CLEAR trial

Treatment arm	Placebo + full-dose GCs (N=23)	Avacopan + low-dose GCs (N=22)	Avacopan + no GCs (N=22)
Any moderate TEAEs	9 (39.1)	7 (31.8)	9 (40.9)
Infections and infestations	2 (8.7)	3 (13.6)	3 (13.6)
Gastrointestinal disorders	3 (13.0)	3 (13.6)	1 (4.5)
Musculoskeletal and connective tissue disorders	1 (4.3)	2 (9.1)	1 (4.5)
General disorders and administration site conditions	1 (4.3)	1 (4.5)	2 (9.1)
Nervous system disorders	0 (0.0)	1 (4.5)	1 (4.5)
Investigations	2 (8.7)	2 (9.1)	3 (13.6)
Respiratory, thoracic, and mediastinal disorders	2 (8.7)	1 (4.5)	1 (4.5)
Metabolism and nutrition disorders	1 (4.3)	0 (0.0)	0 (0.0)

Treatment arm	Placebo + full-dose GCs (N=23)	Avacopan + low-dose GCs (N=22)	Avacopan + no GCs (N=22)
Vascular disorders	1 (4.3)	2 (9.1)	2 (9.1)
Blood and lymphatic system disorders	0 (0.0)	1 (4.5)	0 (0.0)
Injury, poisoning and procedural complications	1 (4.3)	0 (0.0)	0 (0.0)
Psychiatric disorders	1 (4.3)	1 (4.5)	0 (0.0)
Renal and urinary disorders	1 (4.3)	1 (4.5)	1 (4.5)
Cardiac disorders	1 (4.3)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	1 (4.5)
Reproductive system and breast disorders	0 (0.0)	1 (4.5)	1 (4.5)
Based on Table 5 of the CL response GC = glucocorticoid; TEAE = treatment-emergent adverse event			

Table 3.27: Summary of moderate TEAEs by system class in the CLASSIC trial

Treatment arm	Placebo + SoC (N=13)	Avacopan 10 mg + SoC (N=13)	Avacopan 30 mg + SoC (N=16)
Any moderate TEAEs	5 (38.5)	7 (53.8)	7 (43.8%)
Infections and infestations	1 (7.7)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	1 (7.7)	1 (6.3)
Musculoskeletal and connective tissue disorders	1 (7.7)	0 (0.0)	1 (6.3)
General disorders and administration site conditions	1 (7.7)	1 (7.7)	2 (12.5)
Skin and subcutaneous tissue disorders	1 (7.7)	3 (23.1)	0 (0.0)
Nervous system disorders	3 (23.1)	0 (0.0)	1 (6.3)
Investigations	1 (7.7)	3 (23.1)	0 (0.0)
Vascular disorders	1 (7.7)	2 (15.4)	2 (12.5)
Injury, poisoning and procedural complications	1 (7.7)	1 (7.7)	0 (0.0)
Renal and urinary disorders	0 (0.0)	1 (7.7)	0 (0.0)
Cardiac disorders	0 (0.0)	0 (0.0)	3 (18.8)
Eye disorders	0 (0.0)	1 (7.7)	0 (0.0)
Based on Table 6 of the response to request for clarification[1] SoC = standard of care; TEAE = treatment-emergent adverse event			

3.2.7.1.2 Treatment-emergent adverse events related to background treatment

In the ADVOCATE trial, the incidence of AEs was generally higher in patients with CYC as background treatment when compared to those on RTX background treatment, on both avacopan-based and prednisone-based regimen groups.[6]

Table 3.28: Treatment-emergent non-serious AEs in ADVOCATE trial, safety population

Treatment arm	Avacopan + CYC (N=59), n (%)	Avacopan + RTX (N=166), n (%)	Prednisone + CYC (N=57), n (%)	Prednisone + RTX (N=107), n (%)
Any treatment-emergent non-serious AE	58 (98.3)	103 (96.3)	56 (98.2)	105 (98.1)
Infections and infestations	42 (71.2)	62 (57.9)	45 (78.9)	75 (70.1)
Gastrointestinal disorders	43 (72.9)	54 (50.5)	39 (68.4)	43 (40.2)
Musculoskeletal and connective tissue disorders	36 (61.0)	56 (52.3)	34 (59.6)	59 (55.1)
General disorders and administration site conditions	24 (40.7)	50 (46.7)	32 (56.1)	51 (47.7)
Skin and subcutaneous tissue disorders	28 (47.5)	44 (41.1)	30 (52.6)	55 (51.4)
Nervous system disorders	23 (39.0)	48 (44.9)	31 (54.4)	41 (38.3)
Respiratory, thoracic, and mediastinal disorders	9 (15.3)	17 (15.9)	23 (22.8)	13 (12.1)
Investigations	24 (40.7)	40 (37.4)	32 (56.1)	33 (30.8)
Metabolism and nutrition disorders	25 (42.4)	30 (28.0)	22 (38.6)	39 (36.4)
Blood and lymphatic system	24 (40.7)	20 (18.7)	30 (52.6)	20 (18.7)
Vascular disorders	13 (22.0)	29 (27.1)	17 (29.8)	28 (26.2)
Injury, poisoning and procedural complications	17 (28.8)	16 (15.0)	21 (36.8)	25 (23.4)
Psychiatric disorders	10 (16.9)	22 (20.6)	14 (24.6)	28 (26.2)
Eye disorders	8 (13.6)	17 (15.9)	12 (21.1)	30 (28.0)
Renal or urinary disorders	11 (18.6)	13 (12.1)	10 (17.5)	14 (13.1)
Cardiac disorders	12 (20.3)	11 (10.3)	6 (10.5)	12 (11.2)
Ear and labyrinth disorders	3 (5.1)	17 (15.9)	3 (5.3)	13 (12.1)
Immune system disorders	8 (13.6)	12 (11.2)	10 (17.5)	17 (15.9)
Reproductive system, and breast disorders	3 (5.1)	5 (4.7)	3 (5.3)	2 (1.9)
Endocrine disorders	1 (1.7)	4 (3.7)	6 (10.5)	15 (14.0)
Hepatobiliary disorders	2 (3.4)	3 (2.8)	0 (0.0)	3 (2.8)
Neoplasms benign, malignant, and unspecified	0 (0.0)	4 (3.7)	7 (12.3)	5 (4.7)

Based on Table 32 of CS[6]
AE = adverse event; CS = company submission; CYC = cyclophosphamide; RTX = rituximab

3.2.7.2 Glucocorticoid-related adverse events

In the ADVOCATE trial, on the whole, the incidence of GC-related AEs was lower on the avacopan-based regimen arm when compared to the prednisone-based regimen arm (see Table 3.29).

Table 3.29: Incidence of potentially glucocorticoid-related adverse events in ADVOCATE trial

Treatment arm	Avacopan-based regimen (N=166), n (%)	Prednisone-based regimen (N=164), n (%)	Difference (%)	Difference, 95% CI
Any adverse event	110 (66.3%)	132 (80.5%)	-14.2*	-23.7 to -3.8
Cardiovascular	72 (43.4%)	85 (51.8%)	-8.5	-19.2 to 2.6
Dermatological	14 (8.4%)	28 (17.1%)	-8.6*	-16.2 to -1.0
Endocrine/metabolic	23 (13.9%)	48 (29.3%)	-15.4*	-24.3 to -6.0
Gastrointestinal	3 (1.8%)	4 (2.4%)	-0.6	-4.6 to 3.1
Infectious	22 (13.3%)	25 (15.2%)	-2.0	-9.9 to 5.7
Musculoskeletal	19 (11.4%)	21 (12.8%)	-1.4	-8.7 to 5.9
Ophthalmological	7 (4.2%)	12 (7.3%)	-3.1	-8.7 to 2.1
Psychological	27 (16.3%)	39 (23.8%)	-7.5	-16.5 to 1.3

Based on Table 31 of the CS[6]
*p<0.05
CI = confidence interval; N = number of subjects randomised to treatment group in the safety population; n = number of subjects in specified category

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company assessed the feasibility of conducting an anchored indirect treatment comparison (ITC) between avacopan and fixed dose RTX in patients with AAV entering remission following RTX induction treatment because in clinical practice, patients who have achieved remission with avacopan plus RTX may continue RTX maintenance therapy (in line with AAV clinical guidelines) (see Table 3.30).[6] The company identified three relevant RCTs for RTX maintenance: MAINRITSAN[26], MAINRITSAN 2[27], and RITZAREM[28].

MAINRITSAN 2 was ruled out because both study arms received RTX maintenance therapy and so could not be included in an anchored comparison.[6] A comparison of ADVOCATE against MAINRITSAN and RITAZAREM was also ruled out because patients in the ADVOCATE study were randomised prior to induction treatment, and not at the point of entering remission.[6] The maintenance treatment received in the control arm for RITAZAREM was also different from that of the ADVOCATE trial (RTX induction followed by AZA)— thus an ITC against ADVOCATE would be limited to a smaller sample size of RTX-induced patients, and this would reduce the power to detect significant differences in efficacy between treatments.[6]

Table 3.30: Summary of ITC feasibility assessment

Study	Design	RTX maintenance dosing (fixed/flexible)	Maintenance interventions	Outcomes
ADVOCATE	Randomised, double-blind, double-dummy, active-controlled clinical study	Fixed	avacopan (+ AZA/MMF in some patients) prednisone (+ AZA/MMF in some patients)	Proportion maintaining remission, GC toxicity, AEs, VDI damage severity, changes in renal

Study	Design	RTX maintenance dosing (fixed/flexible)	Maintenance interventions	Outcomes
				disease parameters, time to relapse
MAINRITSAN	Randomised, controlled, national, multicentre, prospective trial	Fixed	RTX + prednisone AZA + prednisone	Proportion relapsing, relapse-free survival, AEs, CD19+ B-cell counts
MAINRITSAN 2	Open label, multicentre, randomised controlled trial	Fixed + Flexible	RTX + prednisone	Proportion relapsing, VDI damage severity, AEs, CD19+ B-cell counts, GC duration, relapse-free survival
RITZAREM	International, multicentre, open label, randomised controlled trial	Fixed	RTX + prednisone AZA/MTX/MMF + prednisone	Relapse-free survival, AEs, cumulative GC exposure, CDA damage score, proportion maintaining remission

Based on Table 25 of the CS[6], MAINRITSAN[26], MAINRITSAN 2[27], RITZAREM[28]
AE = adverse event; AZA = azathioprine; CDA = combined damage assessment; CS = company submission; GC = glucocorticoid; MMF = mycophenolate mofetil; MTX = methotrexate; RTX = rituximab; VDI = vasculitis damage index

ERG comment: The ERG is satisfied with the results of the feasibility assessment.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

An indirect comparison was not conducted by the company due to the arguments listed in Section 3.3 of this report.

3.5 Additional work on clinical effectiveness undertaken by the ERG

None.

3.6 Conclusions of the clinical effectiveness section

The CS and response to clarification provided sufficient details for the ERG to appraise the literature searches conducted to identify studies on the clinical efficacy, safety, and tolerability of avacopan.[1, 6] Searches were conducted in June 2018 and updated in June 2020 and June 2021. A good range of databases were searched, however additional searching could have been undertaken for conference proceedings and grey literature. Additional search terms could have been included, and as an RCT filter was applied to the searches, the ERG was concerned about the lack of separate adverse event searches. However, the searches were adequate, and given the range of resources searched, it was unlikely that relevant studies were missed.

The main evidence for the clinical effectiveness of Avacopan was from the ADVOCATE trial (NCT02994927)[23]. The ADVOCATE trial is a Phase III randomised, double-blind, active-

controlled, multicentre international trial in which patients with a clinical diagnosis of GPA or MPA were randomised to either avacopan 30mg twice daily plus cyclophosphamide (CYC) followed by azathioprine (AZA) or prednisone-matching placebo plus rituximab (RTX), or a 20-week tapering oral regimen of prednisone plus CYC followed by AZA or avacopan-matching placebo plus RTX, for 52 weeks of treatment with an 8 week follow-up.[6] A total of 166 patients were randomised to Avacopan, and 164 patients were randomised to the control group. The study consisted of three periods: screening (up to 2 weeks), treatment (52 weeks), and follow-up (8 weeks).[23] Those eligible for the ADVOCATE trial were patients aged at least 18 years, with newly diagnosed or relapsed AAV for which treatment with CYC or RTX was needed, with a clinical diagnosis of GPA or MPA, consistent with Chapel Hill Consensus Conference definitions. Adolescents (12 to 17 years old) may have been enrolled.

The age of randomised subjects ranged from 13 to 88 years old with 3 (0.9%) patients being between 12-17 years while the majority of patients were between 51 and 75 years old.[6, 23] The majority of patients were male (56.5%), white (84.3%), and enrolled at sites in Europe (70.1%).[23]Most patients in the intention-to-treat (ITT) population had been newly diagnosed with ANCA-associated vasculitis (AAV) (69.45%), had renal disease at baseline (81.2%) and were taking IV RTX (64.8%) or IV CYC (30.9%) as standard of care (SoC) treatment, with a range of duration of AAV from 0 months to 362.3 months.

The primary outcomes of the ADVOCATE trial were remission (defined as achieving a BVAS of 0 and not taking GCs for AAV within 4 weeks prior to week 26) and sustained remission (defined as remission at week 26 and remission at week 52, without having a relapse between week 26 and week 52). At week 26, superiority of avacopan was not achieved: 72.3% of patients on the avacopan arm compared to 70.1% on the prednisone arm, had achieved remission in the intention-to-treat (ITT) population. In the per-protocol (PP) population, [redacted] patients on the avacopan arm, and [redacted] patients on the prednisone arm had achieved disease remission at week 26.[23] Thus, Avacopan was found to be non-inferior to the control treatment for remission. For sustained remission, 65.7% of patients in the ITT population achieved sustained remission at week 52 compared to 54.9% of patients on the prednisone arm.[6, 23] In the PP population where [redacted] on the avacopan arm, and [redacted] on the prednisone arm achieved sustained disease remission at week 52.[23]

The company did not pool quantitatively the results of any of the trials they identified as part of their SLR. When the ERG pooled (meta-analyses) the results, they found no differences between avacopan and prednisone for the following outcomes: eGFR, VDI, QOL and remission. However, it is worth noting that for these outcomes, the ERG pooled data from different endpoints i.e., 12, 26 and 52 weeks which needs to be considered when interpreting the findings.

The ERG noted a number of problems with the evidence that render the effect estimates less reliable. For example, the impact of the use of glucocorticoids in the intervention arm is not clear, and the non-inferiority margin chosen may have been too wide to rule out no effect.

Overall, avacopan was found to have slightly better safety and tolerability than the control treatment. At week 13, the least squares mean (LSM) of the GTI-Cumulative Worsening Score (GTI-CWS) for the avacopan arm was 25.7 compared to 36.6 on the prednisone arm, and 39.7 against 56.6 at week 26. Similarly, for the GTI-Aggregate Improvement Score (GTI-AIS), at week 13 the LSM for avacopan was 9.9 compared to 23.2 on the prednisone arm, and 11.2 against 23.4 at week 26.

The ERG noted a number of problems with the assessment of adverse events, including that the additional assessment of GCs in the control group, without an additional assessment of parallel GCs in the avacopan group may have introduced bias.

The description of the comparators in the NICE scope is as follows. To induce remission: established clinical management without avacopan including corticosteroids and rituximab, cyclophosphamide, methotrexate, or mycophenolate mofetil. For maintenance treatment: established clinical management without avacopan including low dose corticosteroids and rituximab (in line with the NHS England commissioning policy), azathioprine, methotrexate, or mycophenolate mofetil. The company considered treatment including azathioprine (AZA) as a comparator treatment for inducing remission, the final NICE scope does not. In addition, the company considered MTX and MMR as alternatives to CYC. The ERG believes that these differences in comparators may impact on the efficacy estimates.

The company undertook a systematic literature review (SLR) to identify studies that provided information on the clinical efficacy, safety, and tolerability of avacopan in combination with CYC or RTX (with or without GCs) compared with relevant comparator therapies for adult patients with GPA or MPA. Their search revealed 46 studies (including 25 RCTs). The company did not synthesize the results or conduct any indirect or mixed treatment comparisons.

However, the ERG required further clarification regarding the language restrictions, the selection of specific databases, the application of eligibility criteria, quality assessments performed, as well as details regarding the data extraction process. The ERG noted a number of potential biases in the review process, including potential bias arising from the way in which quality assessments were undertaken; for example, the ERG noted baseline differences between groups suggesting that randomisation or allocation concealment may have been problematic. The ERG also noted that some data from some of the trials appeared eligible for pooling yet not meta-analysis was undertaken.

4. COST EFFECTIVENESS

4.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search Section (4.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement, and evaluation of health effects as well as for cost and healthcare resource identification, measurement, and valuation.

4.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[13, 14] The submission was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[15] The ERG has presented only the major limitations of each search strategy in the report.

Appendix G of the CS details a literature review using systematic methodology undertaken to identify and summarise the best available cost effectiveness evidence for avacopan and relevant comparator therapies for the treatment of AAV. The searches were conducted in three stages: an initial search on 5 June 2018 and updates on 16 June 2020 and 17 June 2021. The same search strategies were used in the original search and updates.

A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources for the cost effectiveness literature review (as reported in CS)

	Resource	Host/Source	Date Ranges	Dates searched
Electronic Databases	MEDLINE (MEDLINE; Epub Ahead of Print; In-Process, and Other Non-Indexed Citations; MEDLINE Daily)	Ovid	1946-04/06/18 1946-15/06/20 1946-16/06/21	05/06/18 16/06/20 17/06/21
	Embase	Ovid	1974-2018 Wk23 1974-2020 Wk24 1974-2021 Wk23	05/06/18 16/06/20 17/06/21
	NHS EED	Wiley	to 05/06/18	05/06/18
Additional searches	NICE health technology appraisals Scottish Medicines Consortium (SMC)	Internet	Not stated	Not stated
EED = Economic Evaluation Database; NHS = National Health Service; NICE = National Institute for Health and Care Excellence				

ERG comment:

- Searches were undertaken to identify and summarise the best available cost effectiveness evidence for avacopan and relevant comparator therapies for the treatment of AAV. The CS and the Company's response to the ERG's clarification letter provided sufficient details for the ERG to appraise the literature searches.[1, 6]
- MEDLINE, Embase and the NHS EED database were searched, and hand-searching of the reference lists of key included articles was conducted. Health technology appraisals on the NICE and SMC websites were also hand-searched. Supplementary searches of additional databases, conference proceedings, and specialist and organisational websites could have been undertaken to identify further potentially relevant publications.
- The search strategies contained only a population facet, which was then limited to economic evaluation studies. They included a good range of terms for AAV, GPA and MPA, using both free-text and subject indexing terms. Additional free-text terms could have been added to the strategies in order to improve recall, as noted in Section 3.1.1. Searches were clearly documented and structured, making them transparent and reproducible.
- Results were limited to English language only, and with a publication date limit of 1998-date.
- Search filters were applied to limit the results to economic evaluations. Although the filters used were not cited in the CS, they appear comprehensive and likely to retrieve the relevant literature.
- Appendix H of the CS details a literature review using systematic methodology undertaken to identify relevant studies reporting HRQoL and utility data in patients with AAV.[29] The searches were conducted in three stages: an initial search on 9 July 2018 and updates on 16 June 2020 and 17 June 2021. The same search strategies were used in the original search and updates.

A summary of the sources searched is provided in Table 4.2.

Table 4.2: Data sources for the health-related quality of life literature review (as reported in CS)

	Resource	Host/Source	Date Ranges	Dates searched
Electronic Databases	MEDLINE (MEDLINE; Epub Ahead of Print; In-Process, and Other Non-Indexed Citations; MEDLINE Daily)	Ovid	1946-04/06/18 1946-15/06/20 1946-16/06/21	09/07/18 16/06/20 17/06/21
	Embase	Ovid	1974-2018 Wk28 1974-2020 Wk24 1974-2021 Wk23	09/07/18 16/06/20 17/06/21
Additional searches	NICE health technology appraisals	Internet	Not stated	Not stated

ERG comment:

- Searches were undertaken to identify and summarise relevant studies reporting HRQoL and utility data in patients with AAV. The CS and the Company's response to the ERG's clarification letter provided sufficient details for the ERG to appraise the literature searches.[1, 6]

- MEDLINE and Embase were searched, and hand-searching of the reference lists of key included articles was conducted. Health technology appraisals on the NICE website were also hand-searched. Supplementary searches of additional databases, conference proceedings, and specialist and organisational websites could have been undertaken to identify further potentially relevant publications.
- The search strategies contained only a population facet, which was then limited to HRQoL/utility studies. They included a good range of terms for AAV, GPA and MPA, using both free-text and subject indexing terms. Additional free-text terms could have been added to the strategies in order to improve recall, as noted in Section 3.1.1. Searches were clearly documented and structured, making them transparent and reproducible.
- Results were limited to English language only, and with a publication date limit of 1998-date.
- Search filters were applied to limit the results to HRQoL and utility data. Although the filters used were not cited in the CS, they appear comprehensive and likely to retrieve the relevant literature.
- Appendix I of the submission provides details of the systematic literature review undertaken to identify costs associated with the management of AAV and its complications.[30] The searches were conducted in three stages: an initial search on 9 July 2018 and updates on 16 June 2020 and 17 June 2021. The same search strategies were used in the original search and updates.

A summary of the sources searched is provided in 4.3.

Table 4.3: Data sources for the cost and healthcare resource identification, measurement, and valuation literature review (as reported in CS)

	Resource	Host/Source	Date Ranges	Dates searched
Electronic Databases	MEDLINE (MEDLINE; Epub Ahead of Print; In-Process, and Other Non-Indexed Citations; MEDLINE Daily)	Ovid	1946-04/06/18 1946-15/06/20 1946-16/06/21	09/07/18 16/06/20 17/06/21
	Embase	Ovid	1996-2018 Wk28 1974-2020 Wk24 1974-2021 Wk23	09/07/18 16/06/20 17/06/21
Additional searches	NICE health technology appraisals	Internet	Not stated	Not stated

ERG comment:

- Searches were undertaken to identify and summarise the best available cost and healthcare resource use evidence available for avacopan and relevant comparator therapies for the treatment of AAV. The CS and the Company's response to the ERG's clarification letter provided sufficient details for the ERG to appraise the literature searches.[1, 6]
- MEDLINE and Embase were searched, and hand-searching of the reference lists of key included articles was conducted. Health technology appraisals on the NICE website were also hand-searched. Supplementary searches of additional databases, conference proceedings, and specialist and organisational websites could have been undertaken to identify further potentially relevant publications.

- The search strategies contained only a population facet, which was then limited to cost/resource use studies. They included a good range of terms for AAV, GPA and MPA, using both free-text and subject indexing terms. Additional free-text terms could have been added to the strategies in order to improve recall, as noted in Section 3.1.1. Searches were clearly documented and structured, making them transparent and reproducible.
- Results were limited to English language only, and with a publication date limit of 1998-date.
- Search filters were applied to limit the results to cost and resource use data. Although the filters used were not cited in the CS, they appear comprehensive and likely to retrieve the relevant literature.

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the review on cost effectiveness studies, utilities and costs and resource use are presented in Table 4.4.

Table 4.4: Eligibility criteria for the systematic literature reviews

	Inclusion criteria	Exclusion criteria
Patient population (economic evaluations)	Adult patients (≥18 years) with GPA or microscopic polyangiitis, to include renal-limited vasculitis	•Patients aged <18 years •Patients without GPA or MPA
Patient population (HRQoL and cost/resource use)	• Adult patients (≥18 years) with GPA (Wegener's) or MPA	• Patients <18 years • Patients without GPA or MPA
Intervention (economic evaluations)	Avacopan in combination with CYC or RTX, with/without glucocorticoids used for the induction of response/remission and maintenance of remission	Any other treatment not specified in the inclusion criteria
Intervention (HRQoL and cost/resource use)	No limit	
Comparator (economic evaluations)	In combination with/without glucocorticoids: • CYC • RTX • Methotrexate • AZA • MMF • Abatacept • aTNFs • Plasma exchange • Placebo	Any other treatment not specified in the inclusion criteria
Comparator (HRQoL and cost/resource use)	No limit	

	Inclusion criteria	Exclusion criteria
Outcomes(s) 1 (Published economic evaluations)	Cost effectiveness outcomes/model inputs and parameters	Studies not reporting economic evaluations of treatments for GPA or MPA
Outcomes(s) 3 (HRQoL)	• Health-related utility values from empirical data	• Studies not reporting empirical data • Studies reporting outcomes during the maintenance period only • Studies reporting expert opinion only
Outcomes(s) 3 (Cost/resource use studies)	• Direct costs (e.g., medicines, healthcare staff costs, hospitalisations) • Indirect costs (e.g., absenteeism, work productivity, premature death) • Healthcare resource utilisation (e.g., hospitalisations, GP visits, hospital length of stay) • Extraction of additional outcomes: disease progression (ESRD), dialysis, RRT, CV outcomes, ICU/critical care stay	•Studies not reporting empirical data •Studies reporting expert opinion only
Study design 1 (Economic evaluations)	Economic evaluations of treatments for AAV (GPA or MPA), including: Cost-minimisation analysis studies, cost-consequence analysis studies, cost-benefit analysis studies, cost effectiveness studies, cost utility studies, budget impact analyses, or clinical trial–based economic evaluations Any model-based economic evaluations and/or model (e.g., decision trees, Markov models)	• Pharmacokinetic studies and proof-of-concept studies • Studies not reporting empirical data • Studies reporting expert opinion only • Reviews/systematic reviews • Studies indexed as case reports, case series, editorials, and letters
Study design 1 (HRQoL)	• Observational studies reporting on utilities/HRQoL data • RCTs reporting on utilities/HRQoL data	• Reviews/systematic reviews • Studies indexed as case reports, case series, editorials, and letters
Study design 3 (Cost/resource use studies)	• All empirical studies reporting on costs and resource utilisation for the specified patient population	• Reviews/systematic reviews • Studies indexed as case reports, case series, editorials, and letters
Language (all)	English	Publications in non-English language
Publication time (all)	1998-present	Publications <1998
Countries (all)	No limit	
Based on Table 70 of Appendix G[31], Table 72 of Appendix H[29] and Table 74 of Appendix I[30]		

In the cost effectiveness SLR 276, 61 and 51 unique records were identified in the original review, 2020 update and 2021 update respectively.[31] The PRISMA flow schematic in Figure 25 shows that 6 studies were included in the data summary, however the company then state that four studies were selected for inclusion, so it is unclear what happened to the remaining two. One of the four included studies was a conference abstract[32], one a peer review article[33] and two were HTA citations conducted by NICE[3] and the Scottish Medicines Consortium (SMC)[34]. All evaluated the cost effectiveness of RTX compared to AZA[33] or CYC[3, 32, 34]. Three were set in the UK and were full generalisable to the NHS of England and Wales[3, 32, 34]. , whilst the fourth, set in France, was also considered likely to be generalisable[33]. However, none of the studies investigated the cost effectiveness of avacopan; thus, a de novo economic model was required to address the decision problem.

The HRQoL SLR identified 191, 61 and 46 unique records during the original review, 2020 update and 2021 update respectively. [29] Five studies were included as they were judged to report HRQoL outcomes relevant to the decision problem. These included 2 HTAs on RTX [3, 34], a cross-sectional study[35], and 2 RCTs [8, 12]. The two HTAs of RTX with GC for treating AAV reported utility data.[3, 34]

In the cost effectiveness SLR 173, 67 and 53 unique records were identified in the original review, 2020 update and 2021 update respectively.[30] Twenty-five studies were included, of which 15 studies reported directly on the associated costs of the management of AAV, whilst a further 15 studies reported on HRU only. These studies are summarised in Tables 75 and 76 of Appendix I.[30]

4.1.3 Conclusions of the cost effectiveness review

The company submission and response to clarification provided sufficient details for the ERG to appraise the literature searches conducted to identify studies on the cost effectiveness of avacopan. Searches were conducted in June 2018 and updated in June 2020 and June 2021. Searches were transparent and reproducible, and comprehensive strategies were used, although additional search terms could have been included. MEDLINE, Embase and NHS EED were searched. Supplementary searches of additional databases, conference proceedings, and specialist and organisational websites could have been undertaken to identify further potentially relevant publications.

Overall, the SLR seems well conducted. Eligibility criteria were suitable.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 4.5: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	As per the reference case
Perspective on costs	NHS and PSS	As per the reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	As per the reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	As per the reference case

Element of health technology assessment	Reference case	ERG comment on company's submission
Synthesis of evidence on health effects	Based on systematic review	As per the reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	As per the reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Utility multipliers for fracture events were estimated from patient reported data from the ICUROS study. These multipliers were applied to UK general population EQ-5D norms.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Although not explicitly stated, it seems that the UK EQ-5D valuation tariff has been used.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	As per the reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	As per the reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	As per the reference case

EQ-5D = European Quality of Life Five Dimension; NHS = National Health Service; PSS = Personal social services QALY = quality adjusted life-year

4.2.2 Model structure

4.2.2.1 Health states/events and transitions

The model consists of nine core health states: active disease, three remission health states, three relapse health states, ESRD, and death, as shown in Figure 4.1.[6] The model structure reflects the clinical pathway in AAV, which is characterised by induction phases to treat relapsed AAV and maintenance treatment phases aimed at preventing further relapses. ESRD was included as a separate health state for severe renal impairment. The sequential modelling of remission and relapse is similar to the method employed in the NICE technology appraisal of RTX in AAV (TA308).[3]

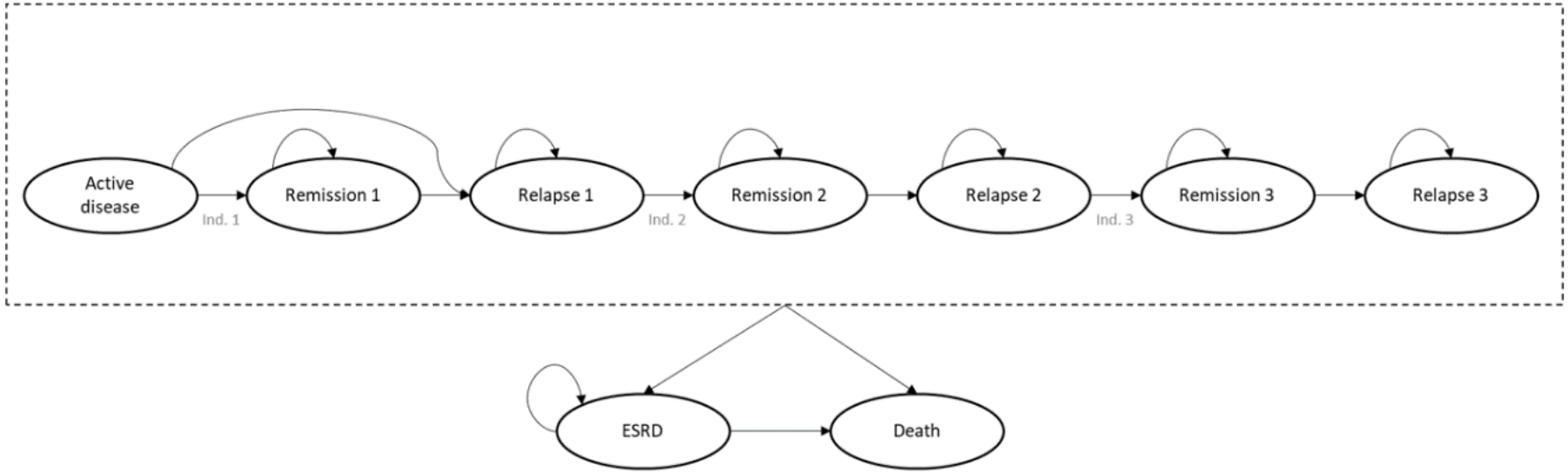
Patients with newly diagnosed or relapsed AAV enter the model in the active disease state, where they receive induction treatment with avacopan in combination with CYC or RTX, or CYC or RTX in combination with GCs.[6] If remission is achieved, patients transition to the remission 1 health state, where they receive maintenance treatment. If remission is not achieved, or if patients relapse after reaching the remission health states, they are treated with an additional course of CYC/RTX in combination with GCs to induce remission in the relapse 1 health state. Patients continue cycling

through remission and relapse health states until death, ESRD, or reaching the relapse 3 health state. Relapse 3 reflects refractory disease, and patients remain in this health state without further induction treatment until progression to ESRD or death.

Patients can develop ESRD in any model cycle from any state. Once in the ESRD state, patients remain there until death. Patients do not receive additional induction or maintenance treatment in the ESRD state. There instead they receive chronic renal replacement therapy until death, or they undergo a renal transplant.

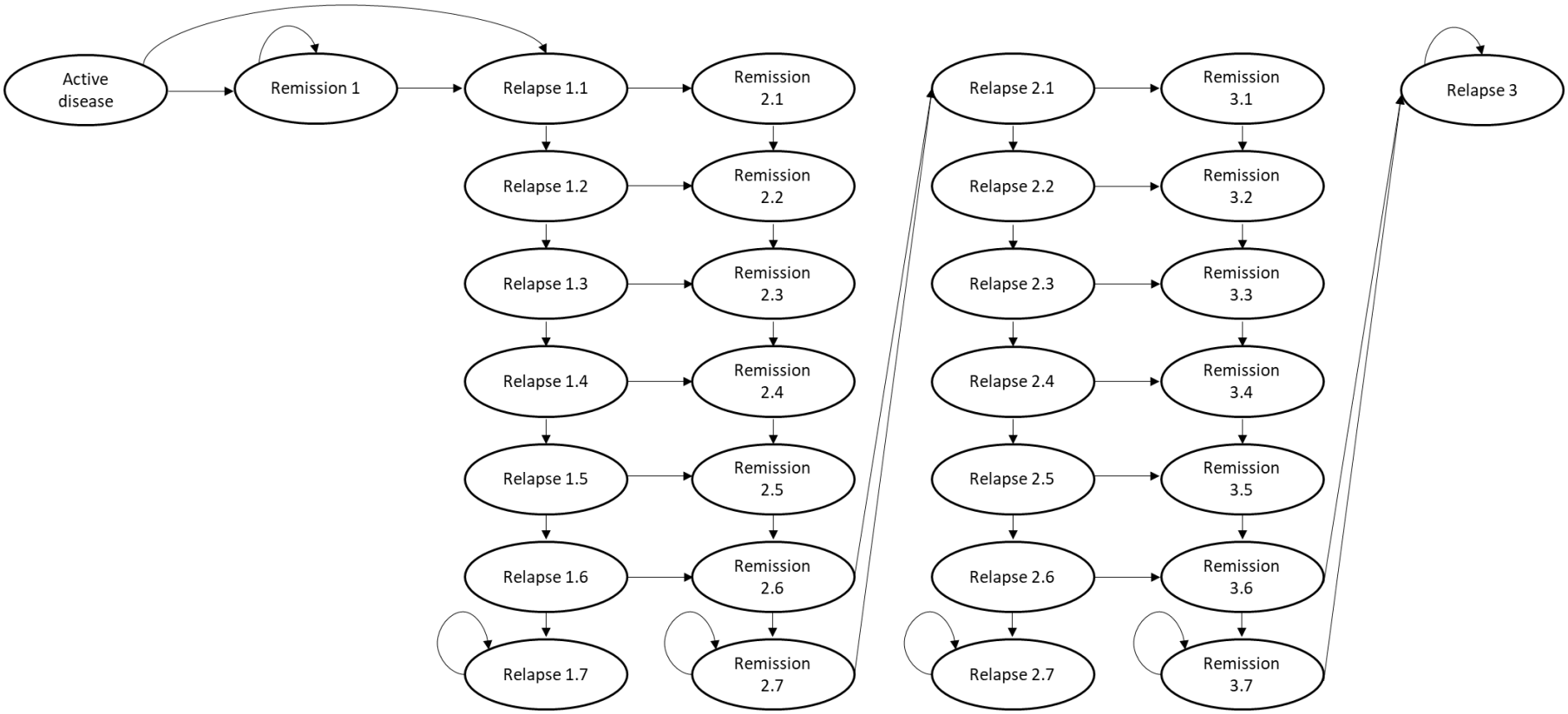
The length of an induction treatment course in AAV is 6 months, per ADVOCATE protocol, which was simplified to six 28-day cycles in the model. Each model cycle during induction and maintenance treatment includes different treatments and dosages. It was therefore necessary to track when patients enter and exit the remission and relapse health states using tunnel states as shown in Figure 4.2.

Figure 4.1: Model structure



Based on Figure 9 of the CS[6]
CS = company submission; ESRD = end-stage renal disease

Figure 4.2: Markov health states and tunnel states



Based on Figure 10 of the CS.[6]

Relapse 1 and relapse 2 health states each have seven tunnel states reflecting the six model cycles of induction therapy, in addition to a seventh tunnel state for patients who do not reach remission and therefore remain in the relapse state until they develop ESRD or die.[6] Patients do not receive further induction treatment courses once they reach the relapse three health state, and the use of tunnel states was therefore not necessary for this health state.

Patients transition from active disease to remission 1 in the first 6 model cycles but continue receiving induction therapy. Patients in remission 1 receive maintenance therapy starting from model cycle 7. The model cycles allow appropriate tracking of patients through the first induction course without the need for tunnel states. However, patients can relapse and enter the subsequent relapse health states at any point from model cycle 7 onwards. Thus, it was necessary to track patients using tunnel states in remission 2 and remission 3. The first five tunnel states are for the second to sixth model cycles of the induction period (patients in remission continue induction therapy until cycle 6). From the sixth tunnel state (seventh cycle since start of re-induction therapy), patients receive maintenance therapy for 24 months per clinical guidelines.[4, 36] A one-off cost of maintenance therapy is applied to patients in the sixth tunnel state.

ERG comment: The ERG considers the model structure to be appropriate in general. However, the ERG has concerns about the plausibility of assuming that patients enter the state of refractory disease once they had their first relapse and failed to reach remission after a second induction course. The ERG considers it possible that in clinical practice these patients would still receive treatment, for example a different induction treatment than the company assumed for their first two induction courses in these patients could be tried. The same argument applies to patients who fail to reach remission after having received a third induction course upon their second relapse (but having reached remission following induction after their first remission). Clinical experts consulted by the ERG for TA308, in which similar assumptions were made regarding retreatment, also suggested that it would be likely that an alternative therapy would be tried for relapsed patients after they had two rounds of induction therapy with rituximab that were unsuccessful at achieving remission.

Another concern brought forward by the ERG in NICE TA 308, following advice from clinical experts, is that treatment options may critically depend on whether a relapse is minor or major. For a minor relapse, another induction course may not be necessary but may possibly be treated with minor treatment such as an increase in corticosteroid dose. It is not clear to the ERG to what extent the definition of relapse in ADVOCATE (i.e., relapse was defined as a return of vasculitis activity on the basis of at least one major BVAS item, at least three minor BVAS items, or one or two minor BVAS items for at least two consecutive trial visits) allows for such minor (i.e., as referred to by the ERG in TA308) relapses to be included.

4.2.3 Population

The population defined in the scope is: People with newly diagnosed or relapsed anti-neutrophil cytoplasmic autoantibody-associated vasculitis.[7] However, in line with the population that avacopan was studied in and the EMA's recommendation to grant marketing authorisation, avacopan is only indicated for use in adult patients with severe, active GPA or MPA.

During the clarification phase, the company provided additional details regarding the characteristics of the patients from the UK that were included in ADVOCATE. These are tabulated below, alongside the characteristics of the ADVOCATE ITT population and patients from the CPRD study, in Table 4.6. The ADVOCATE ITT population can be considered as generalisable to the UK population in terms of age, gender, race, BMI, proportion newly diagnosed patients, median duration of ANCA-associated

vasculitis, positivity for PR3 and MPO, type of vasculitis, BVAS, VDI and standard of care treatment received. No specific details for the UK patients from ADVOCATE were provided on organ involvement, GC use during the screening period, and previous immunosuppressant use. Therefore, the generalisability in terms of these aspects could not be assessed. Based on the available information on patient characteristics in the CPRD study, the ADVOCATE ITT population can be considered as generalisable to the UK population in terms of age and gender.

In the model, a starting age of 60 years is assumed, and it is assumed that 50% of the population are male.

Table 4.6: Baseline characteristics of ADVOCATE ITT population, UK patients from ADVOCATE and in the CPRD study.

Characteristic		ADVOCATE ITT population		ADVOCATE UK patients		CPRD study
		Avacopan	Prednisone	Avacopan	Prednisone	
Sample size		166	164	17	23	567
Mean age (SD)		61.2 (14.6)	60.5 (14.5)	57.6 (11.9)	58.0 (15.1)	62 (unknown)
Male, n (%)		98 (59.0)	88 (53.7)	9 (52.9)	15 (65.2)	313 (55.2)
Race	**White, n (%)**	138 (83.1)	140 (85.4)	17 (100)	21 (91.3)	Unknown
	Asian, n (%)	17 (10.2)	15 (9.1)	0 (0.0)	2 (8.7)	Unknown
	Black, n (%)	3 (1.8)	2 (1.2)	0 (0.0)	0 (0.0)	Unknown
	Other, n (%)	8 (4.8)	7 (4.3)	0 (0.0)	0 (0.0)	Unknown
Mean BMI (SD)		26.7 (6.0)	26.8 (5.2)	28.0 (6.3)	27.2 (5.1)	Unknown
Newly diagnosed, n (%)		115 (69.3)	114 (69.5)	13 (76.5)	16 (69.6)	Unknown
Median duration of ANCA-associated vasculitis, months (range)		0.23 (0 - 362.3)	0.25 (0 - 212.5)	0.23 (0 – 63.7)	0.20 (0 – 64.7)	Unknown
ANCA positivity	**PR3, n (%)**	72 (43.4)	70 (42.7)	8 (47.1)	11 (47.8)	Unknown

Characteristic		ADVOCATE ITT population		ADVOCATE UK patients		CPRD study
		Avacopan	Prednisone	Avacopan	Prednisone	
	MPO, n (%)	94 (56.6)	94 (57.3)	9 (52.9)	12 (52.2)	Unknown
Type of vasculitis	GPA, n (%)	91 (54.8)	90 (54.9)	8 (47.1)	17 (73.9)	Unknown
	MPA, n (%)	75 (45.2)	74 (45.1)	9 (52.9)	6 (26.1)	Unknown
Mean BVAS (SD)		16.3 (5.9)	16.2 (5.7)	15.8 (6.0)	16.6 (5.5)	
Mean VDI (SD)		0.7 (1.5)	0.7 (1.4)	0.5 (1.1)	0.8 (1.6)	
SoC	IV RTX, n (%)	107 (64.5)	107 (65.2)	7 (41.2)	13 (56.5)	Unknown
	IV CYC, n (%)	51 (30.7)	51 (31.1)	7 (41.2)	10 (43.5)	Unknown
	Oral CYC, n (%)	8 (4.8)	6 (3.7)	3 (17.6)	0 (0.0)	Unknown

Based on Table 8 in the CS, Table 11 and Table 12 in the company's response to the clarification questions, and the CPRD study.[1, 6, 37]
ANCA = anti-neutrophil cytoplasmic autoantibody; BMI = body mass index; BVAS = Birmingham Vasculitis Activity Score; CYC = cyclophosphamide; GPA = granulomatosis with polyangiitis; ITT = intention to treat; IV = intravenous; MPA = microscopic polyangiitis; MPO = myeloperoxidase; PR3 = proteinase 3; RTX = rituximab; SD = standard deviation; SoC = standard of care; VDI = Vasculitis Damage Index.

ERG comment: As explained in Section 2.1 of the ERG report, the population used to address the decision problem in the CS is narrower than as defined in the NICE final scope. Based on the details provided by the company, the ADVOCATE ITT population seems generalisable to the UK population. However, it is unfortunate that only age and sex were stated in the CPRD study report, thus limiting the assessment the ERG can do. In Section 3.2.3 it was described, however, that according to the company the CPRD data did show comparability with the population in the ADVOCATE study. Furthermore, the generalisability was confirmed in a retrospective clinical audit of the records of 300 UK AAV patients.[1, 37]

4.2.4 Interventions and comparators

The modelled intervention (avacopan + SoC) during the induction phase (i.e., the first 6 model cycles) consisted of avacopan, 30 mg (i.e., 3 capsules of 10 mg each) twice daily, in combination with RTX, administered intravenously once every week for 4 weeks at a dose of 375 mg/ m^2, or CYC, administered on days 1, 15, 29, 49, 70 and 91 at a dose of 15 mg/ kg.

The modelled intervention during the maintenance phase (i.e., 26 model cycles following the induction phase) consisted of avacopan, 30 mg (i.e., 3 capsules of 10 mg each) twice daily (i.e., same treatment

as induction phase for an additional 6 months) for 7 model cycles in combination with AZA at a dosage of 2 mg/ kg/ day for 26 model cycles. Thereafter, it was assumed that all patients in remission continue to receive AZA at a dosage of 2 mg/ kg/ day.

The modelled comparator (GC + SoC) during the induction phase consists of RTX or CYC, with the same administration schedule and dosing as for the intervention, and prednisone at a starting dose of 60 mg daily tapered to discontinuation over the course of 20 weeks.

The modelled comparator during the maintenance phase (i.e., 26 model cycles following the induction phase) consists of AZA at a dosage of 2 mg/ kg/ day for 26 model cycles. Thereafter, it was assumed that all patients in remission continue to receive AZA at a dosage of 2 mg/ kg/ day.

At the request of the ERG during the clarification phase, the company included (as exploratory analysis) the option to model RTX as maintenance treatment (in line with the BSR/BHPR guidelines that specify RTX maintenance treatment for patients achieving remission after RTX induction) instead of AZA. For this it was assumed that RTX was given at a dose of 500 mg/ m^2 on day 1 and 14 for 7 model cycles, followed by a dose of 500 mg/ m^2 on day 1 of every subsequent model cycle for all patients in remission.

ERG comment: The modelled intervention and comparator follow the protocol for the ADVOCATE trial for the first 52 weeks. However, the non-study supplied GC use was not included in the model, which amounted to 1349 mg prednisone equivalent in the intervention group and 1265 mg in the control group. The costs of prednisone are very low, so not including this in the costs has negligible impact on the ICER. Also, in the base case analysis where all data (both on effectiveness and adverse events) is retrieved from the ADVOCATE study, the impact of the off-protocol use of GC has implicitly already been included. However, when CPRD data is used to model the impact of GC use on adverse events, a substantial amount of GC use is disregarded in the current approach. Given that the off-protocol use is approximately the same in both treatment groups, the impact on the incremental costs and effects could be limited.

As mentioned above, the company included, after clarification, RTX as treatment option during the maintenance phase of the treatment. This means that both the costs of RTX maintenance and the impact on relapse have been included. In their response to the clarification letter, the company explained that they had included an adjustment to the baseline hazard ratio of relapse to reflect the improved effectiveness of maintenance treatment through the addition of RTX instead of AZA, based treatment effectiveness data from the RITAZAREM trial.[1, 28] They warned however, that this non-adjusted naïve comparison should be treated as an exploratory analysis and its conclusions treated with caution due to the high uncertainty associated with this approach.

In the clarification letter the ERG queried if it might be possible that in clinical practice avacopan will be given for longer than a year. The company indicated that there is no data to inform the effectiveness of avacopan treatment beyond the 52-week data from ADVOCATE and that thus clinicians may be cautious about extending the duration of use of avacopan. However, they did consider it possible that some patients may continue avacopan maintenance treatment beyond 52 weeks if the treatment is still effective and tolerated. To facilitate exploratory analyses about prolonged maintenance with avacopan, the company added options for 12, 18, 24, 36 and 48 months of maintenance treatment, with efficacy based on the data between 26 and 52 weeks in the ADVOCATE study.

4.2.5 Perspective, time horizon and discounting

The economic analyses were conducted from the perspective of the NHS and Personal Social Services (PSS), in line with the NICE reference case.[38] The model has a time horizon of 53 years that is

considered appropriate as a lifetime horizon, in line with the NICE reference case,[38] given that the average age of patients at the start of treatment is 60 years. Costs and QALYs were discounted at 3.5% as per the NICE reference case.[38]

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Relapse

Transitions between model states during the induction phase (first 6 cycles) is based on the ADVOCATE trial results at week 26.[6] The company assumed that active disease is equivalent to relapse before 26 weeks and therefore relapses are not explicitly modelled until cycle 7 onwards. The probability of relapse can vary according to treatment and over time according to the natural history of the disease or waning treatment effect.

4.2.6.1.1 Comparator (GC + SoC)

In the first 26 weeks (7 cycles) after treatment with CYC or RTX, the per-cycle probability of relapse was calculated using the proportions of patients in remission at weeks 26 and 52 from ADVOCATE.[6]The company reported that the CPRD study showed that the probability of moving from remission to relapse [redacted].[37] In the absence of long-term data for CYC or RTX, the company assumed that the relapse probability for these treatments was constant up to 2 years and then assumed it to be [redacted] after year 2, based on data from the CPRD study

4.2.6.1.2 Intervention (avacopan + SoC)

The per-cycle probability of relapse in the first 26 weeks (7 cycles) after treatment with avacopan was estimated using a HR derived from the remission rates at 26 and 52 weeks for both treatment arms. This HR was then used to adjust the probability of relapse 26-52 weeks after treatment with CYC or RTX.

The HR for the rate of relapse for avacopan treated patients between week 52 and 60 (cycles 14 and 15), i.e. after the avacopan treatment had stopped, was derived from extension study data reported in the ADVOCATE CSR.[23] After this it was assumed that the treatment effect of avacopan declined linearly over one last cycle, with no residual treatment benefit after cycle 16, from which point the probability of relapse was equal to the GC + SoC group. This assumption was in line with clinical expert opinion consulted by the company, the details from which were provided to the ERG during the clarification phase: from the 10 clinical experts consulted 1 indicated a duration of less than 1 month, 6 indicated a duration between 1 and 3 months, 2 indicated a duration of 3-6 months and 1 indicated a duration of more than 12 months. Scenarios were run to explore alternative assumed durations of residual benefit (i.e., treatment waning).

ERG comment: The ERG agrees that the relapse rates were calculated appropriately based on the numbers of patients in remission at 26, 52 and 60 weeks from ADVOCATE. The ERG also agrees that a 3-month duration of treatment waning once treatment is discontinued is plausible and in line with clinical expert opinion consulted by the company. During the clarification phase, the company explained that the number of patients included in the extension study (i.e., from 52 to 60 weeks) was 157 out of 165 patients in the prednisone arm and 158 out of 166 in the avacopan arm of ADVOCATE. Since no further details were provided, it was not clear to what extent the extension sample was comparable to the ITT population. Notwithstanding, since the dropout rate was low it can be assumed that a resulting bias in the results, if any, would be small. During the clarification phase, the company

provided additional details on how they arrived at the assumption that relapse rates after 2 years are one fifth of those in the preceding time period. This was based on data from the CPRD study on the durations of episodes of either no or no/ low dose GC use where upon failure patients restart GC/ high dose GC treatment, respectively. The results of the CPRD study (i.e., as reported in Table 4 of the CPRD study report)[37] indicate that the incidence rates of treatment episode discontinuation are 1.15 (95% C.I. 1.06 to 1.24) in years 0-2 and 0.19 (95% C.I. 0.15 – 0.25) in subsequent years for non-GC episodes, and 0.45 (95% C.I. 0.41 – 0.50) in years 0-2 and 0.13 (95% C.I. 0.11 – 0.16) in subsequent years for low dose and/or non-GC episodes. These data suggest that the decrease in incidence rates between years 0-2 and subsequent years is about 6-fold based on non-GC episodes and about 3.5-fold based on low dose and/or non-GC episodes. Thus, the ERG considers the assumed 5-fold decrease in relapse rates after year 2 in the company base-case to be in line with the data from the CPRD study.

4.2.6.2 Remission

The per cycle probabilities of transitioning from active disease/relapse to remission for either induction with avacopan + SoC or GC + SoC were estimated from the proportions of patients in ADVOCATE in remission at 26 weeks.[8] This approach assumed a constant hazard over the 26 weeks. These transition probabilities were assumed to apply to transitions from both the active disease state and the relapsed states to remission, for both the intervention and comparator. The probability of remission for RTX and CYC are considered equal, based on non-inferiority of RTX in the RAVE clinical trial.[39]

ERG comment:

- The ERG has concerns regarding some of the assumptions made for the modelling of remission, which are explained below.
- The company assumed that remission rates were the same for patients in the active disease and relapsed disease health states. This assumption is not based on empirical evidence, nor on clinical expert opinion. In Table 24 of the CS, the company provided the proportions of patients in remission at 26 and 52 weeks from ADVOCATE stratified by subgroups. These are summarised below in Table 4.7 for newly diagnosed AAV patients, relapsed AAV patients, patients with GPA, patients with MPA, MPO positivity and PR3 positivity. When comparing the proportions of patients in remission between newly diagnosed and relapsed patients, the data suggest that the differences in remission between the two treatments arms in the ITT population are primarily driven by the difference in proportions for relapsed patients. In contrast, the differences in remission between treatment arms for newly diagnosed patients are relatively small. This undermines the company's assumption that remission rates are the same for patients in the active disease and relapsed disease health states. On the other hand, the group of patients in active disease is a mixture of newly diagnosed AAV and relapsed AAV. For the latter group the assumption of remission rates that are equal to those for patients who relapse later in the model might be reasonable.

Table 4.7: Proportions of patients in remission stratified by subgroup

	Avacopan	Prednisone
Remission at week 26		
ADVOCATE ITT population	72.3%	70.1%
Newly diagnosed AAV	66.1%	66.7%
Relapsed AAV	86.3%	78.0%
GPA	71.4%	72.2%
MPA	73.3%	67.6%

	Avacopan	Prednisone
MPO positive	73.4%	69.1%
PR3 positive	70.8%	71.4%
Remission at week 52		
ADVOCATE ITT population	65.7%	54.9%
Newly diagnosed AAV	60.9%	57.9%
Relapsed AAV	76.5%	48.0%
GPA	61.5%	57.8%
MPA	70.7%	51.4%
MPO positive	70.2%	53.2%
PR3 positive	59.7%	57.1%

Based on Table 24 of the CS.[6]
AAV = anti-neutrophil cytoplasmic autoantibody associated vasculitis; CS = company submission; GPA = granulomatosis with polyangiitis; ITT = intention to treat; MPA = microscopic polyangiitis; MPO = myeloperoxidase; PR3 = proteinase 3.

- The company also assumed that remission rates were the same for patients receiving induction therapy and maintenance therapy, and similarly, that remission rates were the same for all patients regardless of the number of prior relapses and time since the last relapse. None of these assumptions were informed by empirical evidence, nor by clinical expert opinion. The ERG considers that the availability of empirical evidence or clinical expert opinion to inform these assumptions could help to resolve the uncertainty that surrounds these aspects.
- Lastly, the ERG has concerns regarding the assumption that remission rates are constant over time. For example, the data from ADVOCATE clearly indicate (i.e., see Table 14 of the CS) that most remissions had occurred after 4 weeks of treatment. In response to the ERG's clarification questions, the company explained that the assumption of constant remission rates (i.e. which is equivalent to assuming an exponential parametric function) over time was a simplification made to facilitate the extrapolation of the remission rate beyond the time horizon of ADVOCATE and that they expected that the inclusion of remission at week 4 would be favourable for avacopan (i.e. thereby implying that they considered the adopted approach as conservative). According to the ERG, the approach adopted by the company is a potential over-simplification and, in absence of results using other possible approaches, the ERG is not able to confirm that it represents a conservative approach. In the GS + SoC group 68.9% of patients is in remission at 4 weeks, versus 62.7% in the avacopan + SoC group, whilst at 52 weeks the remission rates are 54.9 and 65.7%, respectively. So, if this was presented in a time to remission curve, the curves of the two treatment groups would cross. Thus, it is difficult to immediately see whether the approach chosen by the company represents a conservative approach. The plausibility of the assumed constant remission rate over time could be informed by parametric extrapolations (i.e., using various parametric functions that include, but are not limited to, the exponential distribution) of remission rates over time.

4.2.6.3 End-stage renal disease

ESRD linked to disease activity is reported to have a major impact on survival, QoL and costs in AAV patients.[6] The model includes transition probabilities to ESRD from active disease/relapse, remission, and refractory disease. These transitions can be based on two sources: the literature and CPRD. The probability of relapse was adjusted to reflect renal outcomes in AAV based on eGFR data from the

ADVOCATE trial, the association between eGFR and the probability of ESRD reported in the literature, and assumptions supported by clinical experts.

In the base-case, the probability of ESRD was based on observational data and adjusted for future changes in eGFR. Robson et al. found that the risk of ESRD is substantially higher in the first 6 months following disease onset than in subsequent years.[40] This data was used to estimate the transition probability from active disease or relapse to ESRD. The transition probability from remission to ESRD was based on long-term data up to 7 years of follow-up[40]. It was assumed that the probability of ESRD in refractory disease is equal to that of relapse, based on clinical expert opinion.

AAV relapse is associated with worsening renal outcomes and a 9-fold increase in the risk of ESRD.[23, 41] Current and future eGFR are used in the model to simulate the increasing risk of ESRD with subsequent relapses.[6] The probability of ESRD in active disease is adjusted based on the improvement in eGFR in the avacopan and comparator arms of the ADVOCATE trial observed between weeks 0 and 26 (5.8 ml/min and 2.9 ml/min, respectively). The probability of ESRD in remission is adjusted based on the improvement in eGFR observed between weeks 0 and 52 in the ADVOCATE trial (7.3 ml/min and 4.1 ml/min, respectively). The hazard ratio, and subsequently the probability of ESRD, was adjusted based on a study by Gercik et al., which reported a hazard ratio of 0.90 for ESRD per ml/min change in eGFR from baseline.[42] It was assumed that renal function, and probability of ESRD, for patients in sustained remission is no different between patients previously induced with avacopan or GC SoC. Each subsequent relapse was associated with a 10-ml/min decrease in eGFR. This was a conservative assumption supported by clinical experts, who suggested that a relapse may be associated with a decrease of up to 20 ml/min. The hazard ratio of ESRD was adjusted with each subsequent relapse based on the assumed 10-ml/min drop and the corresponding hazard ratio estimated from the Gercik et al. study.[42]

The CS provides an example of how this works for a hypothetical patient. For a patient treated with avacopan, their eGFR improves by 5.8 points, resulting in a reduction in the risk of ESRD by 45.7%, resulting in a 4-week ESRD probability of 0.0055. If they achieve remission within the first 26 weeks of treatment, their eGFR improvement rises from 5.8 to 7.3 units, resulting in a probability of ESRD of 0.0047. If they remain in sustained remission beyond week 26, their probability of ESRD reduces further to 0.0006. If they experience a relapse after achieving remission, their eGFR drops by 10 points due to the renal impact of AAV and recovers by 2.9 points due to re-induction treatment with GC SoC. This results in a probability of ESRD of 0.0116. If they are brought back into remission with GC SoC, their probability of ESRD reduces to 0.0088 and 0.0011. The probability of ESRD in all health states increases with each subsequent relapse, which reflects worsening renal function over time due to AAV, until it reaches a maximum value of 0.033 in refractory disease after three inductions, which is the worst outcome in the model for patients who remain alive and ESRD-free. Table 34 of the CS provides the calculations of the eGFR-adjusted ESRD transition probabilities.

The model also includes the probability of ESRD calculated from the CPRD stratified by GC dosage as a scenario. ESRD was defined in CPRD using diagnosis codes or presence of 3 dialysis codes within a 6-month period. In the CPRD study, rates of ESRD onset were stratified based on GC dosage ("high dose": patients with a GC dose >10 mg/d; "low dose": patients with a GC dose >0 mg/d and <10 mg/d; and "no GC": patients with 0 mg/d recorded). GC dosage is used strictly as a proxy for AAV activity, rather than assuming a direct relationship between GC dose and ESRD. Therefore, it is assumed that avacopan prevents ESRD through sustained remission and a reduced rate of relapse. The high-dose GC rate is assumed to be a proxy for the rate corresponding to active disease with the highest renal impact of AAV activity. This rate is applied to the first 6 cycles in health states with active disease or relapse

requiring induction treatment. The high-dose rate was also applied to patients with refractory disease. The no-GC rate applies to patients in long-term remission (cycle 7 and onward in first remission and cycle 6 onward in subsequent periods of remission). Table 35 of the CS shows the transition probabilities based on the CPRD study.

ERG comment: Wherever the hazard ratio of developing ESRD was adjusted based on an increase or decrease in eGFR a hazard ratio (HR=0.90) estimated from the Gercik et al. study was used by the company. Though not mentioned in report, the model shows that three other studies have estimated the same hazard ratio, Brix et al. (HR=0.96), Ford et al. (HR=0.96) and Menez et al. (HR=0.913).[43-45] The hazard ratio estimated by Brix et al.[43] was explored by the company in the scenario "Effect of eGFR decrease on probability of ESRD". The ERG considers the studies by Brix et al and Ford et al. as relevant and plausible as the study from Gercik et al. The study by Menez et al. was not included. Whereas the other three studies included the population of patients with AAV with renal involvement, Menez at al included patients with sclerotic ANCA glomerulonephritis, which is a more restricted patient population. Hence, we derived a pooled estimate (based on inverse variance approach) for these three studies, yielding a HR of 0.955 (95% CI 0.926 – 0.985). This estimate will be used in an ERG preferred base case.

The two approaches of the company to estimate the probability of patients to develop ESRD are very different, leading also to very different estimates. Roughly, the approach using literature and ADVOCATE data yields transition probabilities about six times higher than when they are based on the CPRD study.

The estimation based on literature and ADVOCATE tries to link observed changes in kidney function when patients receive avacopan and assumed decrease in kidney function when patients experience a relapse to increases and decreases in the probability of developing ESRD. The approach appears plausible, though the reduction in kidney function due to a relapse is based on only expert opinion.

The alternative approach, based on CPRD data, also appears plausible, as observed development of ESRD is linked to the model health states, based on the assumption that the level of GC use is a proxy for the underlying health state. Comparison of the model-predicted overall incidence of ESRD to the CPRD reported overall incidence clearly shows (see Section 5.3) that the mapping/proxy approach based on the CPRD date leads to more realistic model estimates with regard to ESRD. Hence, this approach will be used for an ERG preferred base case.

4.2.6.4 Mortality

Background mortality was estimated from the 2015-2017 National Life Tables for England.[46] The relative risk of mortality for patients with AAV was derived from Wallace et al., who investigated mortality trends in patients diagnosed with GPA between 1992 and 2013 using the Health Improvement Network (THIN) database in the United Kingdom.[47] This study found that mortality in the first year following a diagnosis of GPA was higher than in subsequent years. Therefore, it was assumed that the relative risk of death compared with the general population was 6.31 in the first year and 2.51 in subsequent years after diagnosis of AAV. Mortality rates in the active disease, remission, and relapse health states were assumed to be equal, based on Jayne et al.[48] Based on the CPRD data, similar relative risks were estimated, 9.61 in the first year and 3.16 in the subsequent years.

To capture the potential benefit of avacopan on reducing mortality, the model considers the risk of death from treatment related infections. Treatment with immunosuppressants in AAV is associated with a significantly increased risk of infections and it is estimated that around half of all deaths in the first year

following AAV diagnosis are caused by infections.[4, 49-51] To reflect the reduced burden of infection-related deaths through the GC-sparing capacity of avacopan, the HR for mortality from literature was adjusted in the first year for avacopan as follows.

$$HR_{adj} = \left[\left(\frac{HR_{yr1}}{HR_{yr2+}} - 1\right) \cdot (1 - \alpha \cdot \beta) + 1\right] \cdot HR_{yr2+}$$

HR_{adj} = Adjusted HR of death in first year in AAV

HR_{yr1} = HR of death in first year in AAV from CPRD or literature

HR_{yr2+} = HR of death in subsequent years in AAV from CPRD or literature

α = Proportion of deaths attributed to GC

β = Proportion of infections avoided using Avacopan

The value for α was set to 0.5, as Little et al. observed that half of the first year AAV deaths are attributable to infections.[51] According to the company, if it is assumed that all infections are prevented by avoiding GCs (β =1), the equation reduces to $HR_{adj} = HR_{yr2+}$; with all excess infection-related deaths in first year avoided and the rate equalling the HR applied in subsequent years of treatment. Assuming no infections can be avoided by using avacopan (β = 0), the equation reduces to $HR_{adj} = HR_{yr1}$; and the probability of death with avacopan is equal to GC-based treatments. The value for β was obtained from the ADVOCATE trial, which reported an incidence of serious infection-related AEs of 1.8% in the AVA+CYC/RTX arm and 6.7% in the CYC/RTX+GC arm. The relative reduction in the incidence was (6.7%-1.8%)/6.7%=73.1%. The annual mortality in the first year was adjusted using a weighted average based on the number of cycles with high- and low-dose GC in comparator arms.

The relative risk of mortality for patients with ESRD (10.3) was estimated from a study by Choi et al., which compared patients with ESRD against the general population in South Korea.[52]

ERG comments: As mentioned above, a South Korean study was used to inform the relative risk of mortality for patients with ESRD. However, The ERG prefers to use the relative risk estimated from the 23rd Annual report of the UK Renal Registry. This UK relative risk amounts to 6.6, based on all prevalent patients in 2019.

A small remark needs to be made concerning the explanation the company provides for the formula for the adjusted hazard ratio of death in the first year from AAV. They suggest that if it is assumed that all infections are prevented by avoiding GCs (β =1), the equation reduces to $HR_{adj} = HR_{yr2+}$. This is not correct when β = 100% and α = 50%; only if also α = 100% (i.e., all deaths can be attributed to GC) does the equation reduce to $HR_{adj} = HR_{yr2+}$. However, the error only has bearing on the illustration of the formula, the formula itself is correct and also correctly implemented.

4.2.7 Health-related quality of life

4.2.7.1 Utilities from the ADVOCATE trial

HRQoL data were collected in ADVOCATE at baseline, 4, 10, 16, 26, 39 and 52 weeks using both the SF-36 and EQ-5D-5L.[8]The EQ-5D-5L HRQoL data was converted into UK EQ-5D-3L utilities using the crosswalk algorithm by van Hout et al.[53] UK EQ-5D-5L utilities were also included in the model as a scenario.

Health state utility values (HSUVs) were obtained by taking the mean of pooled patient utilities at weeks 4, 26 and 52, stratified by treatment arm and disease state (active disease, remission, and relapse). Separate utilities per treatment arm were included to allow for differences that may emerge, for example due to reduced use of GC and reduced AEs. The utilities for model states, by treatment, are displayed in Table 4.8. Though treatment-specific HSUVs are used for the company base case, the model also allows the option to use non-treatment-specific HSUVs, which can also be found in Table 4.8.

The starting age of the model cohort was 60 years. Utilities were adjusted for ageing over time using the UK population norms estimated from Ara and Brazier.[54] The adjustment was based on movement between 5-year age groups and was calculated relative to the age group containing the mean age of the ADVOCATE trial cohort at baseline (61-65 years).

ERG comment: Measurement of HRQoL using the EQ-5D-5L in trial patients and the use of the crosswalk algorithm to translate EQ-5D-5L responses into EQ-5D-3L UK utility values meets the NICE reference case. However, it is surprising that the company included only the measurements at week 4, 26 and 52 weeks in the estimation of HSUVs, as data is available for various other time points. Especially in light of the fact that these HSUVs should also capture the disutility from adverse events, the ERG considers it wasteful to not use all time points. A repeated measure model could have been used to estimate utilities depending on health state and treatment.

In table 10 of the response to the clarification letter the company showed the sample sizes (see also Table 4.8) on which each utility value was based.[1] From this it is clear that the utility estimates for relapse are based on very few observations. This probably explains why for the avacopan + SoC group the utility for relapse is higher than for active disease, whereas for GC + SoC the reverse is true. This suggests that at least for the relapse health state there is not enough data to distinguish between treatments.

The company use treatment specific utilities to allow for differences that may emerge, for example due to reduced use of GC and reduced AEs. Given the EQ-5D's recall period of "today", it is unlikely that the HRQoL impact of all AEs occurred exactly on measurement days a week 4, 26 and 52 and therefore it is unlikely that the impact of AEs is sufficiently captured by using treatment-specific utilities. It is unclear whether the HRQoL impact of GC use would also be captured on these days. It would depend on whether GC was theorised to impact HRQoL fairly constantly, or through infrequent events. If it is the latter, the impact of GC use would also likely be missed.

Given the issue of the recall period, and the small sample sizes, the ERG prefers to use health state utilities that do not vary by treatment, combined with disutilities for observed AEs.

Table 4.8: Utility inputs used in the model

State	Utility value: mean (standard error)	95% confidence interval	Source
Avacopan + SoC (n 26w/n 52w)			
Active disease (34/33)	0.708 (0.022)	0.664-0.751	ADVOCATE trial[8]
Remission (118/107)	0.790 (0.011)	0.767-0.812	
Relapse (-/9)	0.738 (0.055)	0.629-0.847	
GC + SoC (n 26w/n 52w)			
Active disease (36/34)	0.697 (0.024)	0.649-0.744	ADVOCATE trial[8]
Remission (112/89)	0.766 (0.012)	0.741-0.790	
Relapse (-/21)	0.678 (0.056)	0.566-0.790	

State	Utility value: mean (standard error)	95% confidence interval	Source
All patients (n 26w/n 52w)			
Active disease (70, 67)	0.702 (0.016)	0.670-0.734	ADVOCATE trial[8]
Remission (230/196)	0.778 (0.008)	0.761-0.795	
Relapse (-/30)	0.696 (0.042)	0.611-0.780	
ESRD utilities			
Peritoneal dialysis	0.530 (0.027)	0.477-0.583	Lee et al.[55]
Haemodialysis	0.443 (0.023)	0.399-0.487	
Renal transplant	0.712 (0.036)	0.641-0.783	
ESRD distribution			
Peritoneal dialysis	20.5%	Fixed	20th Annual Report of the Renal Association.[56]
Haemodialysis	69.8%	Fixed	
Renal transplant	9.7%	Fixed	
Based on Table 39 of the CS ESRD = end-stage renal disease; GC = glucocorticoid; SoC = standard of care			

4.2.7.2 Utilities from the literature

Utilities for the ESRD health state were obtained from the literature, according to the type of treatment an ESRD patient may receive, as used in the STA for patiromer.[57] This appraisal considered that ESRD patients may be treated with either peritoneal dialysis, haemodialysis, or renal transplant. The distribution of ESRD patients across these potential treatments was sourced from the 20th Annual Report of the Renal Association.[56] The health state utilities for patients undergoing each treatment were sourced from a UK study published in 2005.[55] Data for peritoneal dialysis and haemodialysis were combined to provide the weighted average health state utility for patients receiving dialysis in ESRD. The ESRD health state was decomposed into 2 substates for dialysis or renal transplant using the proportion of patients requiring renal transplant. The overall utility of the ESRD health state was then obtained as the weighted mean of these two substates. The utilities used and proportions for ESRD treatments are presented in Table 4.9.

The literature review identified five studies reporting HRQoL data relevant to the decision problem.[6] Two studies reported utility values in AAV patients. These were HTA submissions to NICE and the SMC on the use of RTX in combination with GCs for treating AAV.[3, 34] The population in both submissions were patients with severe, active GPA and MPA. Utilities in both submissions were derived from SF-36 data collected at baseline and 6 months in the RAVE trial using a previously published mapping algorithm.[39, 58] SF-36 scores were converted to EQ-5D-3L utilities from the non-remission and remission health states and adjusted for age. The model calculated utility values for 3 disease states: uncontrolled disease, remission, and non-remission. The HSUVs used are displayed in Table 4.10 .

Table 4.9: Utility values from the literature

	Study (year)	
	NICE TA308 (2014)	**SMC ID 894/13 (2013)**
Country	United Kingdom	United Kingdom
Patient population	Adult patients with severe, active GPA and MPA	Adult patients with severe, active GPA and MPA

		Study (year)	
		NICE TA308 (2014)	**SMC ID 894/13 (2013)**
Intervention comparator		RTX (in combination with GCs) CYC (in combination with GCs)	RTX (in combination with GCs)
Utility score	**Uncontrolled**	0.71*	0.671
	Remission	0.84	0.837
	Non-remission	0.754	0.754

Based on Table 38 of the CS.[6]
*Utility value adjusted to reflect fact that AAV is rarely left untreated
AAV = anti-neutrophil cytoplasmic antibody–associated vasculitis; CYC = cyclophosphamide; GC = glucocorticoid; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; NICE = National Institute for Health and Care Excellence; RTX = rituximab; SMC = Scottish Medicines Consortium

4.2.7.3 Adverse event disutilities

For the base case, the company has assumed that any impact of adverse events would be captured in the treatment-specific utilities used. However, as explained by the company, GC therapies are associated with numerous side effects, with toxicity increasing with daily use and cumulative dose.[6, 59, 60] Several AEs related to GCs were therefore included in the model, including infections, CV disease, renal disease, bone disease, and ocular disease to reflect potential additional benefits of treatment with avacopan, given its potential GC sparing property.[6] In the company base-case these AE disutilities were not applied, as treatment-specific utilities were assumed to account for the QoL impact of AEs associated with GC use. However, utility decrements were included in the model and used in scenario analysis.

Utility decrements for infections and ocular disease are only applied in the cycle when the event occurs, whereas utility decrements for CV events, renal disease and bone disease event are applied for the remainder of the time-horizon.[6] Separate decrements are provided for the acute phase of an event and the follow-up period. A pragmatic literature search was conducted to source utility data for AEs, resulting in the inputs displayed in Table 4.10.[6] A utility decrement for CV event and renal disease was sourced from a large US population study.[61] The utility decrement due to infection was assumed to be -0.1, given the lack of literature data. The utility decrement for bone disease was derived based on data reported in the ERG critique of the submission in Technology Appraisal 464.[62] An average utility value for 5-year age groups was derived from utility multipliers for hip, spine, shoulder, and wrist fractures. The weighted utility multipliers in first and subsequent years after a fracture were multiplied by the baseline utility for each age group to estimate a utility decrement for the model. The utility decrement associated with ocular disease is derived from a literature review of studies of cataract surgery.[63] The difference in utility levels before and after surgery was assumed to be equivalent to a one-time utility decrease associated with cataract-induced vision loss. It is assumed that patients would undergo surgery halfway through the first year on average following which utility will be restored to pre-cataract levels. A utility decrement of one-half of the annual utility loss is thus applied in the first year after diagnosis.

Table 4.10: Utility inputs used in the model for GC-related adverse events

GC-related adverse events	Utility value		Follow-up period
	Acute	**Post-acute**	
Infections	-0.10	NA	1 year

GC-related adverse events	Utility value		Follow-up period
	Acute	Post-acute	
Cardiovascular event	-0.05	-0.05	Lifetime
Renal disease	-0.05	-0.05	Lifetime
Bone disease	0.00	0.00	Lifetime
Ocular disease	-0.05	N/A	1 year
Based on Table 41 of the CS.[6]			

ERG comment: It is very unlikely, particularly given the small trial population, short trial follow-up and one day recall period of the EQ-5D-5L, that the impact of GC-related AEs has been sufficiently captured in the treatment-specific utility values used in the model.

Equally, it is unclear if the impact of the actual AEs observed in ADVOCATE on HRQoL was sufficiently captured using the treatment specific utilities, given that they are based on the one-day recall period of the EQ-5D-5L. Thus, the ERG requested that the company include disutilities for serious AE that occur in at least 2% in one of the study groups. This concerns 3 adverse events, listed in Table 4.11. The first and third AE represent worsening of the vasculitis, so the approach to estimating the disutility has merit. The assumption made for the pneumonia appears plausible, though the ERG is surprised no disutility was found in literature. The ERG is concerned that the weighted utility decrement per cycle that has been estimated is incorrect. The observed AEs occurred during a 52-week duration, and by using these 1-year frequencies as weights for the per cycle disutility, the latter is grossly overestimated. In Section 6 we will present the impact of correcting this error.

Table 4.11 Disutility derived for adverse events as observed in ADVOCATE

AEs ≥ 2% in one of study groups	GC + SoC % of patients	Avacopan + SoC % of patients	Disutility	Source
Anti-neutrophil cytoplasmic antibody positive vasculitis	12.2%	7.2%	-0.052	Difference in utility level between relapse and remission
Pneumonia	3.7%	4.8%	-0.100	Assumption
Granulomatosis with polyangiitis	0.6%	3.0%	-0.052	Difference in utility level between relapse and remission
Weighted utility decrement per cycle	**-0.0103**	**-0.0101**		
Based on electronic model as supplied by the company after clarification AE: adverse event; GC: glucocorticoid ; SoC: standard of care				

Overall, the ERG considers that given the uncertainties around how well AEs are captured and ensuring sufficient sample sizes to estimate reliable health state utility values, it would be preferable to use either non-treatment specific AEs in the model base-case and include separate disutilities for AEs observed in the ADVOCATE trial or CPRD estimates of AEs. The former option has the advantage of including more than just the typical GC-related AEs, whereas the latter has the benefit of being based on a much

longer observation period. In the ERG base case, the non-treatment specific AEs will be used, and the CPRD estimates for AEs will be explored in a scenario analysis.

4.2.8 Resources and costs

The following cost categories were included in the model: drug acquisition costs, drug administration costs for intravenously administered drugs, disease monitoring costs, hospitalisation costs, costs of end-stage renal disease (ESRD) and costs of treatment-related adverse events (AEs).

4.2.8.1 Drug acquisition costs

In the induction phase patients received either avacopan at a dose of 30 mg twice daily or prednisone starting at 60 mg daily and tapered to discontinuation by the end of the 6th model cycle. Avacopan and prednisone were both administered orally. The list price of avacopan is [redacted] per 10 mg capsule[redacted]. The price for a pack of 28 tablets of 5 mg prednisone is £1.08.[64] The total costs for avacopan and prednisone were adjusted based on the compliance rates as observed in ADVOCATE, which were 86.4% and 98.4% respectively. Concomitantly, all patients received either rituximab (64.8%) or cyclophosphamide (35.2%) as immunosuppressive treatments, which were both assumed to be administered intravenously (although in ADVOCATE 4.8% of patients treated with avacopan and 3.7% of patients treated with prednisone received oral cyclophosphamide).[8, 23] Rituximab was administered at a dose of 375 mg / m^2 body surface area (BSA) once per week for the first 4 weeks (i.e., in the first model cycle) only, and cyclophosphamide was administered at a dose of 15 mg / kg on days 1, 15, 29, 49, 70 and 91 (i.e., twice in model cycles 1 and 2 each, and once in model cycles 3 and 4 each). It was assumed that only full vials were used for intravenous treatments (i.e., rituximab and cyclophosphamide) to account for drug wastage costs. The price of rituximab is £314.33 for a 100 mg / 10 ml solution and £785.84 for a 500 mg / 50 ml solution, the price of cyclophosphamide is £9.66 per 500 mg and £17.91 per 1,000 mg.[64] Treatment with azathioprine was assumed to start in model cycle 4, with titration up to 2 mg / kg / day over 2 weeks starting from week 15, for patients in both the intervention and comparator arm (i.e., although in ADVOCATE azathioprine was only given to patients who received prior cyclophosphamide and no further treatment was provided to patients who received prior rituximab).[8] In ADVOCATE, the mean BSA was 1.92 m^2 and mean body weight was 77 kg.

In the maintenance phase treatment with avacopan and azathioprine continues until the end of model cycle 13 (i.e., at 52 weeks). For patients who remain in remission after the first year it is assumed that treatment with azathioprine continues for another 18 months (i.e., until the end of model cycle 32) at a dose of 2 mg / kg / day and at a cost £3.78 per model cycle.

After patient's transition to refractory disease, it was assumed they receive treatment with azathioprine for the remainder of the time horizon at a dose of 2 mg/ kg/ day and at a cost of £3.78 per model cycle.

An overview of the unit costs, compliance, and costs per mg for each drug is provided in Table 4.12, and an overview of the drug acquisition costs per model cycle is provided in Table 4.13.

Table 4.12: Drug acquisition unit costs, compliance, and costs per milligram

Drug	Cost per pack	Dosage (pack size)	Compliance	Cost per mg
Avacopan	[redacted]	10 mg (1)	86.4%	[redacted]
Rituximab	£785.84	500 mg/50ml (1)	100.0%	£1.572
	£314.33	100 mg/10ml (2)	100.0%	£1.572

Drug	Cost per pack	Dosage (pack size)	Compliance	Cost per mg
Cyclophosphamide	£9.66	500 mg	100.0%	£0.019
	£17.91	1,000 mg	100.0%	£0.018
Azathioprine	£1.99	25 mg (28)	100.0%	£0.003
	£2.52	50 mg (56)	100.0%	£0.001
Prednisone	£1.08	5 mg (28)	98.4%	£0.008

All costs were sourced from the British National Formulary, except for avacopan.[65]
Based on Table 42 in the CS and the electronic model.[6]
mg = milligram; ml = millilitre.

Table 4.13: Drug acquisition costs per model cycle

Drug	Dose per day	Model cycles	Days per model cycle	Costs per model cycle
Avacopan	2 x 30 mg	1 - 13	28	[redacted]
Rituximab	375 mg / m^2	1	4	£5,029.34
Cyclophosphamide	15 mg / kg	1 - 2	2	£55.14
	15 mg / kg	3 - 4	1	£27.57
Azathioprine	75 – 150 mg (titration up to 2 mg / kg over two weeks)	4	28	£4.19
	150 mg	5 - 13	28	£3.78
Prednisone	5 – 60 mg (starting dose of 60 mg tapered to discontinuation by the end of the 6th model cycle)	1	28	£8.50
		2	28	£4.78
		3	28	£2.66
		4	28	£1.59
		5	28	£1.06
		6	28	£1.06

Based on The electronic model.[6]
kg = kilogram; m^2 = square metre; mg = milligram.

4.2.8.2 Drug administration costs

The cost of intravenous administration of rituximab and cyclophosphamide was assumed to be the same as chemotherapy administration at £406.04 (SB14Z: deliver complex chemotherapy, including prolonged infusional treatment, at first attendance) for the first attendance and £341.30 (SB15Z: deliver subsequent elements of a chemotherapy cycle) for subsequent visits, based on the NHS Reference costs 2019/2020.[66]

4.2.8.3 Disease monitoring costs

The frequencies of resource use associated with disease monitoring were sourced from NICE TA308 and combined with unit costs sourced from the NHS Reference costs 2019/2020.[3, 66] An overview of the health care resources, and frequencies of use is provided in Table 4.14 and an overview of unit costs per health care resource is provided in Table 4.14.

Table 4.14: Monitoring and maintenance costs per model cycle

Health state	Treatment	Monitoring costs per cycle		Follow-up visit costs per cycle	
		Number of tests per 6 months	Cost per cycle	Number of visits per 6 months	Cost per cycle
Induction treatment	CYC-based	22 blood tests	£6.64	13	£336.16
	Non-CYC-based	0	£0.00		
Remission	AZA maintenance	13 blood tests and 12 LFTs	£6.32	2	£51.72
Refractory disease				3	£77.58
ESRD		22 blood tests	£6.64	13	£336.16

Based on Table 44 in the CS and the electronic model.[6]
AZA = azathioprine; CYC = cyclophosphamide; ESRD = end-stage renal disease; LFTs = liver function tests.

ERG comment: The company assumed that the number of blood tests is the same as the total number of blood tests and liver function tests combined from TA308. It is not clear to the ERG whether the assumption of 0 test costs for patients receiving non-cyclophosphamide-based treatments is plausible. However, given the low unit costs of these tests these assumptions are very likely to have a negligible impact on the cost effectiveness results. The assumed frequencies for outpatient visits are in line with the ERG-preferred assumptions in TA308, which were based on clinical expert advice. It is not clear to the ERG to what extent it is plausible to assume that the monitoring costs for ESRD are the same as those during the induction phase. In response to the ERG's request during the clarification phase, the costs of X-rays and CT scans were included in line with TA308. A frequency of 4 scans per 6 months was assumed in all health states except Remission (i.e., no scans assumed), assuming 80% of scans were X-rays and 20% CT-scans, at a cost of £22.16 (sourced from the ERG report for TA308 and inflated to 2019/2020 using the NHS Cost Inflation Index (NHSCII) from the Personal Social Services Research Unit (PSSRU) 2020) per X-ray and £77.31 (NHS Reference Costs 2019/20: RD20A Computerised Tomography Scan of One Area, without Contrast, 19 years and over, weighted average) per CT-scan.

4.2.8.4 Hospitalisation costs

The costs of inpatient hospital treatments were included to account for AAV relapse and treatment-related AEs, based on data from ADVOCATE. The mean number of hospitalisations over the 52-week follow-up period was 0.47 in the avacopan arm and 0.68 in the prednisone arm, and the mean length of stay was 13.80 days in the avacopan arm and 19.60 in the prednisone arm. The unit cost of hospitalisation was estimated as the weighted average cost of elective inpatient admissions and non-elective long stays for HRG codes DZ29G - DZ29J in the NHS Reference costs 2019/2020 and it was assumed that these costs represented the mean length of stay as provided in the NHS Reference costs 2017/2018. Since the mean lengths of stay in ADVOCATE were longer than the mean length of stay in

the NHS Reference costs 2017/2018, the weighted average costs of excess bed days, as provided in the NHS Reference costs 2017/2018, were applied to the additional number of days.

ERG comment: The ERG has concerns about the validity of the approach used for the costing of hospitalisations, in particular regarding the application of the 2017/2018 cost for excess bed days to the differences between the mean length of stay in the NHS Reference costs 2017/2018 and the lengths of stay in the data from ADVOCATE. Firstly, it is not clear that a difference in length of stay should imply an excess bed day at all. Secondly, the most recent 2019/2020 version of the NHS Reference costs no longer includes the cost of an excess bed day. This suggest a difference in the way the unit costs were calculated between the 2017/2018 version and the 2019/2020 version of the NHS Reference cost. Thirdly, the unit cost for all but Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, with Interventions (i.e., for Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with CC Score 5+; Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with CC Score 2-4; and Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with CC Score 0-1) decreased substantially. This might suggest that care is given in a different way and that the excess bed day rate from the earlier period might not be applicable. Therefore, the ERG prefers to only use the most recent (i.e., 2019/2020) unit costs with no adjustment for excess bed days. This change increased the ICER by about £5,000 when applied in isolation of other ERG changes.

4.2.8.5 End-stage renal disease costs

The costs for the treatment of ESRD were sourced from Kent et al., 2015 and inflated to the cost year 2019/2020 using the NHSCII from PSSRU 2020.[67, 68] This resulted in cost estimates of £27,038 for the annual cost of maintenance dialysis (i.e., initiated in a previous year), and £28,517 and £1,331 for the annual costs of a renal transplant in the first year and subsequent years respectively. The proportions of patients with ESRD receiving peritoneal dialysis, haemodialysis or a renal transplant were sourced from the revised company submission for NICE TA623,[57] and were 20.5%, 69.8% and 9.7%, respectively.

ERG comment: The ERG agrees that the costs and probabilities for receiving treatments for ESRD were sourced appropriately. However, the ERG notes that the first-year cost of maintenance dialysis in Kent et al. is substantially lower than the cost in subsequent years. The consequence of not taking this difference into account is a slight overestimation of the costs of ESRD treatments that is in favour of the intervention (i.e., it leads to a lower ICER than if the difference had been taken into account). Different costs for maintenance dialysis in the first and subsequent years could be implemented in a similar way as for the differentiation between the costs in the first year and subsequent years for renal transplants, but substantial changes to the structure of the model (e.g., an additional 13 tunnel states for patients with ESRD receiving dialysis in the first year) would be required for this. Therefore, this change has not been implemented by the ERG.

4.2.8.6 Adverse event costs

In the company's base-case analysis, the costs of treatment-related AEs were assumed to be included in the hospitalisation costs that were based on data (i.e., the mean number of hospitalisations and the mean lengths of stay) from ADVOCATE as described in Section 4.2.8.3 above. The model also includes the option to disable the inclusion of hospitalisation costs based on ADVOCATE, and to use cost estimates for AEs either based on the incidence of AEs in ADVOCATE in combination with the corresponding costs of treatment (i.e., as provided in Table 36 of the CS) or based on the incidence of AEs in the CPRD database and corresponding costs of treatment.[6]

The following AEs were identified based on the CPRD database: infections, cardiovascular (CV) events (i.e., coronary heart disease, stroke, and hypertension), bone disease and ocular disease.

For infections the number of events for each type of infection in the CPRD database and corresponding costs are provided in Table 49 of the CS. The number of events as provided in Table 49 of the CS corresponds to the events in the overall AAV population, whilst the model uses those in the incident AAV population.[6] Therefore, a corrected version of Table 49 in the CS is provided below as Table 4.15. For infections, a weighted average (by type of infection) cost was estimated of £1,319.95.

Table 4.15: Cost of infections (corrected version of Table 49 in the CS)

Infection type	Number of events in CPRD	Costs	
		Unit cost	Currency code and description in NHS Reference costs[64]
Upper respiratory infection	[redacted]	£1,214	Weighted average Unspecified Acute Lower Respiratory Infection with Interventions: DZ22K-Q Total HRG*
Lower respiratory infection	[redacted]		
Gastrointestinal infection	[redacted]	£1,366	Weighted average Gastrointestinal Infections with Multiple Interventions: FD01A-J Total HRG
Skin/wound infection	[redacted]	£1,479	Weighted average Skin Disorders without Interventions: JD07A-K Total HRG
Urinary infection	[redacted]	£1,725	Weighted average Kidney or Urinary Tract Infections, with Interventions: LA04H-S Total HRG

*The cost of upper respiratory infection is assumed to be the same as the cost for lower respiratory infection.
Based on Table 49 in the CS and the electronic model.[6]
CPRD = clinical practice research datalink; HRG = healthcare resource group.

For cardiovascular events, the weighted average (by proportion of patients with coronary heart disease, stroke, and hypertension) annual costs of £3,962.16 in the first year and £1,818.86 in subsequent years were estimated using the proportions as provided in Table 50 of the CS and the costs as provided in Table 51 of the CS.[6]

For bone disease, the annual costs of osteoporotic fractures were estimated per age group, for the first and subsequent years after a fracture, as provided in Table 54 of the CS. These were based on the distribution of fracture types (i.e., as provided in Table 52 of the CS) and unit costs (i.e., as provided in Table 53 of the CS) that were sourced from NICE TA 464, and the age-adjusted annual risk of fracture estimated using the QFracture risk calculator.[6, 62, 69]

For ocular disease, a weighted average (by setting and type of procedure) cost of £919.03 was estimated using the same approach as in NICE Guideline NG77 assuming phacoemulsification surgery as the standard approach for cataract surgery.[70] The inputs used for this are provided in Table 55 of the CS.[6]

ERG comment: During the clarification phase, the ERG requested the company to justify the assumption that all relevant costs for the treatment of all adverse events were captured by including hospitalisations data from ADVOCATE. The company responded by noting that given the seriousness of the included AEs it was highly likely that their management and treatment required hospital attendance and that many AEs were identified and treated during hospital attendance for routine treatment monitoring. As such, the company argued that any costs resulting from AEs other than during hospital attendance were likely to be negligible. Furthermore, the company noted that the results would likely be biased against avacopan if all relevant costs were not captured by hospitalisations since the majority of AEs was more frequent in patients treated with GCs. According to the ERG, the assumption that hospitalisations captured all relevant costs resulting from AEs was in contrast with the results from analyses where AE costs were based on either AE data from ADVOCATE or the CPRD. The latter indicated substantially higher ICERs than when AE costs were assumed to be included in the hospitalisations data. However, the ERG notes that hospitalisations from ADVOCATE could have been either due to relapse or due to AEs. When the costs of hospitalisations were excluded and AEs costed separately (i.e., using AE data either from ADVOCATE or the CPRD), the resulting increase in the ICER could (at least in part) be explained by the fact that the costs of hospitalisations due to relapse (i.e., which occur more often in patients treated with GCs) were no longer included. The ERG retained the assumption that all relevant AE costs were captured in hospitalisation costs and performed scenario analyses assuming AE costs based on data from ADVOCATE and the CPRD.

The ERG noted an inconsistency in the calculation of the annual hip fracture risk. The model contains annual risks of fracture estimated using QFracture separately for hip fractures only and for the combination of hip, wrist, shoulder, and spine fractures. In addition, the model contains estimates for the distribution of the different fracture types for all people with fractures. Although the annual risk of hip fracture was calculated directly using QFracture, this risk was subsequently multiplied by the proportion of hip fractures in all people with fractures. This is incorrect, since the annual risk of hip fracture can be used as such (i.e., no further multiplication with the proportion of hip fractures is necessary). For the annual risk of shoulder fractures, an error was made because of multiplying the risk of a hip fracture (i.e., instead of the combination of hip, wrist, shoulder, and spine fractures) with the proportion of shoulder fractures. After this was corrected by the ERG, the impact on the results (i.e., when the CPRD data is used as the source of AEs) was negligible.

4.2.8.7 ERG comment on annual total health care costs in the model:

During the clarification phase, the ERG requested the company to comment on the comparability of the annual total health care costs as estimated in the CPRD study, fluctuating around £25,000, and those included in the current analysis. The company responded by referring to a crude estimate of annual total costs for CYC/RTX+GC of approximately £13,400 in the model, calculated using the modelled costs over a 10-year horizon with discount rates set to 0% divided by the accrued patient life-years. As such, the modelled annual costs are considerably lower than the cost estimates from the CPRD study. The company explained the lack of comparability between the two estimates as a consequence from ADVOCATE being an international, multi-centre trial where levels of resource use may not be equivalent between countries, where in- and exclusion criteria where used that may lead to differences between the study populations, and where the clinical trial context may have also led to differences in resource use in comparison to the CPRD data. Moreover, the CPRD data were considered as unsuitable

for use in the cost effectiveness model for avacopan since they did not provide information on changes in resource use that result from treatment with avacopan and could not be stratified according to disease state to inform health state costs in the model. The company furthermore argues that since the impact of avacopan treatment is to help sustain AAV remission, the use of higher estimates of resource use would likely have favoured avacopan. Although the ERG does not argue against the company's adopted approach, they do note that the mismatch between the modelled costs and those from the CPRD data could be indicative of the modelled costs not being fully representative for the costs of AAV treatment in UK clinical practice.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

Table 5.1 shows the company's deterministic base-case results. Total costs associated with AVA + CYC/RTX were estimated at [redacted] and total costs associated with CYC/RTX + GC were estimated at [redacted], indicating that AVA + CYC/RTX increases total costs by [redacted]. Total QALYs associated with AVA + CYC/RTX were estimated at [redacted] and total QALYs associated with CYC/RTX + GC were estimated at [redacted], indicating an incremental number of [redacted] QALYs gained with AVA + CYC/RTX. This gives an incremental cost effectiveness ratio (ICER) for AVA + CYC/RTX versus CYC/RTX + GC of [redacted] per QALY gained. The disaggregated results are shown in Table 5.2.

Table 5.1: Company base-case deterministic cost effectiveness results, original submission

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
AVA + CYC/RTX	£[redacted]	[redacted]	[redacted]				
CYC/RTX + GC	£124,679	9.30	6.07	[redacted]	[redacted]	[redacted]	£18,537

Based on: Table 59 in CS.[6]
AVA = avacopan; CYC = cyclophosphamide; GC = glucocorticoid; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years; RTX = rituximab.

Table 5.2: Disaggregated base-case results

Outcomes	AVA + CYC/RTX	CYC/RTX + GC	Increment
Costs			
Drug costs	[redacted]	[redacted]	[redacted]
Resource use*	[redacted]	[redacted]	[redacted]
ESRD	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Health outcomes			
Life year	[redacted]	9.30	[redacted]
QALYs	[redacted]	6.07	[redacted]

*Cost of treatment of AEs included in resource use category in the model base case
Based on Table 60 of the CS.[6]
AVA = avacopan; CYC = cyclophosphamide; ESRD = end-stage renal disease; GC = glucocorticoid; QALY = quality-adjusted life year; RTX = rituximab

After clarification, the company provided an updated version of the model with slightly different results due to the addition of monitoring costs for X-rays and CT scans, the ICER decreased by £45. These are provided in Table 5.3 below.

Table 5.3: Company base-case deterministic cost effectiveness results, after clarification (discounted)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
AVA + CYC/RTX	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	18,492

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CYC/RTX + GC	£[redacted]	[redacted]	[redacted]				
Based on the company preferred version of the electronic model as provided alongside their clarification response. AVA = avacopan; CYC = cyclophosphamide; GC = glucocorticoid; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years; RTX = rituximab.							

5.2 Company's sensitivity and scenario analyses

5.2.1 Probabilistic sensitivity analysis

A PSA of 5,000 runs was conducted using the probability distributions shown in Table 56 of the CS.[6] Results of the PSA in Table 5.4 below show that probabilistic results are well aligned with the deterministic base-case. The cost effectiveness plane in Figure 5.1 shows that the vast majority of the simulations fell in the north-east quadrant. Based on the cost effectiveness acceptability curve in Figure 5.2, the probability that avacopan is cost-effective at thresholds of £20,000 and £30,000 per QALY gained is 55% and 80% using the company base-case assumptions.

Table 5.4: Company base-case probabilistic cost effectiveness results (PAS price for romosozumab)

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
AVA + CYC/RTX	[redacted]	[redacted]			
CYC/RTX + GC	£125,774	6.09	[redacted]	[redacted]	£18,909
Based on Table 61 of the CS[6] AVA = avacopan; CYC = cyclophosphamide; GC = glucocorticoid; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; RTX = rituximab					

Figure 5.1: Probabilistic sensitivity analysis cost effectiveness plane

Based on Figure 15 of the CS.[6]

AVA = avacopan; CYC = cyclophosphamide; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; RTX = rituximab

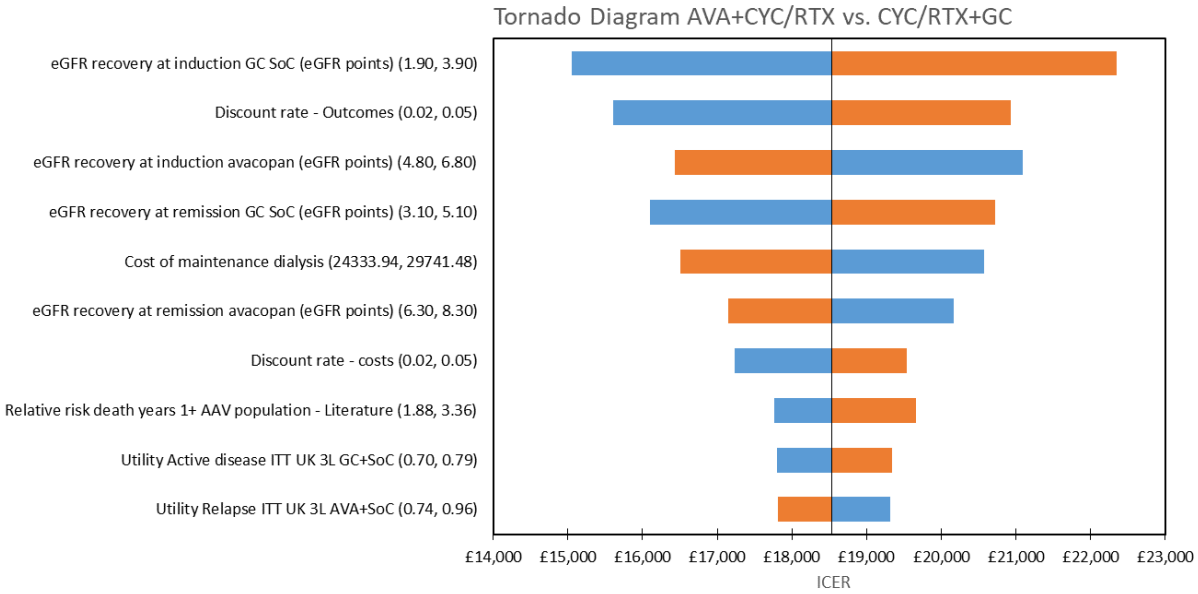
Figure 5.2: Probabilistic sensitivity analysis cost effectiveness acceptability curve

Based on Figure 16 of the CS.[6]
AVA = avacopan; CYC = cyclophosphamide; GC = glucocorticoid; RTX = rituximab

5.2.2 Deterministic sensitivity analysis

The results of the company's DSA are displayed in Figure 5.3. Parameters relating to eGFR recovery at induction and remission in both treatment groups had the largest impact on the ICER. Cost of maintenance dialysis, as the main cost component of ESRD, also had a substantial impact on results.

Figure 5.3: Tornado diagram



Based on Figure 17 of the CS.[6]
AAV = Anti-neutrophil cytoplasmic autoantibody–associated vasculitis; AVA = avacopan; CYC = cyclophosphamide; eGFR = Estimated glomerular filtration rate; GC = glucocorticoid; ITT = intention to treat; RTX = rituximab; SoC = standard of care

5.2.3 Scenario analyses

Company scenario analysis results are presented in Table 5.5. The rationale for each scenario is outlined in Table 62 of the CS. Outside of reducing the time horizon, the scenario with the largest impact on results is testing the alternative source of HR for the effect of eGFR decrease on the probability of ESRD, which increases the assumed HR from 0.9 to 0.96. This scenario increased the ICER to £31,655 per QALY gained. In all other scenarios (except the one which reduced the time horizon to 5-years) the ICER remained below £30,000.

Table 5.5: Scenario analysis results

Scenario	Assumption	Incr. costs	Incr. QALYs	ICER
Base-case		[redacted]	[redacted]	£18,537
Time horizon	5 years	[redacted]	[redacted]	£75,316
	10 years	[redacted]	[redacted]	£28,214
	20 years	[redacted]	[redacted]	£18,833
Discount rate	1.5%	[redacted]	[redacted]	£14,508
	5.0%	[redacted]	[redacted]	£22,057
Number of induction courses	1	[redacted]	[redacted]	£24,797
	2	[redacted]	[redacted]	£21,414
No. of reinductions with avacopan	1	[redacted]	[redacted]	£17,698
	2	[redacted]	[redacted]	£19,194
Treatment effect after avacopan discontinuation	No treatment effect after 52 weeks	[redacted]	[redacted]	£19,259
	Waning treatment effect for 6 months	[redacted]	[redacted]	£16,549
GC use alongside avacopan treatment		[redacted]	[redacted]	£18,596
ESRD probability from CPRD		[redacted]	[redacted]	£23,351
eGFR decrease with relapse	5ml/min	[redacted]	[redacted]	£24,869
	20 ml/min	[redacted]	[redacted]	£12,534
Effect of eGFR decrease on probability of ESRD	HR 0.96	[redacted]	[redacted]	£31,655
Hospitalisation data from ADVOCATE	Not included	[redacted]	[redacted]	£24,433
Health state utility values	Not treatment-specific	[redacted]	[redacted]	£19,559

Based on Table 63 of the CS[6]

AVA = avacopan; CYC = cyclophosphamide; ESRD = end-stage renal disease; GC = glucocorticoid; QALY = quality-adjusted life year; RTX = rituximab

5.2.4 Subgroup analysis

The following pre-specified subgroups in the ADVOCATE trial were included in the model:

- Newly diagnosed AAV
- Relapsed AAV

- GPA
- MPA
- RTX background therapy
- CYC background therapy
- MPO positive
- PR3 positive

Subgroup analyses were informed by remission data at week 26 and week 52 reported in Table 24 of the CS and EQ-5D-5L subgroup data from the ADVOCATE trial.[6] All other clinical inputs were assumed to be the same as in the base-case, based on the ADVOCATE ITT population. The cost of induction treatment was adjusted accordingly in the RTX and CYC subgroups. Subgroup analysis results are displayed in Table 5.6.

Table 5.6: Results of the cost effectiveness analysis within the ADVOCATE subgroups

Subgroup	Incr. Costs	Incr. QALYs	ICER per QALY
Newly diagnosed AAV	[redacted]	[redacted]	£33,537
Relapsed AAV	[redacted]	[redacted]	£15,267
GPA	[redacted]	[redacted]	£51,991
MPA	[redacted]	[redacted]	£467
RTX background therapy	[redacted]	[redacted]	£17,731
CYC background therapy	[redacted]	[redacted]	£25,471
MPO positive	[redacted]	[redacted]	£13,668
PR3 positive	[redacted]	[redacted]	£54,284

Based on Table 64 of the CS.[6]
AAV = Anti-neutrophil cytoplasmic autoantibody–associated vasculitis; CYC = cyclophosphamide; GPA = Granulomatosis with polyangiitis; MPA = Microscopic polyangiitis; MPO = Myeloperoxidase; PR3 = Proteinase 3; RTX = rituximab

5.3 Model validation and face validity check

In Section B.3.10 in the CS, the company's validation of the cost effectiveness analysis is described. This consisted of two parts: internal validation included checks for coding accuracy and consistency in model calculations, a verification process where input parameters are adjusted to detect inconsistent model behaviour, and verification of model functionality; external validation included an assessment of the predictive accuracy of the model by comparing simulated outcomes to observed data. The latter is summarised below.

The company presented the findings of two studies against which the predicted OS in the model was compared. Wallace et al., 2016 studied an observational cohort of 465 patients with GPA in the UK between 2003 and 2013 and Flossman et al., 2011 studied 535 patients with WG or MPA who were recruited at the time of diagnosis to four randomised controlled trials between 1995 and 2002 in 15 countries.[47, 50] According to the company, OS at 1 year in both studies is similar to the model and lower in Flossman et al. for subsequent years than in Wallace et al., and the model. The company note that the difference could be explained by Wallace et al. having recruited patients diagnosed after 2003, with a better prognosis due to improvements in disease management, or being restricted to UK patients with better AAV outcomes and/or lower background mortality compared to countries included in Flossman et al., and therefore Wallace et al. matches the population included in the model

ERG comment: The ERG notes that that there are substantial differences between OS as predicted by the model and as found by Wallace et al. At 1, 2, 5, and 8 years, OS for the RTX+GC arm predicted by the model was approximately 97%, 93%, 83% and 70%, respectively. In Wallace et al., OS at 1, 2, 5, and 8 years was approximately 91%, 90%, 85% and 79%, respectively. In Flossman et al., OS at 1, 2, 5, and 8 years was approximately 88%, 85%, 77% and 70%, respectively. As such, the model appears to overestimate OS in the first two years in comparison to both studies, is roughly in line with Wallace et al. at 5 years and shows the same estimate for OS as in Flossman et al. at 8 years.

Overall, the efforts of the company to assess the validity of their model are rather minimal, by only focusing on overall survival. For example, more effort could have been made to explain the large difference between the modelled costs of AAV versus the yearly costs observed in the CPRD study. The latter issue raises questions to what extent the modelled resource use is reflective of the true resource use in the UK. Also making a comparison of the model-predicted ESRD cases with observed data is relevant, since the model outcomes are quite sensitive to changes in input related to ESRD. This is due to the high costs of dialysis and the large negative impact of dialysis on HRQoL.

The ERG used the model outcomes to estimate the overall ESRD incidence, by dividing the total number of ESDR cases by the number of years at risk of ESDR. The latter is the total number of life years not in ESDR. For the company base case (after clarification), this approach leads to 89 per 1000 patient-years. This is very high compared to the overall CPRD estimated incidence of 23 per 1000 patient-years. If we select a different approach to estimating the transition probability to ESRD (see also section 4.2.6.3), based on CPRD data rather than literature and ADVOCATE data, we find a model-predicted incidence of 39 per 1000 patient-years. The latter is much closer to the observed real-world incidence.

Based on this finding, the ERG decided to use CPRD as data source for the estimation of transition probabilities. For the ERG preferred base case (see Section 6), the model-predicted incidence was 29 per 1000 patient-years, which is very near the observed value of 23.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Meta-analyses undertaken by the ERG

The ERG undertook meta-analysis of two of the trials identified by the company's SLR (see section 3.1).

6.2 Exploratory and sensitivity analyses undertaken by the ERG

6.2.1 Explanation of the company adjustments after the request for clarification

During the clarification phase, the ERG requested the company to make the following amendments to the model:

- Include additional monitoring costs for X-rays and CT-scans in line with TA308. In the updated model, these were included in cells D153:154 and incorporated into the monitoring costs in the "Cost data" sheet.
- Include options for durations of maintenance treatment of 12, 36 and 48 months (i.e., in addition to options for 18 and 24 months). These were included as options from the drop-down menu in cell C27 in the "Model settings" sheet.
- Include option to model RTX (i.e., instead of AZA) as maintenance therapy. This was implemented as an adjustment to the baseline hazard ratio of relapse to reflect an increase in effectiveness relative to AZA, based on a non-adjusted naïve comparison. The option to model RTX as maintenance therapy can be selected from the drop-down menu in cell C32 in the "Model settings" sheet.

6.2.2 Explanation of the ERG adjustments

The changes that the ERG can make (to the model received with the response to the clarification letter) can be subdivided into the following three categories (according to Kaltenthaler et al. 2016[71]):

- Fixing errors (correcting the model where the company's electronic model is unequivocally wrong).
- Fixing violations (correcting the model where the ERG considers that the NICE reference case, scope, or best practice has not been adhered to).
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred).

In the current assessment, four errors were fixed, and four matters of judgement played a role. After the proposed changes were implemented in the company's model, additional scenario analyses were explored by the ERG in order to assess the impact of alternative assumptions on the CE results.

6.2.2.1 Fixing errors

The following errors were corrected by the ERG in the model provided in response to the clarification letter:

- The ERG corrected an error that occurred in the model after clarification that was not present in the original model. In the model after clarification, in the company base-case the costs of only 6 months of maintenance treatment were taken into account. To correct this, the model setting for *Length of treatment* needs to be set to *Induction + 24 months*, rather than *Induction + 6 months.* This correction has a minimal impact on the company base-case.
- The ERG corrected the calculations for the annual risk of hip and shoulder fractures, as described in Section 4.2.8.5 of the ERG report. This did not affect the company's base-case results, and only has a negligible effect when the CPRD data are used as the source of AEs.

- The ERG corrected the per cycle disutility based on observed AEs during the ADVOCATE study. As explained in Section 4.2.7.3, the estimated disutility actually reflects a full year. To correct the error the company's estimate was divided by 13 cycles. This does not affect the company's base-case as these disutilities are only applied when treatment independent health state utilities are used.
- The ERG noted that when CPRD data is used for the AEs, the QALYs accumulated in the AVA-RTX group differed from those in the AVA-CYC group, whilst these should be the same. Tracking the cause of this difference, the ERG found that the formulae for new patients having a GC-related AE allowed all ESRD patients (new, dialysis, and transplant) to have such event for the AVA-CYC group but only new ESRD patients for the AVA-RTX, CYC-GC and RTX-GC groups. The ERG has assumed the approach for AVA-CYC was correct and has made the appropriate changes on the relevant Engine worksheets. In Appendix 1, the ERG shows the exact position of the error, plus a few other discrepancies between the formulae that were compared. Note that this error has no impact on the company base-case, as in the base-case the impact of AEs was based on treatment specific health state utility values from the ADVOCATE study.

6.2.2.2 Fixing violations

No violations were applicable to this appraisal.

6.2.2.3 Matters of judgement

The ERG's preferences regarding alternative assumptions led to the following changes to the company base-case analysis:

- The ERG prefers to use the most recent (i.e., 2019/2020) unit cost for hospitalisation, with no adjustment for excess bed days, as described in Section 4.2.8.3 of the ERG report. This change increased the ICER by about £5,000 when applied in isolation of other ERG changes.
- The ERG prefers to use the CPRD data for the estimation of the probability of ESRD. (See Section 4.2.6.3)
- A hazard ratio of developing ESRD per unit change in eGFR was used to adjust the probability of developing ESRD for avacopan patients (higher eGFR than comparator) and after a relapse (decrease in eGFR). The ERG prefers to use a pooled estimate (0.955) based on three similar studies identified by the company, rather than selecting one of these studies for the base-case (0.90).
- The relative risk of mortality for patients with ESRD is changed from 10.3 to 6.6. (See Section 4.2.6.4).
- Health state utilities not treatment specific, with disutility for AEs during the ADVOCATE study. (See Sections 4.2.7.1 and 4.2.7.3).

The overview of the changes and the bookmarks for the justification of the ERG changes are presented in Table 6.1.

Table 6.1: Company and ERG base-case preferred assumptions

Base-case preferred assumptions	Company	ERG	Justification for change
Hospitalisation costs	Include excess bed days	Exclude excess bed days	Section 4.2.8.3
Data source risk of ESRD	Literature and ADVOCATE	CPRD	Section 4.2.6.3

Base-case preferred assumptions	Company	ERG	Justification for change
Hazard ratio of developing ESRD per unit change in eGFR	0.90	0.955	Section 4.2.6.3
Relative risk of mortality for patients with ESRD	10.3	6.6	Section 4.2.6.4
Health state utilities	Treatment specific	Treatment independent	Section 4.2.7.1 and 4.2.7.3
ERG = evidence review group; ESRD = end-stage renal disease; eGFR = estimated glomerular filtration rate			

6.2.3 Additional scenarios conducted by the ERG

The ERG conducted a series of scenario analyses to explore the impact of key assumptions and uncertainties within the CE analyses.

6.2.3.1 Scenario 1: CPRD source for AE

The ERG performed scenario analyses using the CPRD data to estimate the impact of GC-related AEs on costs and HRQoL. In Section 4.2.7.3 it was discussed that including only AE as they occurred in the ADVOCATE study might lead to missing important AE as they occur after a longer observation period. The drawback though is that only GC-related AEs are included in this scenario.

6.2.3.2 Scenario 2: Maintenance treatment with rituximab

According to the BSR/BHPR guidelines RTX is an option for maintenance treatment.[72] After clarification the company provided the option in the model to explore the impact of RTX, though with the warning that the adjusted relapse rate was based on a non-adjusted naïve comparison and the conclusions of this exploratory analysis should be treated with caution due to the high uncertainty associated with this approach.

6.2.3.3 Scenario 3: Source for mortality data CPRD

Whilst the company base-case uses literature estimates for the relative risk of mortality in AAV, the CPRD study also provided these relative risks. For the first year in the model as for the subsequent years is the CPRD-based relative risk somewhat higher than the literature derived relative risks. In this scenario we will explore the impact of these alternative values.

6.2.3.4 Scenario 4: Literature and ADVOCATE as source for transition to ESRD

As discussed in Section 4.2.6.3, the company explored two different approaches to estimate the probability to transition the ESRD. Both these approaches have merit but lead to very different results. When the transition probabilities are based on literature and ADVOCATE, they are about six times higher than when they are based on CPRD data. In this scenario we will explore the impact of this difference on the ICER. In doing this, the ERG prefers to use a pooled estimate (0.955) for the hazard ratio of developing ESRD based on three similar studies identified by the company, rather than using the one study favoured by the company (0.90). (See Section 4.2.6.3).

6.2.3.5 Scenario 5: Varying the duration of avacopan maintenance

In the clarification letter the ERG queried if it might be possible that in clinical practice avacopan will be given for longer than a year. The company indicated that there is no data to inform the effectiveness of avacopan treatment beyond the 52-week data from ADVOCATE and that clinicians may thus be cautious about extending the duration of use of avacopan. However, they did consider it possible that

some patients may continue avacopan maintenance treatment beyond 52 weeks if the treatment is still effective and tolerated. To facilitate exploratory analyses about prolonged maintenance with avacopan, the company added options for longer periods of maintenance treatment, with efficacy based on the data between 26 and 52 weeks in the ADVOCATE study.

6.3 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.3.1 Results of the ERG preferred base-case scenario

The ERG preferred base-case incremental cost effectiveness results, provided in Table 6.2, indicate that the ICER, compared to the company base-case, has substantially increased. The company BC ICER after clarification amounted to £18,492, whereas the ICER for the ERG preferred base-case is £102,973.

Table 6.2: ERG base-case deterministic cost effectiveness results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
AVA + CYC/RTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	102,973
CYC/RTX + GC	[redacted]	[redacted]	[redacted]				

Based on the ERG preferred version of the electronic model.
AVA = avacopan; CYC = cyclophosphamide; GC = glucocorticoid; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years; RTX = rituximab.

Results of the PSA in Table 6.3 below show that probabilistic results are well aligned with the deterministic base-case. The cost effectiveness plane in Figure 6.1 shows that the vast majority of the simulations fell in the north-east quadrant. Based on the cost effectiveness acceptability curve in Figure 6.2, the probability that avacopan is cost effective at thresholds of £20,000 and £30,000 per QALY gained is 0% using the ERG base-case assumptions.

Table 6.3: ERG base-case probabilistic cost effectiveness results (discounted)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
AVA + CYC/RTX	[redacted]	[redacted]	[redacted]	[redacted]	103,279
CYC/RTX + GC	[redacted]	[redacted]			

Figure 6.1: Probabilistic sensitivity analysis cost effectiveness plane – ERG base-case

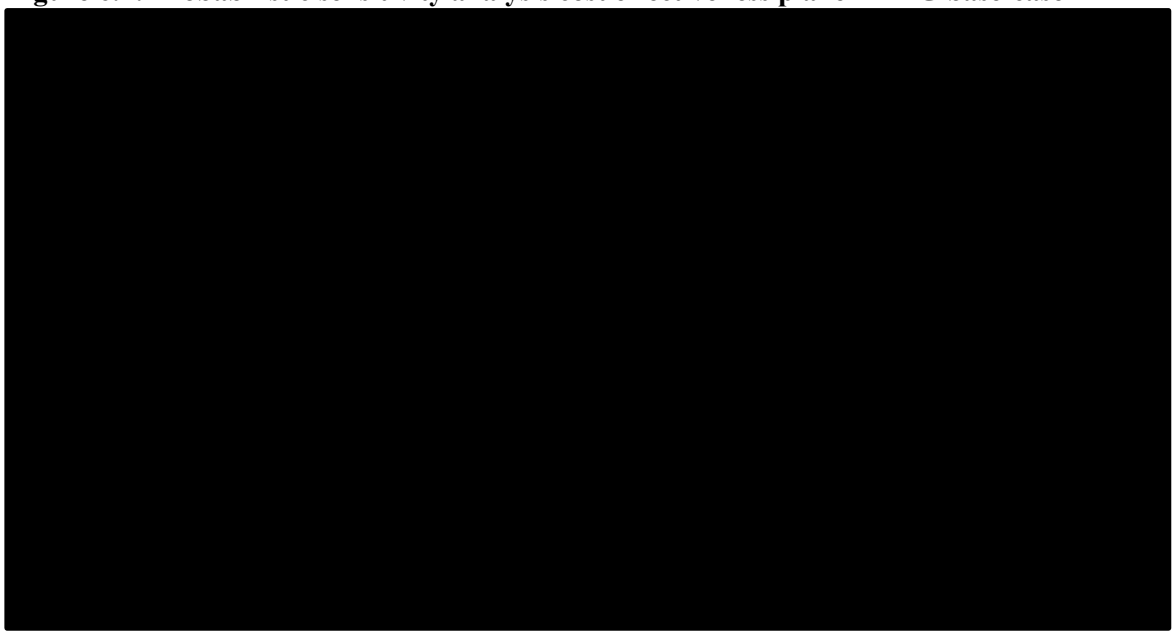
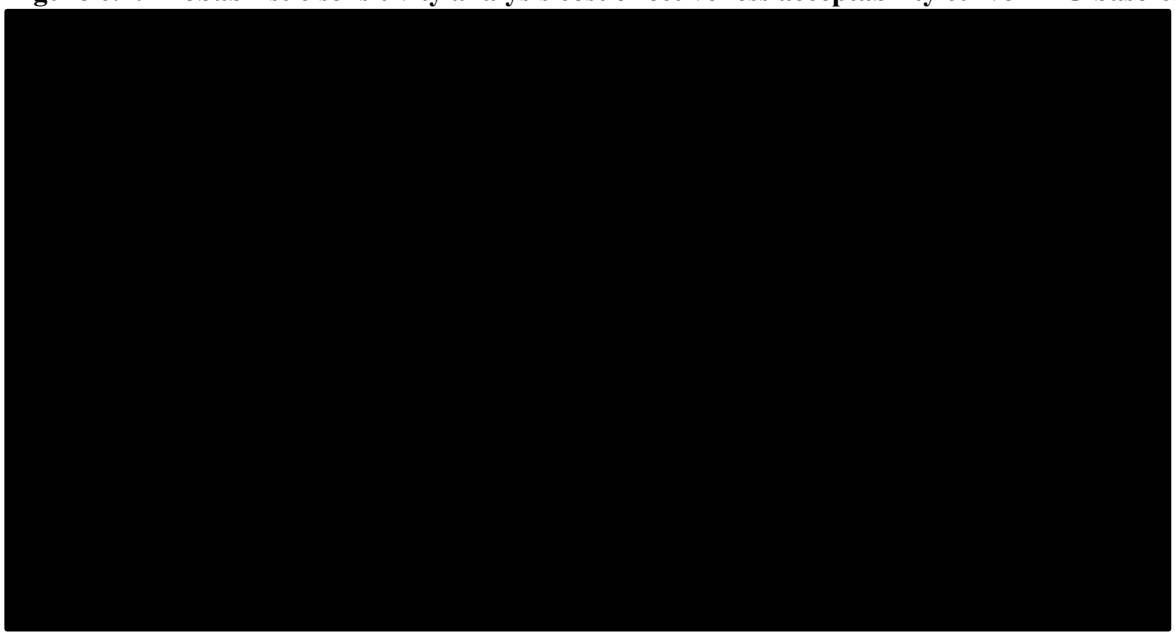


Figure 6.2: Probabilistic sensitivity analysis cost effectiveness acceptability curve ERG base-case



6.3.2 Results of the ERG additional exploratory scenario analyses

The results of the scenario analyses are provided in Table 6.4. Using CPRD as source for the AE has little impact on the ICER.

We see that the explorative analysis when RTX is given during the maintenance phase leads to a much higher ICER. As expected, the accumulated QALYs increase whilst costs decrease, however, the incremental costs increase whilst the incremental QALYs decrease. However, as remarked earlier, this result should be regarded as highly uncertain.

When the mortality rate in based on CPRD data instead of literature, leading to smaller mortality rates, the ICER decreases to about £85,000.

The scenario in which the probability of transitioning to ESRD is based on literature and ADVOCATE rather than CPRD data leads to much lower ICER of almost £40,000 per QALY gained. With the alternative approach much higher transition probabilities are estimated, giving avacopan more scope to reduce the number of patients transitioning.

Finally, the analyses in which longer periods of avacopan maintenance were explored show that up until 24 months of avacopan maintenance treatment the ICER changes little. For longer durations the ICER increases significantly, which can be explained by the relapse probabilities becoming smaller after 2 years of treatment, leaving less scope for avacopan to improve HRQoL and save non-drug costs.

Table 6.4: Results of exploratory scenario analyses by the ERG

Scenario	AVA + CYC/RTX		CYC/RTX + GC		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
ERG BC (including all ERG changes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	102,973
Sc1: AE source CPRD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	110,568
Sc2: Maintenance treatment RTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	138,744
Sc3: Mortality source CPRD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	83,938
Sc4: Transition to ESRD source Literature + ADVOCATE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	38,906
Sc5a: Duration avacopan maintenance 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	111,899
Sc5b: Duration avacopan maintenance 18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	109,210
Sc5c: Duration avacopan maintenance 24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	126,817
Sc5c: Duration avacopan maintenance 36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	154,587
Sc5c: Duration avacopan maintenance 48 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	177,119

Based on the ERG preferred version of the electronic model.[6]
AVA = avacopan; CYC = cyclophosphamide; GC = glucocorticoid; Incr. = incremental; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years; RTX = rituximab; HSUV = health state utility values;
CPRD = Clinical Practise Research Datalink; ESRD = end-stage renal disease.

6.3.3 Subgroup analysis

The ERG repeated the subgroup analyses that were presented for the company base-case in Section 5.2.4 (see Table 6.5).

Table 6.5: Results of the cost effectiveness analysis within the ADVOCATE subgroups

Subgroup	Incr. Costs	Incr. QALYs	ICER per QALY
ERG Base-case	[redacted]	[redacted]	£102,973
Newly diagnosed AAV	[redacted]	[redacted]	£150,267
Relapsed AAV	[redacted]	[redacted]	£72,630
GPA	[redacted]	[redacted]	£152,054
MPA	[redacted]	[redacted]	£63,653
RTX background therapy	[redacted]	[redacted]	£97,092
CYC background therapy	[redacted]	[redacted]	£133,900
MPO positive	[redacted]	[redacted]	£90,955
PR3 positive	[redacted]	[redacted]	£159,836

Based on Table 64 of the CS.[6]
AAV = Anti-neutrophil cytoplasmic autoantibody–associated vasculitis; CYC = cyclophosphamide; GPA = Granulomatosis with polyangiitis; MPA = Microscopic polyangiitis; MPO = Myeloperoxidase; PR3 = Proteinase 3; RTX = rituximab

6.4 ERG preferred assumptions

Table 6.6 shows the step-by-step changes made by the ERG to the company base-case. The change with by far the largest impact on the results was changing the source for the transition probabilities from literature and ADVOCATE to CPRD. This change leads to increase of the ICER to over £50,000. Also important is the use of a hazard ratio based on pooling three studies, with an ICER of around £30,000. The impact of changing to hospitalisation costs is much smaller but still substantial, with an increase in ICER of around 25%. The change in the relative risk for mortality due to ESRD actually lowers the ICER by 25%, both through a reduction in incremental costs and a decrease in the number of QALYs gained.

Table 6.6: Incremental impact of ERG preferred assumptions

Preferred assumption	AVA + CYC/RTX		CYC/RTX + GC		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
Company base-case (original)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,537
Company base-case (after clarification)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,492
Company base-case (errors corrected by ERG)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,513
Corrected Company BC + ESRD HR for	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,174

Preferred assumption	AVA + CYC/RTX		CYC/RTX + GC		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
mortality of 6.6							
Corrected Company BC + Exclude excess bed days for hospitalisation costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,519
Corrected Company BC + CPRD as source for ESRD transition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,746
Corrected Company BC + HR eGFR based on pooled estimate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,519
Corrected Company BC + treatment independent HSUV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,537
ERG BC (including all ERG changes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	102,973

Based on the ERG preferred version of the electronic model[6]
AVA = avacopan; CYC = cyclophosphamide; GC = glucocorticoid; Incr. = incremental; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years; RTX = rituximab; HSUV = health state utility values

6.5 Conclusions of the cost effectiveness section

An SLR was well conducted by the company, based on suitable eligibility criteria.

The company developed a "de novo" Markov microsimulation model in Microsoft Excel that includes the key elements of the disease pathway in AAV, including remission and relapse of AAV, ESRD, and complications of GC treatment. The sequential modelling of remission and relapse was done in a similar way as in TA308.[3] The ERG has concerns about the plausibility of assuming that patients enter the state of refractory disease once they had their first relapse and failed to reach remission after a second induction course, as well as for assuming that patients enter the state of refractory disease for patients who fail to reach remission after having received a third induction course upon their second relapse (but having reached remission following induction after their first remission). The cost effectiveness analysis was performed in line with the NICE Reference case in terms of perspective, time horizon and discounting.[38]

The population in the final scope by NICE is defined as "People with newly diagnosed or relapsed anti-neutrophil cytoplasmic autoantibody-associated vasculitis".[7] However, in line with the population that avacopan was studied in and the EMA's recommendation to grant marketing authorisation, avacopan is only indicated for use in adult patients with severe, active GPA or MPA. As such, the population used to address the decision problem in the CS is narrower than as defined in the NICE final scope. Based on the details provided by the company, the ADVOCATE ITT population seems generalisable to the UK population.

The modelled intervention (avacopan + SoC) consisted of avacopan in combination with RTX or CYC during the induction phase (i.e., the first 6 months), followed by another 6 months of avacopan in combination with 2 years of AZA during the maintenance phase. The modelled comparator (GC + SoC) consisted of RTX or CYC during the induction phase, followed by AZA during the maintenance phase. After the maintenance phase, for both treatment arms it was assumed that all patients in remission continued to receive AZA.

In the model, the relapse rates were calculated based on the numbers of patients in remission at 26, 52 and 60 weeks from ADVOCATE. A 3-month duration of treatment waning once treatment is discontinued was assumed. It was assumed that relapse rates after 2 years are one fifth of those in the preceding time period, based on data from the CPRD study. The ERG considers these assumptions as appropriate. The per cycle probabilities of transitioning from active disease/relapse to remission for either induction with avacopan + SoC or GC + SoC were estimated from the proportions of patients in ADVOCATE in remission at 26 weeks. This approach assumed a constant hazard over the 26 weeks. These transition probabilities were assumed to apply to transitions from both the active disease state and the relapsed states to remission, for both the intervention and comparator. Based on data on the proportions of patients in remission at 26 and 52 weeks from ADVOCATE stratified by subgroups, it seems that the differences in remission between the two treatments arms in the ITT population are primarily driven by the difference in proportions for relapsed patients. In contrast, the differences in remission between treatment arms for newly diagnosed patients are relatively small. This undermines the company's assumption that remission rates are the same for patients in the active disease and relapsed disease health states. On the other hand, the group of patients in active disease is a mixture of newly diagnosed AAV and relapsed AAV. For the latter group the assumption of remission rates that are equal to those for patients who relapse later in the model might be reasonable. The company also assumed that remission rates were the same for patients receiving induction therapy and maintenance therapy, and similarly, that remission rates were the same for all patients regardless of the number of prior relapses and time since the last relapse. None of these assumptions were informed by empirical evidence, nor by clinical expert opinion. It was assumed that remission rates are constant over time, which, according to the ERG, was a potential over-simplification and, in absence of results using other possible approaches, it was not possible to assess what impact the adopted approach had on the results.

The model includes transition probabilities to ESRD from active disease/relapse, remission, and refractory disease. These transitions can be based on two sources: the literature in combination with ADVOCATE or CPRD. In the first approach, the probability of relapse was adjusted to reflect renal outcomes in AAV based on eGFR data from the ADVOCATE trial, the association between eGFR and the probability of ESRD reported in the literature, and assumptions supported by clinical experts. The hazard ratio of developing ESRD was updated by the ERG to reflect the availability of multiple studies for this input parameter.

With the CPRD data estimates of transitioning to ESRD were made for different levels of GC use. These levels were then used as proxies for the health state of the patient, i.e. high GC use for active disease, relapse, and refractory disease and no GC for remission.

The transitions derived using literature and ADVOCATE data yielded transition probabilities about six times higher than when they are based on the CPRD study. Comparison of the model-predicted overall incidence of ESRD to the CPRD reported overall incidence clearly showed that the mapping/proxy approach based on the CPRD date leads to more realistic model estimates with regard to ESRD.

Mortality was split in excess mortality due to patients having AAV and excess mortality due to patients having ESRD. The latter was based on a South Korean study, which the ERG prefers to replace with an estimate from the UK Renal Registry. For the AAV mortality, the company base-case used literature estimates for the relative risk of mortality in AAV. However, the CPRD study also provided these relative risks. Both for the first year in the model as for the subsequent years are the CPRD-based relative risks somewhat higher than the literature derived relative risks.

HRQoL data were collected in ADVOCATE using the EQ-5D-5L.[8]The EQ-5D-5L HRQoL data was converted into UK EQ-5D-3L utilities using the crosswalk algorithm.[53] Health state utility values (HSUVs) were obtained by taking the mean of pooled patient utilities at weeks 4, 26 and 52, stratified by treatment arm and disease state (active disease, remission, and relapse). Separate utilities per treatment arm were included to allow for differences that may emerge, for example due to reduced use of GC and reduced AEs. The starting age of the model cohort was 60 years. Utilities were adjusted for ageing over time using the UK population norms estimated from Ara and Brazier.[54]

The company response to the clarification letter made it clear that the utility estimates for relapse are based on very few observations. This probably explains why for the avacopan + SoC group the utility for relapse is higher than for active disease, whereas for GC + SoC the reverse is true. This suggests that at least for the relapse health state there is not enough data to distinguish between treatments.

The company use treatment specific utilities to allow for differences that may emerge, for example due to reduced use of GC and reduced AEs. Given the EQ-5D's recall period of "today", it is unlikely that the HRQoL impact of all AEs occurred exactly on measurement days a week 4, 26 and 52 and therefore it is unlikely that the impact of AEs is sufficiently captured by using treatment-specific utilities. Given the issue of the recall period, and the small sample sizes, the ERG prefers to use health state utilities that do not vary by treatment, combined with disutilities for observed AEs.

For the base-case, the company has assumed that any impact of adverse events would be captured in the treatment-specific utilities used. However, they included several AEs related to GCs in the model, including infections, cardiovascular disease, renal disease, bone disease, and ocular disease to reflect potential additional benefits of treatment with avacopan, given its potential GC sparing property. Disutilities for those were taken from literature. In addition, the company also provided disutilities for the more frequent SAE from the ADVOCATE study, which can be combined with HSUVs that do not vary with treatment.

Regarding resource use and costs, the model included drug acquisition costs, drug administration costs for intravenously administered drugs, disease monitoring costs, hospitalisation costs, costs of ESRD and costs of treatment-related AEs. The ERG agreed that these costs were appropriately included, except for hospitalisation costs. For this the company used an approach based on the most recent unit costs for hospitalisation in combination with costs for excess bed days that were sourced from an earlier version of the NHS Reference costs (i.e., the most recent version does not include excess bed days).

The ERG did not consider this approach to be appropriate and excluded the excess bed day costs from the model. It was assumed that the costs for all AEs were covered by the hospitalisation costs that were based on data from ADVOCATE, but the model also included the option to use AE incidence rates from ADVOCATE in combination with unit costs for the treatment of each specific AE and to use CPRD data for the costs of AEs related to infections, cardiovascular events, bone disease and ocular disease. A final concern regarding the costs in the model was that these differed substantially from the annual costs as estimated in the CPRD study, with the costs in the model being only about half of those in the CPRD study. This could be indicative of the modelled costs not being fully representative for the costs of AAV treatment in UK clinical practice.

The company's base-case deterministic cost effectiveness results, based on the updated model after clarification, indicated that the total costs associated with AVA + CYC/RTX were [redacted] and the total costs associated with CYC/RTX + GC were [redacted]. As such, AVA + CYC/RTX increases total costs by [redacted]. Total QALYs associated with AVA + CYC/RTX were estimated at [redacted] and total QALYs associated with CYC/RTX + GC were estimated at [redacted], indicating an incremental number of [redacted] QALYs gained with AVA + CYC/RTX. This gives an ICER for AVA + CYC/RTX versus CYC/RTX + GC of [redacted] per QALY gained.

The PSA showed that the probability that avacopan is cost effective at thresholds of £20,000 and £30,000 per QALY gained is 55% and 80%. Furthermore, the results of the company's DSA showed that parameters relating to eGFR recovery at induction and remission in both treatment groups had the largest impact on the ICER. Cost of maintenance dialysis, as the main cost component of ESRD, also had a substantial impact on results. Finally, of all scenarios explore by the company, the scenario with the largest impact on results was testing the alternative source of HR for the effect of eGFR decrease on the probability of ESRD, which increases the assumed HR from 0.9 to 0.96. This scenario increased the ICER to £31,655 per QALY gained. In all other scenarios, except the one which reduced the time horizon to 5-years, the ICER remained below £30,000.

The ERG base-case differed from the company base-case for the following aspects: using the most recent (i.e., 2019/2020) unit cost for hospitalisation, with no adjustment for excess bed days; changing the source to estimate the transition probability of developing ESRD from literature and ADVOCATE to CPRD; changing the relative risk of mortality for patients with ESRD from 10.3, based on a South Korean study to 6.6, based on the UK Renal Registry; using health state utilities not treatment specific, with disutility for AEs during the ADVOCATE study.

The ERG preferred base-case incremental results, indicate that the ICER, compared to the company base-case, has doubled. The company BC ICER after clarification amounted to £18,492, whereas the ICER for the ERG preferred base-case is £102,973. This is to a large extent explained by the fact that in the ERG base case, fewer patients develop ESRD, making the absolute reduction in ESRD occurrence with avacopan smaller.

When looking at the step-by-step changes made by the ERG to the company base-case we again saw that source of the estimate for the transition probabilities to ESRD has the largest individual effect, followed by the hazard rate to adjust transition probabilities for eGFR. The impact of changing to hospitalisation costs is much smaller but still substantial, with an increase in ICER of around 25%. The change in the relative risk for mortality due to ESRD actually lowered the ICER by 25%, both through a reduction in incremental costs and a decrease in the number of QALYs gained.

The ERG explorative scenario analyses showed that when RTX is given during the maintenance phase this leads to a much higher ICER. As expected, the accumulated QALYs increase whilst costs decrease, however, the incremental costs increase whilst the incremental QALYs decrease. However, this result

should be regarded as highly uncertain. The scenario in which the probability of transitioning to ESRD is based on literature and ADVOCATE (with an ERG derived pooled HR) instead of CPRD leads to an ICER just below £40,000 per QALY gained. Finally, the analyses in which longer periods of avacopan maintenance were explored show that up until 24 months of avacopan maintenance treatment the ICER changes little. For longer durations the ICER increases significantly, which can be explained by the relapse probabilities becoming smaller after 2 years of treatment.

In conclusion, in contrast to the company's base-case that resulted in an ICER of £18,492 per QALY gained, the ERG preferred base-case results in an ICER of £102,973 per QALY gained. Various analyses show that the model is quite sensitive to changes related to ESRD, as the dialysis that is required in this state comes at high costs and leads to a substantial drop in HRQoL.

7 END OF LIFE

The company has not provided relevant information regarding whether the intervention is likely to meet the end-of-life criteria published by the National Institute for Health and Care Excellence (NICE). The Evidence Review Group (ERG) does not believe that the intervention meets the criteria published by NICE, especially because the treatment is not indicated for patients with a short life expectancy (normally less than 24 months).

8 REFERENCES

[1] Vifor. *Avacopan for treating anti-neutrophil cytoplasmic autoantibody–associated vasculitis [ID1581] - Response to request for clarification from the ERG*: Vifor, 2021. 59p.

[2] Chalisey A, Karim M. *Guidelines for the management of ANCA-associated vasculitis with renal involvement [Internet]*: Norfolk and Norwich University Hospitals NHS Foundation Trust, James Paget University Hospitals NHS Foundation Trust, 2021 [accessed 6.12.21]. 18p. Available from: https://www.nnuh.nhs.uk/publication/download/guidelines-for-the-management-of-anca-associated-vasculitis-v1-2

[3] National Institute for Health and Care Excellence. *Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis. Technology appraisal guidance [TA308]*. London: NICE, 2014 Available from: https://www.nice.org.uk/Guidance/TA308

[4] Ntatsaki E, Carruthers D, Chakravarty K, D'Cruz D, Harper L, Jayne D, et al. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. *Rheumatology (Oxford)* 2014;53(12):2306-9.

[5] Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis* 2016;75(9):1583-94.

[6] Vifor. *Avacopan for treating anti-neutrophil cytoplasmic autoantibody–associated vasculitis [ID1581]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Document B - Company evidence submission*: Vifor, 2021. 178p.

[7] National Institute for Health and Care Excellence. *Avacopan for treating anti-neutrophil cytoplasmic autoantibody-associated vasculitis [ID1581]: Final scope [Internet]*. London: NICE, 2021 [accessed 10.11.21]. 4p. Available from: https://www.nice.org.uk/guidance/gid-ta10740/documents/final-scope

[8] Jayne DRW, Merkel PA, Schall TJ, Bekker P. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med* 2021;384(7):599-609.

[9] Merkel PA, Niles J, Jimenez R, Spiera RF, Rovin BH, Bomback A, et al. Adjunctive treatment with avacopan, an oral C5a receptor inhibitor, in patients with antineutrophil cytoplasmic antibody–associated vasculitis. *ACR Open Rheumatol* 2020;2(11):662-671.

[10] ChemoCentryx. *Clinical study report. 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*: ChemoCentryx, 2016

[11] ChemoCentryx. *Clinical study report. 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.: ChemoCentryx, 2016

[12] Jayne DRW, Bruchfeld AN, Harper L, Schaier M, Venning MC, Hamilton P, et al. Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis. *J Am Soc Nephrol* 2017;28(9):2756.

[13] McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline statement. *J Clin Epidemiol* 2016;75:40-6.

[14] Canadian Agency for Drugs and Technologies in Health. *PRESS - Peer Review of Electronic Search Strategies: 2015 Guideline Explanation and Elaboration (PRESS E&E) [Internet]*. Ottawa: CADTH, 2016 [accessed 10.11.21] Available from: https://www.cadth.ca/resources/finding-evidence/press

[15] National Institute for Health and Care Excellence. *Single Technology Appraisal: company evidence submission template [Internet]*. London: NICE, 2015 [accessed 03.11.21]. 28p. Available from: http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/specification-for-company-submission-of-evidence-2015-version.docx

[16] Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. *Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021) [Internet]*: Cochrane, 2021 [accessed 10.11.21] Available from: https://training.cochrane.org/handbook

[17] Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *J Med Libr Assoc* 2006;94(1):41-7.

[18] Haynes RB, McKibbon KA, Wilczynski NL, Walter SD, Werre SR. Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ* 2005;330(7501):1179.

[19] Centre for Reviews and Dissemination. *Systematic Reviews: CRD's guidance for undertaking reviews in health care [Internet]*. York: University of York, 2009 [accessed 10.11.21] Available from: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm

[20] National Institute for Health and Care Excellence. *Avacopan for treating anti-neutrophil cytoplasmic autoantibody–associated vasculitis [ID1581]: Clarification letter*. London: NICE, 2021

[21] Vifor. *Avacopan for treating anti-neutrophil cytoplasmic autoantibody–associated vasculitis [ID1581]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Appendix D: Identification, selection, and synthesis of clinical evidence*: Vifor, 2021. 48p.

[22] Cochrane Methods. Risk of Bias 2 (RoB 2) tool [Internet]. [accessed 8.11.21]. Available from: https://methods.cochrane.org/risk-bias-2

[23] ChemoCentryx. *Clinical study report. 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*: ChemoCentryx, 2020

[24] Division of Rheumatology and Transplant Medicine, Office of Immunology and Inflammation, Office of New Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration. *FDA Briefing Document. Arthritis Advisory Committee Meeting. May 06, 2021. NDA# 214487. Drug name: avacopan. Proposed indication: treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]). Applicant: ChemoCentryx, Inc [Internet]*. Silver Spring, MD: US Food and Drug Administration, 2021 [accessed 24.11.21] Available from: https://www.fda.gov/media/148176/download

[25] ChemoCentryx. *Protocol CL010_168. Week 52 Final Tables [PDF provided with company's submission]*: ChemoCentryx, 2021. 4001p.

[26] Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaître O, Cohen P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 2014;371(19):1771-80.

[27] Charles P, Terrier B, Perrodeau E, Cohen P, Faguer S, Huart A, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). *Ann Rheum Dis* 2018(77):1144-50.

[28] Smith R, Jayne D, Merkel P. A randomized, controlled trial of rituximab versus azathioprine after induction of remission with rituximab for patients with ANCA-associated vasculitis and relapsing disease. In: 2019 ACR/ARTP Annual Meeting; 8-13 Nov 2019; Atlanta, GA, 2019.

[29] Vifor. *Avacopan for treating anti-neutrophil cytoplasmic autoantibody–associated vasculitis [ID1581]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Appendix H: Health-related quality-of-life studies*: Vifor, 2021. 19p.

[30] Vifor. *Avacopan for treating anti-neutrophil cytoplasmic autoantibody–associated vasculitis [ID1581]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Appendix I: Cost and healthcare resource identification, measurement and valuation*: Vifor, 2021. 19p.

[31] Vifor. *Avacopan for treating anti-neutrophil cytoplasmic autoantibody–associated vasculitis [ID1581]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Appendix G: Published cost-effectiveness studies*: Vifor, 2021. 14p.

[32] Harland D, Naisbett-Groet B, Chang S, Sungher DK, Sawyer L, Diamantopoulos A. Mabthera® (rituximab) for the treatment of severe granulomatosis with polyangiitis (Gpa) and microscopic polyangiitis (Mpa) - a cost-utility model for the United Kingdom. *Value Health* 2014;17(7):A382.

[33] Montante A, Le Bras A, Pagnoux C, Perrodeau E, Ravaud P, Terrier B, et al. Cost-effectiveness of rituximab versus azathioprine for maintenance treatment in antineutrophil cytoplasmic antibody-associated vasculitis. *Clin Exp Rheumatol* 2019;37(2 Suppl 117):137-43.

[34] Scottish Medicines Consortium (SMC). Rituximab (MabThera®) in combination with glucocorticoids for the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA). 2013. Available from: https://www.scottishmedicines.org.uk/medicines-advice/rituximab-mabthera-fullsubmission-89413/

[35] Cazzador D, Padoan R, Colangeli R, Pendolino AL, Felicetti M, Zanoletti E, et al. Health-related quality of life in patients with ANCA-associated vasculitis and sinonasal involvement: a single-center cross-sectional study. *J Clin Rheumatol* 2020.

[36] Yates M, Watts R. ANCA-associated vasculitis. *Clin Med (Lond)* 2017;17(1):60-4.

[37] PHMR Ltd. *An investigation of the adverse outcomes and resource use associated with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) in England and their relationship with glucocorticoid (GC) treatment: a clinical practice research datalink*. London, UK: PHMR Ltd., 2019

[38] National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013 (2018 revision) [Internet]*. London: NICE, 2013 (revised 2018) [accessed 10.11.21]. 93p. Available from: https://www.nice.org.uk/process/pmg9/

[39] Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010;363(3):221-32.

[40] Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Höglund P, et al. Damage in the ANCA-associated vasculitides: long-term data from the European Vasculitis Study group (EUVAS) therapeutic trials. *Ann Rheum Dis* 2015;74(1):177-84.

[41] Wester Trejo MAC, Floßmann O, Westman KW, Höglund P, Hagen EC, Walsh M, et al. Renal relapse in antineutrophil cytoplasmic autoantibody-associated vasculitis: unpredictable, but predictive of renal outcome. *Rheumatology (Oxford)* 2019;58(1):103-9.

[42] Gercik O, Bilgin E, Solmaz D, Cakalagaoglu F, Saglam A, Aybi O, et al. Histopathological subgrouping versus renal risk score for the prediction of end-stage renal disease in ANCA-associated vasculitis. *Ann Rheum Dis* 2020;79(5):675-6.

[43] Brix SR, Noriega M, Tennstedt P, Vettorazzi E, Busch M, Nitschke M, et al. Development and validation of a renal risk score in ANCA-associated glomerulonephritis. *Kidney Int* 2018;94(6):1177-1188.

[44] Ford SL, Polkinghorne KR, Longano A, Dowling J, Dayan S, Kerr PG, et al. Histopathologic and clinical predictors of kidney outcomes in ANCA-associated vasculitis. *Am J Kidney Dis* 2014;63(2):227-35.

[45] Menez S, Hruskova Z, Scott J, Cormican S, Chen M, Salama AD, et al. Predictors of renal outcomes in sclerotic class anti-neutrophil cytoplasmic antibody glomerulonephritis. *Am J Nephrol* 2018;48(6):465-71.

[46] Office for National Statistics. *National life tables, UK: 2015 to 2017*. London, UK: Office for National Statistics, 2018

[47] Wallace ZS, Lu N, Unizony S, Stone JH, Choi HK. Improved survival in granulomatosis with polyangiitis: a general population-based study. *Semin Arthritis Rheum* 2016;45(4):483-9.

[48] Jayne D. Treating vasculitis with conventional immunosuppressive agents. *Cleve Clin J Med* 2012;79(suppl 2):S46-S49.

[49] McGregor JG, Hogan SL, Hu Y, Jennette CE, Falk RJ, Nachman PH. Glucocorticoids and relapse and infection rates in anti-neutrophil cytoplasmic antibody disease. *Clin J Am Soc Nephrol* 2012;7(2):240-7.

[50] Flossmann O, Berden A, de Groot K, Hagen C, Harper L, Heijl C, et al. Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011;70(3):488-94.

[51] Little MA, Nightingale P, Verburgh CA, Hauser T, De Groot K, Savage C, et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. *Ann Rheum Dis* 2010;69(6):1036-43.

[52] Choi H, Kim M, Kim H, Pyo Lee J, Lee J, Tak Park J, et al. Excess mortality among patients on dialysis: comparison with the general population in Korea. *Kidney Res Clin Pract* 2014;33(2):89-94.

[53] van Hout B, Janssen MF, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012;15(5):708-15.

[54] Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. *Value Health* 2011;14(4):539-45.

[55] Lee AJ, Morgan CLI, Conway P, Currie CJ. Characterisation and comparison of health-related quality of life for patients with renal failure. *Curr Med Res Opin* 2005;21(11):1777-83.

[56] UK Renal Registry. 20th Annual Report of the Renal Association. *Nephron* 2018;139(suppl 1):1-372.

[57] National Institute for Health and Care Excellence. *Patiromer for treating hyperkalaemia. Technology appraisal guidance [TA623]*. London: NICE, 2020 Available from: https://www.nice.org.uk/guidance/ta623/resources/patiromer-for-treating-hyperkalaemia-pdf-82609015577029

[58] Ara R, Brazier J. Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). *Value Health* 2008;11(7):1131-43.

[59] Manson SC, Brown RE, Cerulli A, Vidaurre CF. The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. *Respir Med* 2009;103(7):975-94.

[60] Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Höglund P, et al. Glucocorticoid treatment and damage in the anti-neutrophil cytoplasm antibody-associated vasculitides: long-term data from the European Vasculitis Study Group trials. *Rheumatology (Oxford)* 2015;54(3):471-81.

[61] Sullivan PW, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making* 2006;26(4):410-20.

[62] National Institute for Health and Care Excellence. *Bisphosphonates for treating osteoporosis. Technology appraisal guidance [TA464]*. London: NICE, 2017 Available from: https://www.nice.org.uk/guidance/ta464/resources/bisphosphonates-for-treating-osteoporosis-pdf-82604905556677

[63] Lansingh VC, Carter MJ. Use of global visual acuity data in a time trade-off approach to calculate the cost utility of cataract surgery. *Arch Ophthalmol* 2009;127(9):1183-93.

[64] Leahy TP, Ramagopalan S, Sammon C. The use of UK primary care databases in health technology assessments carried out by the National Institute for Health and Care Excellence (NICE). *BMC Health Serv Res* 2020;20(1):675.

[65] Joint Formulary Committee. British National Formulary 2018. London: BMJ Group and Pharmaceutical Press. Available from: https://bnf.nice.org.uk/

[66] NHS. 2019/20 National cost collection data. 2020. Available from: https://www.england.nhs.uk/national-cost-collection/

[67] Curtis LA, Burns A. *Unit costs of health and social care 2020 [Internet]*. Canterbury: Personal Social Services Research Unit (PSSRU), University of Kent, 2020 [accessed 10.11.21] Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/

[68] Kent S, Schlackow I, Lozano-Kühne J, Reith C, Emberson J, Haynes R, et al. What is the impact of chronic kidney disease stage and cardiovascular disease on the annual cost of hospital care in moderate-to-severe kidney disease? *BMC Nephrol* 2015;16(1):65.

[69] ClinRisk Ltd. QFracture®-2016 risk calculator [Internet]. [accessed 16.12.21]. Available from: https://qfracture.org/index.php

[70] National Institute for Health and Care Excellence. *Cataracts in adults: management. NICE guideline [NG77]*. London: NICE, 2017 Available from: https://www.nice.org.uk/guidance/ng77

[71] Kaltenthaler E, Carroll C, Hill-McManus D, Scope A, Holmes M, Rice S, et al. The use of exploratory analyses within the National Institute for Health and Care Excellence single technology appraisal process: an evaluation and qualitative analysis. *Health Technol Assess* 2016;20(26):1-48.

[72] National Institute for Health and Care Excellence. *Single technology appraisal: User guide for company evidence submission template*. London: NICE, 2017 Available from: https://www.nice.org.uk/guidance/pmg24/resources/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pdf-72286715419333

Appendix 1

Since the ERG found a difference in QALYs accumulated between avacopan + CYC and avacopan + RTX, the ERG compared the formula for cell DY21 on both engine sheets. We have marked all places where a difference is spotted. The actual cause of the observed difference turned out to be the last difference, where on the AVA CYC sheet we see SUM(CV20:CY20)*TP_Infections_NoGC and on the AVA RTX sheet we see CV20*TP_Infections_NoGC. CV20 contains the number of patients entering ESRD, and CW, CX and CZ contain the number of patients receiving dialysis or a transplant. We have assumed that the code for AVA CYC is correct for this part of the formula, and we have changed this on all 3 other engine sheets, for infections, CV events, osteoporosis, and ocular disease.

AVA CYC cell DY 21	AVA RTX cell DY 21

=IF(AND(A21<=13,inf_data_source=2),
(1-DN20)*'Clinical data'!$J$141,
(C20+D20)*IF(GC_use_AVA=1,
IF(A20<=IF(nb_cycles_lowGC=1,4,5),
 	
TP_Infections_LdGC,TP_Infections_NoGC),
TP_Infections_NoGC)+
IF(nb_cycles_lowGC=1,
SUM(F20:I20,AQ20:AT20),
SUM(F20:J20,AQ20:AU20))*
IF(ava_reinduction=1,
TP_Infections_LdGC,
IF(GC_use_AVA=1,
TP_Infections_LdGC,
TP_Infections_NoGC))+
IF(nb_cycles_lowGC=1,
SUM(J20:L20,AU20:AW20),
SUM(K20:L20,AV20:AW20))*
TP_Infections_NoGC+
CB20*IF(nb_induction>1,
IF(ava_reinduction=1,
TP_Infections_HdGC,IF(GC_use_AVA,
 	
TP_Infections_LdGC,TP_Infections_NoGC)),
TP_Infections_NoGC)+
IF(nb_cycles_lowGC=1,
SUM(CC20:CF20),SUM(CC20:CG20))*
IF(nb_induction>1,
IF(ava_reinduction=1,TP_Infections_LdGC,
IF(GC_use_AVA=1,
TP_Infections_LdGC,
TP_Infections_NoGC)),
TP_Infections_NoGC)+
CK20*IF(nb_induction=3,
 	
IF(ava_reinduction<3,TP_Infections_HdGC,
IF(GC_use_AVA, TP_Infections_LdGC,
TP_Infections_NoGC)),
TP_Infections_NoGC)+
IF(nb_cycles_lowGC=1,SUM(CL20:CO20),
	=IF(AND(A21<=13,inf_data_source=2),
	(1-DN20)*'Clinical data'!$J$141,
	((C20+D20)*IF(GC_use_AVA=1,
	IF(A20<=IF(nb_cycles_lowGC=1,4,5),
	
	TP_Infections_LdGC,TP_Infections_NoGC),
	TP_Infections_NoGC)+
	IF(nb_cycles_lowGC=1,
	SUM(F20:I20,AQ20:AT20),
	SUM(F20:J20,AQ20:AU20))*
	IF(ava_reinduction=1,
	TP_Infections_LdGC,
	IF(GC_use_AVA=1,
	TP_Infections_LdGC,
	TP_Infections_NoGC))+
	IF(nb_cycles_lowGC=1,
	SUM(J20:L20,AU20:AW20),
	SUM(K20:L20,AV20:AW20))*
	TP_Infections_NoGC+
	CB20*IF(nb_induction>1,
	IF(ava_reinduction=1,
	
	TP_Infections_HdGC,IF(GC_use_AVA=1,
	
	TP_Infections_LdGC,TP_Infections_NoGC)),
	TP_Infections_NoGC)+
	IF(nb_cycles_lowGC=1,
	SUM(CC20:CF20),SUM(CC20:CG20))*
	IF(nb_induction>1,
	IF(ava_reinduction=1,TP_Infections_LdGC,
	IF(GC_use_AVA,
	TP_Infections_LdGC,
	TP_Infections_NoGC)),
	TP_Infections_NoGC)+
	CK20*IF(nb_induction=3,
	
	IF(ava_reinduction<3,TP_Infections_HdGC,
	TP_Infections_NoGC),
	TP_Infections_NoGC)+

SUM(CL20:CP20))*
IF(nb_induction=3,
IF(ava_reinduction<3,TP_Infections_LdGC,
IF(GC_use_AVA=1,
 	
TP_Infections_LdGC,TP_Infections_NoGC)),
TP_Infections_NoGC)+
IF(nb_cycles_lowGC=1,SUM(CG20,CP20),0)*
TP_Infections_NoGC+CHOOSE(longterm_GC,
 	
SUM(CH20,CQ20,CS20)*TP_Infections_NoGC,
 	
SUM(CI20,CR20,CT20)*TP_Infections_LdGC+((CH20-CI20)+(CQ20-CR20)+(CS20-CT20))*TP_Infections_NoGC)+
SUM(CV20:CY20)*TP_Infections_NoGC)
	IF(nb_cycles_lowGC=1, SUM(CL20:CO20),
	SUM(CL20:CP20))*
	IF(nb_induction=3,
	IF(ava_reinduction<3,TP_Infections_LdGC,
	IF(GC_use_AVA=1,
	
	TP_Infections_LdGC,TP_Infections_NoGC)),
	TP_Infections_NoGC)+
	IF(nb_cycles_lowGC=1, SUM(CG20,CP20),0)*
	TP_Infections_NoGC+CHOOSE(longterm_GC,
	
	SUM(CH20,CQ20,CS20)*TP_Infections_NoGC,
	
	SUM(CI20,CR20,CT20)*TP_Infections_LdGC+((CH20-CI20)+(CQ20-CR20)+(CS20-CT20))*TP_Infections_NoGC)+
	CV20*TP_Infections_NoGC))

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Avacopan for maintenance treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm** on **26 January 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Number of ADVOCATE trial respondents for each of the health state utilities (Section 4.2.7.1, Page 105)

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG comment</th></tr>
<tr>
<td>The numbers of ADVOCATE trial respondents for each of the health state utilities reported in Table 4.7 of the ERG report (Section 4.2.7.1, page 105) are incorrect.</td>
<td>Table 4.7 should be as follows:
<table>
<tr><th>State</th><th>Utility value: mean (standard error)</th><th>95% confidence interval</th><th>Source</th></tr>
<tr><td colspan="3">Avacopan + SoC (n 26w/n 52w)</td><td></td></tr>
<tr><td>Active disease (34/33)</td><td>0.708 (0.022)</td><td>0.664-0.751</td><td rowspan="3">ADVOCATE trial[8]</td></tr>
<tr><td>Remission (118/107)</td><td>0.790 (0.011)</td><td>0.767-0.812</td></tr>
<tr><td>Relapse (-/9)</td><td>0.738 (0.055)</td><td>0.629-0.847</td></tr>
<tr><td colspan="3">GC + SoC (n 26w/n 52w)</td><td></td></tr>
<tr><td>Active disease (36/34)</td><td>0.697 (0.024)</td><td>0.649-0.744</td><td rowspan="3">ADVOCATE trial[8]</td></tr>
<tr><td>Remission (112/89)</td><td>0.766 (0.012)</td><td>0.741-0.790</td></tr>
<tr><td>Relapse (-/21)</td><td>0.678 (0.056)</td><td>0.566-0.790</td></tr>
<tr><td colspan="4">All patients (n 26w/n 52w)</td></tr>
<tr><td>Active disease (70, 67)</td><td>0.702 (0.016)</td><td>0.670-0.734</td><td rowspan="3">ADVOCATE trial[8]</td></tr>
<tr><td>Remission (230/196)</td><td>0.778 (0.008)</td><td>0.761-0.795</td></tr>
<tr><td>Relapse (-/30)</td><td>0.696 (0.042)</td><td>0.611-0.780</td></tr>
</table>
</td>
<td>The company incorrectly reported the number of respondents for each of the health state utilities at clarification stage (within Table 10 of the clarification report). Table 10 of the clarification response should be as follows:
<table>
<tr><th>Health State</th><th>26 weeks</th><th>52 weeks</th></tr>
<tr><td colspan="3">Active disease</td></tr>
<tr><td>Both trial arms</td><td>70</td><td>67</td></tr>
<tr><td>Avacopan + SoC</td><td>34</td><td>33</td></tr>
<tr><td>Prednisone + SoC</td><td>36</td><td>34</td></tr>
<tr><td colspan="3">Remission</td></tr>
<tr><td>Both trial arms</td><td>230</td><td>196</td></tr>
<tr><td>Avacopan + SoC</td><td>118</td><td>107</td></tr>
<tr><td>Prednisone + SoC</td><td>112</td><td>89</td></tr>
<tr><td colspan="3">Relapse</td></tr>
<tr><td>Both trial arms</td><td>NA</td><td>30</td></tr>
<tr><td>Avacopan + SoC</td><td>NA</td><td>9</td></tr>
<tr><td>Prednisone + SoC</td><td>NA</td><td>21</td></tr>
<tr><td colspan="3">Abbreviations: SoC, standard of care</td></tr>
</table>
The proposed amendment does not impact the outcome of the cost-effectiveness model.</td>
<td>Table has been modified as well as text referring to this table.

The key issue regarding the small sample size has also been removed.</td>
</tr>
</table>

	ESRD utilities					
	Peritoneal dialysis	0.530 (0.027)	0.477-0.583	Lee et al.[55]		
	Haemodialysis	0.443 (0.023)	0.399-0.487			
	Renal transplant	0.712 (0.036)	0.641-0.783			
	ESRD distribution					
	Peritoneal dialysis	20.5%	Fixed	20th Annual Report of the Renal Association.[56]		
	Haemodialysis	69.8%	Fixed			
	Renal transplant	9.7%	Fixed			
	Based on Table 39 of the CS[6] ESRD = end-stage renal disease; GC = glucocorticoid; SoC = standard of care					

Issue 2 Comparators (Section 1.3, Page 13; Section 2.3, Page 27)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG report states that ''the company considers treatment including azathioprine (AZA) as a comparator treatment for inducing remission''. The company, however, does not consider AZA as a comparator treatment for inducing remission.	Remove this statement	The company does not consider AZA as a comparator treatment for inducing remission. AZA has been added as an option for maintenance of remission and applied to both the avacopan and comparator arm of the model. The proposed amendment does not impact the outcome of the cost-effectiveness model.	Not a factual inaccuracy. Table 1 of Document B of the company submission states that the comparators are as follows: "*Remission induction* • *GCs in combination with CYC, followed by AZA/MMF*

			• *GCs in combination with RTX* *Maintenance treatment* • *Low-dose GCs in combination with AZA/MMF* *RTX in combination with low-dose GCs*”
The ERG report states that ‘’the company uses methotrexate (MTX) and MM[F] as alternatives to cyclophosphamide (CYC)”. The company has not included MTX or MMF in the submitted cost-effectiveness model.	Remove this statement	The company does not consider MTX or MMF to be alternatives to CYC. MTX and MMF are recommended as alternatives to CYC (followed by AZA/MMF) or RTX for remission induction in patients with localised disease at low risk of suffering organ damage. The use of avacopan, in combination with a CYC or RTX regimen, is indicated for severe, active GPA or MPA. As such, the population in the decision problem did not include patients with localised disease at low risk of suffering organ damage. The proposed amendment does not impact the outcome of the cost-effectiveness model.	Not a factual inaccuracy. The company submission (page 12) states: “*MTX and MMF are recommended as alternatives to CYC (followed by AZA/MMF) or RTX for remission induction in patients with localised disease at low risk of suffering organ damage. These patients were not studied in the key avacopan clinical trials and so, in this setting, they are not relevant comparators for Avacopan.*”

Issue 3 Measurement of glucocorticoid-related AEs (Section 1.4, Page 14)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG report states that ''measurement of glucocorticoid toxicity, in the absence of a comparable measure of potential avacopan-associated toxicities (such as hepatoxicity) may lead to biased estimate of adverse events of avacopan in the ADVOCATE trial''. The ERG recommend that related adverse events in the avacopan group could be measured as well, or the additional outcomes removed. The company, however, did not include the glucocorticoid toxicity measured in the trial within the economic model. Adverse events reported for both the avacopan and standard of care arms of ADVOCATE informed the safety of treatments in the model.	Amend the suggested approach and suggested additional analyses as adverse events of both avacopan and GC-based standard of care have been included in the model. The submitted model reflects the outcomes specified in the final NICE scope.	Corticosteroid toxicity is included as an outcome measure in the final scope. However, the company did not include the glucocorticoid toxicity measured in the trial within the economic model. Adverse events reported for both the avacopan and standard of care arm of ADVOCATE informed the safety of treatments in the model. The proposed amendment does not impact the outcome of the cost-effectiveness model.	Key issue 4 related to this removed.

ACIC marking corrections

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG comment
ID1581 acacopan ERG report 16012022CM ACIC, Page 61	Statement: ''5.8 and 2.9 ml/min/1.73m^2'' is highlighted as AIC. However, these data are	Remove confidential marking: ''5.8 and 2.9 ml/min/1.73m^2''	Confidential marking removed.

	already published and do not need to be marked as confidential.		

NICE National Institute for Health and Care Excellence

Technical engagement response form

Avacopan for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Friday, 4 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Vifor Pharma
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. The narrower population in the company submission may impact generalisability of the findings	No	Avacopan was only studied (ADVOCATE, CLASSIC and CLEAR) in patients with severe, active GPA or MPA and, therefore, is only indicated, in combination with a RTX or CYC regimen, for the treatment of adult patients with severe, active GPA or MPA; EGPA is not part of the marketing authorisation for avacopan. In the company submission, severe GPA and MPA (also referred to as 'organ-threatening' disease) is defined as disease activity that threatens the function of the affected organ and has the potential to cause permanent organ damage or to threaten the patient's life unless effective therapy is implemented quickly. Non–organ-threatening disease describes patients with no evidence of organ damage. The population in the decision problem did not include patients with localised disease at low risk of suffering organ damage.
2. The inclusion of glucocorticoids in the intervention group may have generated biased effect estimates of the intervention	No	The ADVOCATE study protocol envisioned the use of some GCs in both groups as a function of administration during screening and prior to randomisation; as co-administration with RTX (to prevent hypersensitivity reactions per the RTX prescribing information), and, for example, to manage adrenal insufficiency. During the trial, extra IV and/or oral GC treatment was administered to subjects who experienced a relapse of their AAV, tapered according to the subject's condition, which is in line with the anticipated use of avacopan in clinical practice. Such GC use was reasonably well balanced between the two groups; therefore, the benefits

		can be ascribed to the avacopan treatment arm and compared to the tapered GC dosing regimen in the comparator arm. The cost and adverse event consequences of GCs are included in the model for both intervention and comparator.
3. The list of comparators differs from the list in the final scope issued by NICE, potentially affecting the relative apparent efficacy, safety, and cost of avacopan	No	The comparators considered in the company submission scope are aligned with the current SoC and NICE recommendations for treatment of severe, active AAV in England [1-3]. The relevant comparators considered for the scope of this submission are: • CYC in combination with GCs (induction), followed by AZA in combination with low-dose GCs as maintenance treatment • RTX in combination with GCs (induction), followed by RTX in combination with low-dose GCs as maintenance treatment The use of avacopan, in combination with a CYC or RTX regimen, is indicated for severe, active GPA or MPA; the population in the decision problem did not include patients with localised disease at low risk of suffering organ damage. MTX and MMF are recommended as alternatives to CYC or RTX for remission induction in patients with localised disease at low risk of suffering organ damage; as such, they were not considered as relevant comparator treatments.
4. The model assumes only azathioprine is used during the maintenance phase of the treatment. However, BSR/BHPR guidelines specify that rituximab may be used for maintenance treatment for patients achieving remission after rituximab induction	No	The company have provided an amended cost-effectiveness model in response to the clarification questions by the ERG before the technical engagement meeting with NICE. The revised model included a full list of options for maintenance treatment, including rituximab, which can be used in scenario analysis.
5. The estimated hazard ratio (pooled estimate versus single study) of developing ESRD has a	Yes	**ERG comment:** Wherever the hazard ratio of developing ESRD was adjusted based on an increase or decrease in eGFR a hazard ratio (HR=0.90) estimated from the Gercik et al. study was used by the company [4]. Though not mentioned in report, the model shows that three other studies have estimated the same hazard ratio. The

large impact on the cost effectiveness results		ERG considers the studies by Gercik et al. in addition to two other studies to be equally relevant The ERG derived a pooled estimate (based on inverse variance approach) for these three studies, yielding a HR of 0.955 (95% CI 0.926 – 0.985). This estimate will be used in an ERG preferred base case. **Company response:** We do not believe that it is appropriate to combine the estimated GFR hazard ratios of developing ESRD across multiple studies. This is due to the fact that parameter estimates obtained from Cox proportional hazards regression models are, in fact, conditional on the other covariates that are included in the model. The estimated coefficients obtained from multiple Cox proportional hazards models that each adjust for a different set of covariates are, therefore, inconsistent [5]. We did consider a pooled approach but abandoned it for this reason. Instead, we selected the single most appropriate estimate from the available sources. The Gercik et al. study [4] was chosen on the basis of it being the most recent work and having a large sample size. Moreover, the same HR as in Gercik et al. study is also reported in a study based on trial and registry data from the EUVAS studies with the largest sample size. (Gopaluni et al.)[6]. The patient population ("All patients diagnosed with AAV according to biopsy and/or antineutrophil cytoplasmic antibody (ANCA) serology") and the treatments received ("Cyclophosphamide or rituximab in conjunction with high-dose GCs for induction or major relapses, and maintenance treatment combination of oral methylprednisolone and azathioprine, rituximab or mycophenolate mofetil for at least 24 months") were also most closely aligned with the modelled patient population for avacopan.
6. The company explored two different approaches to estimate the probability to transition the ESRD leading to very different results	Yes	**Issue:** The ERG pointed out that there are important differences in the modelled incidence of ESRD depending on the source used for the baseline probability. It was stated that both the approach based on the Robson et al. study [7] and based on the CPRD were considered plausible. The ERG then selected the CPRD approach for their base case on the basis that this produced an incidence of ESRD that reflected real-world incidence from CPRD. **Company response:** i) Is it appropriate to assume that the CPRD provides a standard for validating model outputs?

		The company agrees with the ERG statement that the probability of ESRD is sensitive to the choice of data source to inform the baseline probability. However, we would question the use of the CPRD study as the gold-standard with which to judge the validity of methods for modelling ESRD incidence. Estimation of event rates from CPRD linked data is not necessarily free from bias. The means through which bias can emerge when using CPRD linked data is discussed in Padmanabhan et al [8]. For a specific example of how different approaches to the construction of linked data can lead to substantial differences in estimated event rates, see Gallagher et al [9]. Although from a very different disease area this study does demonstrate the complexity of estimating event rates from linked data. ii) An updated approach calibrated to multiple published sources In order to examine the external validity of the ESRD estimates produced in the model, the cumulative incidence of ESRD based on Robson et al. and CPRD was compared against the cumulative incidence reported in published studies carried out in AAV. The company carried out a targeted literature search to identify relevant studies, which are reported in Table 1. The estimated proportion of patients reported with ESRD ranged from 19.7% to 28.0% across the studies. However, it was difficult to draw a comparison between studies due to differences in the median length of follow-up. An approach using a pooled estimate was not considered to be appropriate due to the differences in the study design and length of follow-up. Instead, the cumulative incidence reported in each study was plotted against the estimated cumulative incidence in our model based on the alternative approaches considered by the ERG (Robson et al. and CPRD) in Figure 1. Based on the estimates reported in the studies identified in the targeted literature search, the plausible range for the rate of ESRD lies between the projected estimates in the company base case and the ERG's preferred base case informed by CPRD. In order to ensure that the estimates produced in the model maintain external validity compared to previously published evidence, the baseline rates of ESRD in the model were calibrated in order to reflect the rate of ESRD expected in

		real-world practice. The calibrated company base case is represented using the dotted line in Figure 1. The company identified an error in the application of CPRD ESRD rates in the model. Patients who are in the sustained remission health state (cycle 7+) for both avacopan and GC SoC were erroneously applied the rate associated with relapse, which corresponds to the overall rate of ESRD reported in CPRD ([redacted] per 1000 patient-years). The correct probability for this health state corresponds to the rate for patients with no GC prescription ([redacted] per 1000 patient-years). The company corrected this error in the updated model. Changing this transition probability had no impact on the company base case, as it uses Robson et al. as the source of ESRD probabilities. However, this change has an impact on the scenario analysis which uses CPRD as the source of ESRD probabilities, which was the ERG's preferred base case (Table 4). **Key issue 6: further detail on the population in CPRD in comparison to published studies** Within their response to the technical engagement questions from the company, the ERG have asked for additional information regarding the population of the CPRD study, and how it compares against the target population for avacopan. The inclusion criteria in the CPRD study includes diagnosis codes for Wegener's granulomatosis and microscopic polyangiitis. The target population of avacopan, as described in the SmPC, is severe, active GPA or MPA. It is therefore likely that the CPRD study population included patients with less severe GPA and MPA compared to the target population for avacopan, and thus the population in the economic model. This may explain the considerably lower rate of ESRD observed in CPRD compared to other published studies as reported in the validation section above.
7. Validity of costing approach used for hospitalisation costs	Yes	**Issue:** The ERG had concerns about the chosen approach to estimate the cost of hospitalisation using data from ADVOCATE. Using the unit cost from NHS Reference Costs 2019/20 combined with excess bed days and cost from NHS

		Reference Costs 2017/18 may produce incorrect estimates due to differences in the way these two versions estimate the cost of inpatient care. **Company response:** The ERG provide three reasons for excluding the cost of excess bed days in their preferred base case: 1. **ERG:** Firstly, it is not clear that a difference in length of stay should imply an excess bed day at all. **Company response:** we disagree that a longer hospital length of stay may not represent additional bed days associated with extra cost. Ignoring differences in length of stay is likely to underestimate the cost of hospital care and thus produce biased estimates in the model 2. **ERG:** Secondly, the most recent 2019/2020 version of the NHS Reference costs no longer includes the cost of an excess bed day. This suggest a difference in the way the unit costs were calculated between the 2017/2018 version and the 2019/2020 version of the NHS Reference cost. **Company response:** the company acknowledge that there may be a difference in the way that costs were calculated in the two versions of NHS Reference Costs. However, there is no evidence to suggest that excess bed days have been incorporated into the cost estimates in the 2019/20 version. The unit costs reported in the NHS Reference Costs represent a weighted average across all episodes reported, and thus is representative of a hospital spell with an average length of stay. The length of stay reported in the ADVOCATE trial is likely to be longer than the average length of stay in clinical practice in the UK, based on the most recent version of NHS Reference Costs which reported mean length of stay for this category of hospital spell. This means that an adjustment is required in order to ensure that the cost estimate in the model reflects the true cost of hospital care for this population. 3. **ERG:** Thirdly, the unit cost for all but Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, with Interventions (i.e., for Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with

		CC Score 5+; Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with CC Score 2-4; and Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with CC Score 0-1) decreased substantially. **Company response:** The ERG statement contains an error: in addition to Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, with Interventions (DZ29G), the costs associated with Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with CC Score 5+ (DZ29H) also increased for both elective and non-elective episodes, in addition to Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with CC Score 0-1 (DZ29K) for non-elective episodes. The various unit costs for AAV hospital episodes both increased and decreased, which is expected given the high levels of uncertainty and low episode counts recorded in NHS Reference Costs for this rare disease. A modest increase in the weighted average unit cost across all relevant HRG codes was observed between 2017/18 and 2019/20 (Table 2). The company disagrees with the ERG preferred approach of excluding excess bed day costs as this will underestimate the cost of hospital care and ignore the differences in the length of stay between the avacopan and comparator arms observed in the ADVOCATE trial. The company has revised the approach for the estimation of hospital cost in the model. NHS Reference Costs 2017/18 will be used as the source of both the base unit costs and excess bed day cost. The final cost which is adjusted for excess bed days will be inflated to 2020 prices using the NHS cost inflation index. The cost of hospitalisation estimated in the model was compared against the estimates in the CPRD study to verify their external validity. The total per-member cost reported in the first five years associated with rheumatology, nephrology, and ENT visits in the CPRD study was [redacted]. The undiscounted 5-year cost estimated in the CYC+GC comparator of the model (patient group which most closely matches the population in the CPRD study) was £11,848. The total hospital

		cost estimated in the model was therefore reflective of the cost observed in clinical practice in the UK and may in fact be an under-estimate.
8. Representativeness of modelled annual health care costs	Yes/No	**Issue:** the ERG raised its concern that the total healthcare cost estimated in the model is substantially lower compared to the cost reported in the CPRD study. **Company response:** the company acknowledge that there is a substantial difference in the total undiscounted cost estimated in the SoC arm of the model and the cost reported in the CPRD study. This difference may be explained by the fact that the total cost estimate in CPRD included the aggregate cost of all healthcare episodes, which included treatment of comorbidities unrelated to AAV. The total costs of specific episodes which were likely to be related to AAV (inpatient and outpatient episodes for rheumatology, nephrology and ENT) and drug treatments for AAV were similar to the corresponding costs in the model. It is possible that the total cost in the model did not account for hidden costs of AAV which were not considered within the parametrisation of the model. Given that a larger cost associated with worsening AAV (i.e. relapse and ESRD) would favour avacopan, it is reasonable to consider the current cost assumptions in the model to be conservative.
Abbreviations: AAV, anti-neutrophil cytoplasmic antibody–associated vasculitis; AZA, azathioprine; CYC, cyclophosphamide; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MTX, methotrexate; RTX, rituximab		

Table 1. Summary of studies reporting the cumulative incidence of ESRD in AAV

Study	Country	Recruitment period	N	Median follow-up	Cumulative incidence
Booth et al.[10]	UK	1995-2000	246	5.0	28.0%
Huang et al.[11]	China	2003-2017	141	5.3	25.5%
Lionaki et al. [12]	USA	1986-2007	523	5.3	26.0%
Mohammad et al. [13]	Sweden	1997-2009	183	4.6	20.2%
Scott et al. [14]	Ireland	2012-2020	332	3.4	22.0%

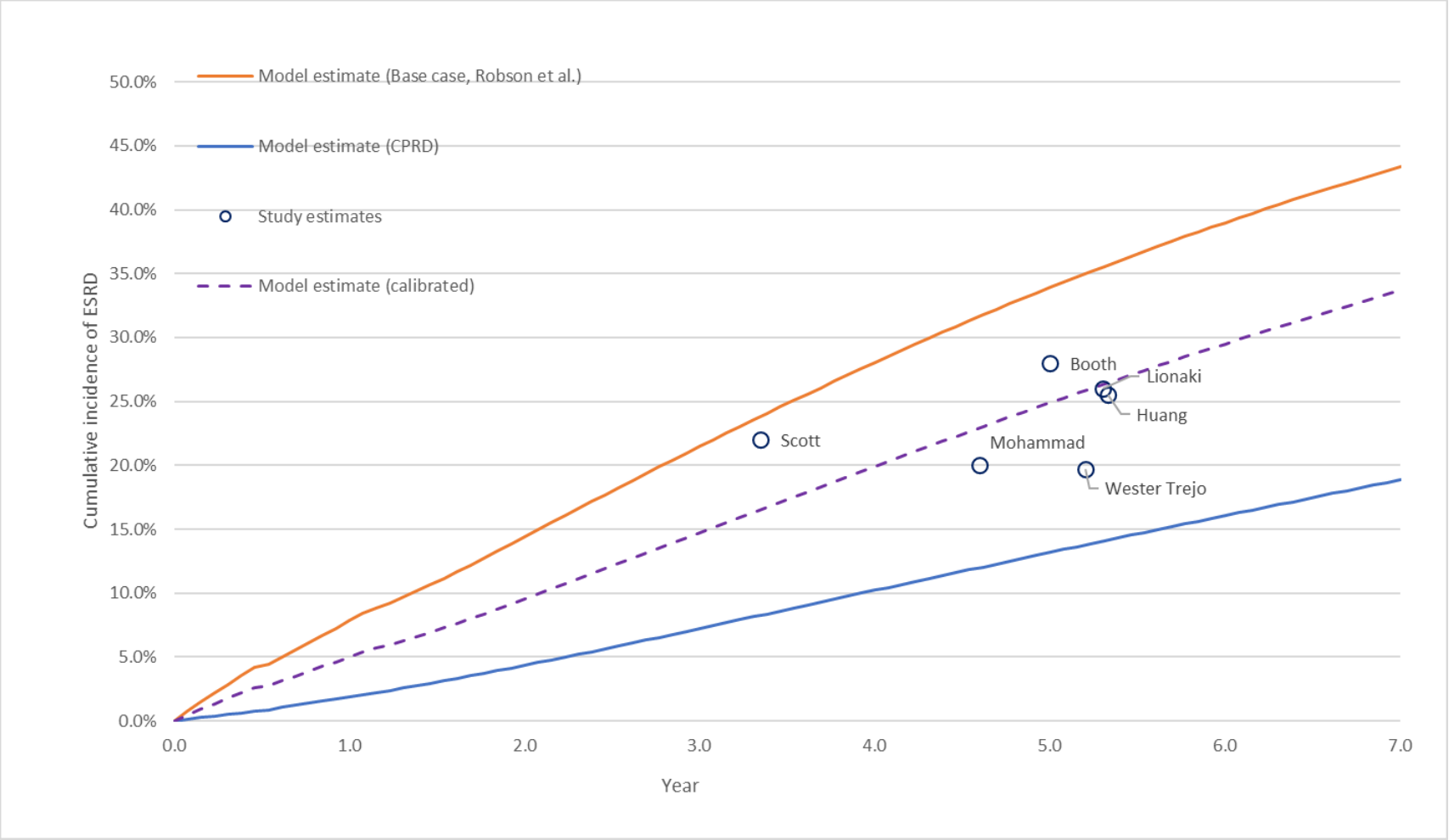
Wester Trejo et al. [15]	Multiple	1995-2002	535	5.2	19.7%

Table 2. Comparison of unit costs for granulomatous, allergic alveolitis or autoimmune lung disease from NHS Reference Costs 2017/18 and 2019/20

HRG	Cost (£) from NHS Reference Costs 2017/18	Cost (£) from NHS Reference Costs 2019/20	% change from 2017/18 to 2019/20
Elective			
DZ29G	5,232	5,900	13%
DZ29H	3,054	3,489	14%
DZ29J	2,069	1,955	-6%
DZ29K	1,450	1,012	-30%
Weighted average	2,692	2,724	1%
Non-elective			
DZ29G	5,292	5,511	4%
DZ29H	2,621	2,962	13%
DZ29J	2,076	1,930	-7%
DZ29K	1,506	1,714	14%
Weighted average	2,748	2,887	5%

DZ29G: Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, with Interventions;
DZ29H: Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with CC Score 5+
DZ29J: Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with CC Score 2-4
DZ29K: Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with CC Score 0-1

Figure 1. Comparison of cumulative incidence of ESRD reported in published studies in AAV and the model



Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Transition probabilities from active disease and remission into relapse	Section 4.2.6.2	Yes	**Issue:** the ERG raised its concerns regarding the company's assumption that remission rates are the same for patients in the active disease and relapsed disease health states. The ERG noted that analyses of pre-specified subgroup analyses from the ADVOCATE trial submitted by the company showed that the difference in remission rates between the two treatment arms were reported for relapsed patients, but not for newly diagnosed patients. Given that the ADVOCATE ITT population consisted of a mixed population of relapsed and newly diagnosed patients, it may not be reasonable to assume that remission rates are the same in the active disease and relapsed health states. **Company response:** the company agree with the ERG that remission rates may be different in the active disease and relapsed health states. In the technical engagement meeting, the company noted that relapse rates in 'remission 1' and 'remission 2' health states should not be assumed to be the same, given the difference in relapse rates in the newly diagnosed and relapsed subgroups from ADVOCATE. Therefore, the company updated the transition probabilities in the model to ensure that both the rates of remission and relapse reflect the correct patient population.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Company response: The company agree with the following model changes reported in the ERG report:

1. Model errors corrected by ERG
2. Corrected ESRD HR for mortality of 6.6
3. Treatment independent health state utility values (HSUV)

The changes above have been incorporated before calculating the starting ICER in "corrected company BC + accepted ERG changes" below. The incremental impact of each model change implemented by the company in response to the technical engagement, as well as the aggregate impact on the model results are shown in the table below.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Corrected company BC + accepted ERG changes (base case before additional company changes)	N/A	N/A	£15,043

Key issue 6	ESRD transition probabilities based on Robson et al. adjusted for decreasing eGFR due to relapse	Calibrated transition probabilities in line with previously published estimates of cumulative incidence of ESRD in AAV	£23,215
Key issue 7	Hospital costs based on unit costs from NHS Reference Costs 2019/20 and excess bed day costs from NHS Reference Costs 2017/18	Both base and excess bed day costs derived from NHS Reference Costs 2017/18 and inflated to 2020 using the NHS cost inflation index	£15,035
Additional issue 1	Probability of remission and relapse after first relapsed in the model informed by ADVOCATE ITT population	Probability of remission and relapse after first relapsed in the model informed by ADVOCATE relapsed subgroup	£13,273
All company changes combined (new company base case)	**N/A**	**N/A**	**£19,441**

Sensitivity analyses around revised base case

Deterministic sensitivity analysis: Tornado diagram

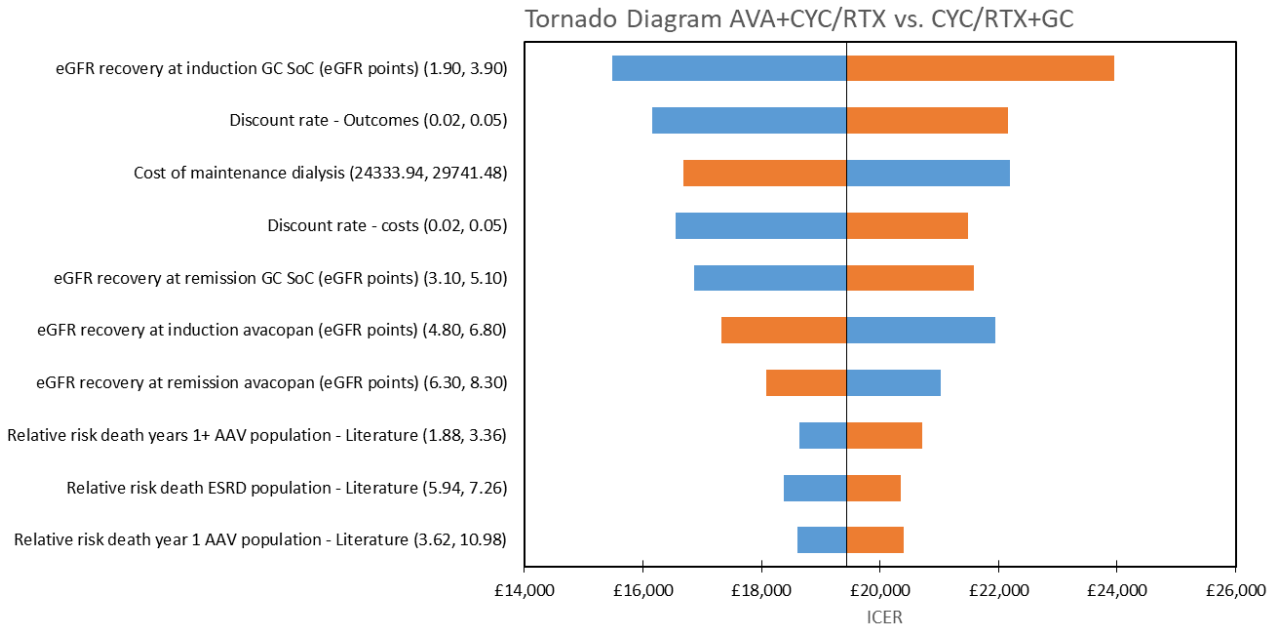


Table 3. Probabilistic sensitivity analysis results

Comparison	Incr. cost	Incr. QALYs	ICER per QALY
AVA+CYC/RTX vs. CYC/RTX+GC	[redacted]	[redacted]	£20,635

Figure 2. Probabilistic sensitivity analysis scatter diagram

Figure 3. Probabilistic sensitivity analysis cost-effectiveness acceptability plane

Table 4. Scenario analysis

Scenario	Incr. cost	Incr. QALYs	ICER per QALY
Updated company base case	[redacted]	[redacted]	£19,441
CPRD as the source of ESRD transition probabilities	[redacted]	[redacted]	£44,523

References

1. Chalisey, A. and M. Karim, *Guidelines for the management of ANCA-associated vasculitis with renal involvement*. 2021: NNUH.
2. NICE. *Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis.* 2014 [cited 2021 9th September]; Available from: https://www.nice.org.uk/guidance/ta308.
3. Ntatsaki, E., et al., *BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis.* Rheumatology (Oxford), 2014. **53**(12): p. 2306-9.
4. Gercik, O., et al., *Histopathological subgrouping versus renal risk score for the prediction of end-stage renal disease in ANCA-associated vasculitis.* Ann Rheum Dis, 2020. **79**(5): p. 675-676.
5. Ford, I., J. Norrie, and S. Ahmadi, *Model inconsistency, illustrated by the Cox proportional hazards model.* Stat Med, 1995. **14**(8): p. 735-46.
6. Gopaluni, S., et al., *Effect of Disease Activity at Three and Six Months After Diagnosis on Long-Term Outcomes in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis.* Arthritis Rheumatol, 2019. **71**(5): p. 784-791.
7. Robson, J., et al., *Damage in the anca-associated vasculitides: long-term data from the European vasculitis study group (EUVAS) therapeutic trials.* Ann Rheum Dis, 2015. **74**(1): p. 177-84.
8. Padmanabhan, S., et al., *Approach to record linkage of primary care data from Clinical Practice Research Datalink to other health-related patient data: overview and implications.* Eur J Epidemiol, 2019. **34**(1): p. 91-99.
9. Gallagher, A.M., et al., *The Impact of the Choice of Data Source in Record Linkage Studies Estimating Mortality in Venous Thromboembolism.* PLoS One, 2016. **11**(2): p. e0148349.
10. Booth, A.D., et al., *Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study.* Am J Kidney Dis, 2003. **41**(4): p. 776-84.
11. Huang, X., et al., *Antineutrophil Cytoplasmic Antibody-Associated Vasculitis With Acute Kidney Injury: Short-Term Recovery Predicts Long-Term Outcome.* Front Immunol, 2021. **12**: p. 641655.
12. Lionaki, S., et al., *The clinical course of ANCA small-vessel vasculitis on chronic dialysis.* Kidney Int, 2009. **76**(6): p. 644-51.
13. Mohammad, A.J. and M. Segelmark, *A population-based study showing better renal prognosis for proteinase 3 antineutrophil cytoplasmic antibody (ANCA)-associated nephritis versus myeloperoxidase ANCA-associated nephritis.* J Rheumatol, 2014. **41**(7): p. 1366-73.
14. Scott, J., et al., *A cohort study to investigate sex-specific differences in ANCA-associated glomerulonephritis outcomes.* Sci Rep, 2021. **11**(1): p. 13080.
15. Wester Trejo, M.A.C., et al., *Renal relapse in antineutrophil cytoplasmic autoantibody-associated vasculitis: unpredictable, but predictive of renal outcome.* Rheumatology (Oxford), 2019. **58**(1): p. 103-109.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Avacopan for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with anti-neutrophil cytoplasmic antibody-associated vasculitis or caring for a patient with the condition. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report in Table 1.1.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Friday, 4 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with anti-neutrophil cytoplasmic antibody-associated vasculitis

Table 1 About you, anti-neutrophil cytoplasmic antibody-associated vasculitis, current treatments and equality

1. Your name	Zoι Αναστασα
2. Are you (please tick all that apply)	☒ A patient with this condition? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with this condition? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Vasculitis UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: A)I am a patient with ANCA associated vasculitis (AAV).

	B) I am a trustee of Vasculitis UK, a patient support organisation for people with all forms of vasculitis. I am one of our team that answers the helpline and I answer the emails sent to our organisation from patients reaching out for advice and support. Patients reach out to us daily. Furthermore I am an admin on two of our Facebook groups (the main group has more than 5,000 members) and on our HealthUnlocked online group (more than 7,000 members). Members of the groups share their personal worries, discuss their treatments and get peer to peer support. Side effects of steroids are frequently the subjects of discussions. Members have been asked to offer their experiences of being on steroids. ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with anti-neutrophil cytoplasmic antibody-associated vasculitis? **If you are a carer (for someone with anti-neutrophil cytoplasmic antibody-associated vasculitis) please share your experience of caring for them**	There are three (3) distinct types of ANCA associated vasculitis. The severity of the disease depends on how aggressive it is, what organs have been affected, how early it is diagnosed, the treatment plan and how the patient reacts to it. Vasculitis is a serious chronic illness, and it can be fatal if not diagnosed early and treated properly. I was diagnosed in 2014 and was treated by the guidelines. My initial treatment included high dose of steroids (prednisolone) and cyclophosphamide infusions. Maintenance treatment was oral immunosuppressant (azathioprine) and slowly tapering prednisolone. The side effects of taking prednisolone for prolonged time have affected my life in different ways over the time and are still affecting me, years after I stopped them.

	My personal journey: In September 2014 I went to my GP with two ulcers, one on every leg. I had to return many times and get treated with antibiotics and creams. It took 7 weeks to heal. Tuesday 4th of November 2014 a rash appeared at the back of my left knee. By the next day it has spread in both legs, my joints were stiff and painful, and I couldn't walk without support. My GP surgery is just around the corner of my home, they were my first call. I was extremely lucky and the GP that examined me had come across vasculitis before. They sent me to hospital with a letter to the rheumatology team. I deteriorated fast, the first weeks in hospital are a blur. Vasculitis had affected sinuses, lungs, abdomen, skin and joints. I couldn't move at all; the pain was unbearable, and codeine and morphine were needed to subside the pain. Three (3) weeks later and after having daily blood tests, 2 CT scans, a visit to the dermatology department, a bronchoscopy, a nose biopsy and daily visits from the rheumatology team, I was diagnosed with Granulomatosis with polyangiitis (GPA). My first treatment plan started with 60mg prednisolone daily, followed by 6 cyclophosphamide infusions. A few days after starting prednisolone I started being able to move and take my first steps aided. The next few months I only left my house to attend medical appointments. My mobility slowly got better, but I was very fatigued. Having insomnia didn't help. It got harder and harder to keep a good diet. I was ravenous all the time, I craved sugary foods that I never liked. My weight increased, my face got round, and I didn't recognise myself. I started having bad mood swings and night sweats. It was a very difficult time for my family. My rheumatologist and my GP agreed these were side effects of the steroids and they put me on antidepressants. In May 2015 I am declared in clinical remission, and I start my maintenance treatment plan. I am still on steroids although a lower dose (30mg) and I start an oral immunosuppressant. I slowly started to feel better, but I could still not walk

	more than 200 steps. My first DEXA scan shows osteopenia in my hips and osteoporosis in my spine despite being on calcium and vitamin D from the start of my treatment. Another side effect of steroids. I was on steroids for a bit more than 3 years, but their side effects are still part of my life. The osteoporosis in the spine has caused degeneration of the spine, collapsed disks and a trapped nerve causing pains on my lower back and across my right leg. Furthermore, in my last vision check I was surprised to get diagnosed with cataracts in both eyes. The optician said it is a common side effect of steroids and that I will need a surgery in a few years. I was declared in full remission seven (7) months ago and up to now I haven't flared up. I still have mobility issues and fatigue episodes. I work, but it has been increasingly more difficult. Life with vasculitis has good and bad days and that affects me and the people around me.
7a. What do you think of the current treatments and care available for anti-neutrophil cytoplasmic antibody-associated vasculitis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	a) I understand the necessity of treatment, without the current treatments I wouldn't be alive. I wish though they came with less side effects as they have affected my quality of life. b) Patients given steroids are often concerned about the side effects. Insomnia, mood swings, increased appetite and weight gain are what concern them most, but many are aware of the risk of osteoporosis, cataracts and diabetes. Questions about alternative medication are commonly raised.
8. If there are disadvantages for patients of current NHS treatments for avacopan (for example, how avacopan is given or taken, side effects of treatment, and any others) please describe these	Avacopan will be used in the same way as the current treatment. As all medication it comes with possible side effects. Side effects from Avacopan are only known from the trials, most side effects from steroids are well documented.

9a. If there are advantages of avacopan over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does avacopan help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	A) Comparing Avacopan and the current treatment (steroids), Avacopan promises better quality of life to the patients taking it while having similar effectiveness to the current treatment. B) N/A C) Use of Avacopan would result in reduction of steroid toxic effects as shown on the Advocate trial.
10. If there are disadvantages of avacopan over current treatments on the NHS please describe these. For example, are there any risks with avacopan? If you are concerned about any potential side effects you have heard about, please describe them and explain why	The greatest risk according to the trials is that it can cause liver problems. How regularly will the patient need to be monitored (LFT blood tests)?
11. Are there any groups of patients who might benefit more from avacopan or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Most patients suffering from vasculitis have steroids included in their treatment plan. These with ANCA associated vasculitis and having other comorbidities will benefit mostly from the use of Avacopan. There is a group of patients who suffer from vasculitis (Large Vessel Vasculitis/ Giant Cell Arteritis) and who are often relapsing and therefore have to often increase their steroid dose who could but will not benefit from Avacopan.
12. Are there any potential equality issues that should be taken into account when considering anti-neutrophil cytoplasmic antibody-associated vasculitis and avacopan? Please explain if you think any groups of people with this condition are particularly disadvantaged	None as far as I know.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	ANCA associated vasculitis is a serious chronic illness and most patients look forward to new effective treatments, especially if they have less side effects. Having a good quality of life, being able to be a contributing citizen, being less of a burden to the system are important to vasculitis patients. According to the ADVOCATE trial, Avacopan is possibly a new effective treatment. It may be beneficial to award a temporal approval so its effectiveness could be properly assessed.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

1. The narrower population in the company submission may impact generalisability of the findings.	
2. The inclusion of glucocorticoids in the intervention group may have generated biased effect estimates of the intervention.	

3. The list of comparators differs from the list in the final scope issued by NICE, potentially affecting the relative apparent efficacy, safety, and cost of avacopan.	
4. The model assumes only azathioprine is used during the maintenance phase of the treatment. However, BSR/BHPR guidelines specify that rituximab may be used for maintenance treatment for patients achieving remission after rituximab induction.	My understanding is that the model was planned according to the guidelines. In more recent time the guidelines changed allowing the use of Rituximab as a maintenance treatment. Treatment will always be evolving, and trials are planned and run at a certain time following the existing guidelines. Therefore the best way to see the effectiveness of Avacopan in patients treated according to the newest guidelines would be to award a temporal approval.
5. The estimated hazard ratio (pooled estimate versus single study) of developing ESRD has a large impact on the cost effectiveness results.	

Patient expert statement

6. The company explored two different approaches to estimate the probability to transition the ESRD leading to very different results.	
7. Validity of costing approach used for hospitalisation costs	
8. Representativeness of modelled annual health care costs	
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Steroids are almost always part of the treatment plan to manage ANCA associated vasculitis, a serious chronic illness that can be fatal if not treated.
- The side effects from steroids decrease the quality of life of the patients and in some cases increase comorbidities.
- According to the ADVOCATE trial Avacopan is a safer medication that is effective in controlling active ANCA associated vasculitis.
- On that basis, approval of Avacopan (at least temporarily) should be considered.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Avacopan for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report in Table 1.1. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Clinical expert statement

Avacopan for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Friday, 4 March 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

Avacopan for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating anti-neutrophil cytoplasmic antibody-associated vasculitis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Lorraine Harper
2. Name of organisation	University of Birmingham
3. Job title or position	Professor of Nephrology and Honorary Consultant
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with this condition? ☒ A specialist in the clinical evidence base for this condition or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none

8. What is the main aim of treatment for anti-neutrophil cytoplasmic antibody-associated vasculitis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	ANCA associated vasculitis is a chronic inflammatory relapsing-remitting disease. Disease is manged in 2 phases; initial induction therapy is given to control inflammation and induce disease remission and reduce damage associated with disease, especially kidney damage. Maintenance therapy is given to prevent the disease relapsing and causing further damage. .
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement in BVAS with best response being BVAS 0 – BVAS is a tool developed to help assess total disease system involvement. BVAS =0 implies no evidence of any disease activity Improvement in kidney function – any improvement is good as the longterm outcome is predicted by kidney disease and deterioration in kidney function predicts ESKD
10. In your view, is there an unmet need for patients and healthcare professionals in anti-neutrophil cytoplasmic antibody-associated vasculitis?	
11. How is anti-neutrophil cytoplasmic antibody-associated vasculitis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Widely implemented guidelines exist including from the British Society of Rheumatology, BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis | Rheumatology | Oxford Academic (oup.com) and the American College of Rheumatology 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis Induction therapy for those with severe or organ threatening disease included cyclophosphamide or rituximab and are given with high dose tapering corticosteroids. Maintenance therapy is commenced 4-6 months after induction therapy and is with an anti-proliferative agent such as azathioprine or methotrexate (if no renal

	disease) or rituximab in setting of low-dose corticosteroids, which are continued for at least 2 years. Methotrexate is contra-indicated in those with renal disease. Induction therapy for mild/limited disease is with methotrexate or mycophenolate with high-dose tapering steroids. Methotrexate is continued into maintenance therapy, mycophenolate has less benefit for maintenance therapy and is changed to azathioprine. Patients who relapse are re-induced usually with a standard induction regimen and then provided with rituximab maintenance especially if there is concern about further organ damage. Pathways for the management of AAV is well defined and supported by NHS specialist commissioning policies. Specific details of pathways will vary dependent on presenting symptoms. Although patients may present to ENT or respiratory specialties most patients are managed by rheumatology or nephrology specialties; in some regions joint specialty clinics will manage these patients. Regional networks exist in many regions that facilitate expert management and sharing of best practice. Initiation of treatment occurs in secondary care and maintenance treatment is manged often under shared care agreements between secondary and primary care. NHS commissioning recommend discussion of rituximab maintenance therapy with specialist services prior to commencing rituximab maintenance therapy. Avacopan will be used as a corticosteroid replacement and it is unlikely that it will have an impact on current treatment pathways.

	Corticosteroids, particularly at high dose or with high cumulative dose, are associated with significant toxicity which contributes to patient morbidity and mortality. A targeted therapy, such as avacopan, with fewer off target adverse events will reduce healthcare costs associated with diagnosis and management of corticosteroid toxicities. Reduced relapse rates will be associated with reduced organ damage and better longterm outcomes.
12. Will avacopan be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Avacopan is not currently available except on compassionate use from the company. Avacopan will be used to replace corticosteroids and will be used in the same way as current care pathways. It is likely that healthcare resource use will be lower in patients receiving avacopan compared with corticosteroids. In the ADVOCATE trial corticosteroid related toxicity was significantly lower in patients receiving avacopan. Lower steroid use in the PEXIVAS trial suggests reduced risk on infection and its expected that this will also be seen when using avacopan in real world settings compared with high dose steroids. The greatest risk of infection is during the first 3-6 months after diagnosis when steoid dose is high. Infection and cardiovascular disease are the commonest causes of death in patients with AAV and both have been associated with corticosteroid usage, even at low dose (wu cmaj 2019; Pujades-Rodriguez M Plos Med 2020). Corticosteroids are associated with hypertension (Mebrahtu CMAJ 2020), an important risk factor for CKD progression. Management of chronic kidney disease and risk of progression is an important use of healthcare resource, which is likely to be reduced by

	avacopan due to its improved effects on kidney function and proteinuria and lack of impact on hypertension. It should be noted that in those patients who received rituximab as induction therapy in the original trial they did not receive further maintenance therapy beyond avacopan or placebo between 6-12 months. This would not reflect standard of care. However it should be noted that the effect size seen in those patients who received avacopan and rituximab was greater compared to those receiving cyclophosphamide and azathioprine. This maybe of importance as rituximab reduces response to vaccination and avacopan may allow avoidance of longterm B cell depletion. Current treatment pathways are initiated in secondary care and its expected this would be similar for avacopan. No specific investment is required. Strengthening of local networks and physician/patient education will continue to improve all aspects of the management of this disease
13. Do you expect avacopan to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Mortality associated with AAV remains over 2 fold greater than the standardised mortality rate at 5 years despite improvements in care pathways. The commonest causes of death are infection and cardiovascular disease, both increased by corticosteroid use. Specifically reducing infection and cardiovascular disease, amongst other adverse events associated with steroids, will help to increase length of life compared to current standard of care. The ADVOCATE trial showed an improvement in quality of life in those treated with avacopan as compared to corticosteroids, which was also seen in the phase 2 studies. Quality of life remains persistently diminished for many patients with AAV despite successful treatment (O'Malley J Rheum 2019). Studies have

	suggested that much of this can be explained by fatigue. Using the SF36 vitality scale, there was considerably less fatigue in patients treated with avacopan compared with corticosteroids in the ADVOCATE trial. These findings suggest that health-related quality of life will considerably improve compared with current care.
14. Are there any groups of people for whom avacopan would be more or less effective (or appropriate) than the general population?	There is no evidence that there will be any patients where avacopan is less effective. However patients with a GFR of <15ml/min were excluded from the study. Previous trials that have excluded these patients when used in the real world have not shown differences in response to therapy (eg rituximab) Avacopan may be more effective in patients with severe renal involvement as there was a significant difference in improvement of renal function between the avacopan and corticosteroid group, especially in those with CKD stage 4. The reduction in proteinuria is also likely to reduce the risk of progression of CKD to ESKD if treated with avacopan compared with corticosteroids. Over 20% of patients gain >10kg in weight when treated with high dose steroids for AAV (Wung PK arthritis rheum 2008) and approximately 10% of patients develop steroid induced diabetes. In addition, many patients with a previous diagnosis will develop reduced control on high dose steroids increasing risk of diabetes-associated damage. These risks and increased healthcare usage will be mitigated by use of avacopan in over-weight/obese or diabetic patients. Patients with osteoporosis will not be exposed to further risk of bone demineralisation through steroid avoidance if treated with avacopan
15. Will avacopan be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?	It is likely that avacopan will be easier to use as there is no tapering of dose compared to corticosteroids which can be complicated for both physicians and patients. Due to this complexity, patients are often exposed to higher doses of steroids than is ideal or necessary increasing risk of toxicity.

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	No specific concomitant medication was administered for avacopan in the trial and vaccination against encapsulated organisms such as meningococcus is not required. No additional tests or monitoring is required beyond that used for current treatments.
16. Will any rules (informal or formal) be used to start or stop treatment with avacopan? Do these include any additional testing?	Anticipated that start/stop treatment will reflect current care pathways dependent on disease activity and adverse event monitoring.
17. Do you consider that the use of avacopan will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The main anticipated benefits not discussed 1. Reduced tablet burden and reduced complexity of dose tapering by avoiding corticosteroids 2. Patients report salient emotional, physical, and social effects of corticosteroids, including depression, anxiety, irritation, weight gain and change in appearance, and effects on family and work, that impact their quality of life (Robson Rheumatol Int 2018).
18. Do you consider avacopan to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is avacopan a 'step-change' in the management of the condition? • Does the use of avacopan address any particular unmet need of the patient population?	Avacopan is an innovative therapy that has potential to make a significant and substantial impact on the management of AAV. Avacopan has consistently shown improved renal function and proteinuria compared with steorids in both the phase 1 and 3 trials; improving renal function is one of the key targets of disease management. Avacopan has clearly shown a reduction in corticosteroid associated side-effects, a huge unmet need for this patient population. The persistent use of

	corticosteroids despite their impact of damage clearly highlights an unmet need for an alternative to this therapy. Robson et al showed that patients followed longterm after recruitment to the EUVAS trials showed the mean length of corticosteroid use was 40 months with 28% of patients still on steroids at 60 months despite 60% of patients having at least on treatment related adverse event and 17% having 3 or more treatment related damage items. (robson J Rheumatol 2015).
19. How do any side effects or adverse effects avacopan affect the management of the condition and the patient's quality of life?	The side-effects and adverse events seen in the ADVOCATE trial were not significantly dissimilar between the two limbs apart from steroid related adverse events. The number of events was not unexpected and comparable to previous trials recruiting patients with AAV and severe/organ threatening disease. The lack of steroid-associated toxicity is likely to improve the management of the condition and patient quality of life.
20. Do the clinical trials on avacopan reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The trial reflects current practice apart from the lack of maintenance therapy in those treated with rituximab induction therapy. However, patients who received cyclophosphamide induction did receive maintenance therapy which reflects current practice, reassuring that results are valid for the UK population. The trial used remission at 26 weeks (defined by BVAS 0 and no steroids for the previous 4 weeks) and sustained remission at 52 weeks as primary outcomes both are important. Failure to achieve remission at 6 months or early relapse are associated with worse clinical outcomes. BVAS a score of disease activity is used universally in clinical trials of AAV, a score of 0 suggests no disease activity. Renal function, glucocorticoid toxicity, relapse, quality of life are all very important outcomes and measured appropriately. No important outcomes were missed in this trial. Renal function is a particularly important outcome as it predicts progression to ESKD and mortality.

	No known adverse effects not apparent in the clinical trial that I am aware of.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA308?	No
23. How do data on real-world experience compare with the trial data?	Real-world experience is not available
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	No equality issues that I am aware of

• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

1. The narrower population in the company submission may impact generalisability of the findings.	It is unlikely that the narrower population will impact generalisability. ANCA associated vasculitis consists of microscopic polyangiitis, granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis (EGPA). EGPA is generally excluded from clinical trials of AAV, which focus on MPA and GPA. EGPA responds differently to therapy, has a different pathogenesis from the other 2 conditions,is significantly rarer and generally managed differently dependent on presentation. It would not be appropriate based on current knowledge to include EGPA in the submission. The submission focuses on patients with severe MPA or GPA, as these were the patients recruited to the trial. Patient management is usually divided into patients with severe/organ threatening disease treated with rituximab or cyclophosphamide based induction regimens or limited disease treated with methotrexate or mycophenolate based regimens. All receive corticosteroids but dosing may vary with higher doses given to those with more severe disease. The submission is based on severe disease for patients requiring induction with cyclophosphamide or

Clinical expert statement

	rituximab who have organ threatening disease and often includes those with so-called limited disease. In a large cohort of incident GPA patients over 80% of individuals were treated with cyclophosphamide initially despite routine use of methotrexate as induction therapy (holle J 2011 arthritis and rheumatology). Although patients with limited disease often receive "milder" induction therapy with lower doses of steroids, patients with limited disease often progress to develop organ threatening disease requiring re-induction with cyclophosphamide or rituximab in combination with steroids. A large cohort of patients with GPA identified only 5% had localised disease without systemic involvement. Patients with localised disease frequently required cyclophosphamide induction therapy (47%) due to destructive disease (holle j ARD 2010). The disease is very rare in children.
2. The inclusion of glucocorticoids in the intervention group may have generated biased effect estimates of the intervention.	Please provide your response to this key issue, including any new evidence, data or analyses The inclusion of corticosteroids within the intervention during screening and rescue reflects real world practice. The use of steroids during screening may have reduced effect estimates on toxicity of the intervention but is less likely to have effected effect size at 6 or 12 months as the expected duration of effect of steroid use prior to inclusion in the study would be less than 3 months. This assumption is supported by the PEXIVAS trial which included 1.5-3g IV methylprednisolone prior to randomisation to the low or standard of care prednisolone. The initial dose of steroids was very similar between the two limbs. In this study there was a 40% reduction in cumulative dose of steroids for patients 50-75kg by 6 months (from week 2-24) with similar dosing from 6-12months. This study showed there was a clear benefit to patients randomised to the low dose regimen with fewer infections by 1 year but no difference in remission (walsh m NEJM 2020) suggesting the importance of the cumulative dosing on morbidity. This trial was twice the size of the avacopan study which may explain the lack of demonstration of steroid dose reduction on infection risk in the avacopan trial.

	Although corticosteroids are associated with significant toxicity at high dose and from the cumulative dose with side-effects such as osteoporosis and cataracts developing over time, they are frequently used prior to a definitive diagnosis being made. They are very effective anti-inflammatory drugs and as such are often prescribed as rescue prior to diagnosis. They are also used as part of maintenance therapy; 37% of patients included in the study had disease relapse disease and would likely be on corticosteroids as part of the maintenance therapy prior to relapse. Excluding corticosteroids at screening and rescue would have made the trial impossible and would not reflect standard of care in the UK. The prior use of corticosteroid appeared balanced between the two groups in the trial. Despite this the reported use of steroids in the avacopan group was 63% less and there was evidence of significantly less toxicity and improved quality of life, although their was no reduction in serious infections. This is as important as maintaining remission. The impact of toxicity of steroids on patients cannot be under-estimated and is a significant area of unmet clinical need.
3. The list of comparators differs from the list in the final scope issued by NICE, potentially affecting the relative apparent efficacy, safety, and cost of avacopan.	Please provide your response to this key issue, including any new evidence, data or analyses Avacopan was used in the ADVOCATE trial to treat those with severe disease and the comparator was corticosteroids. Corticosteroids were only allowed in the avcopan intervention during screening and as rescue for relapse. Induction therapy for patients in the UK with severe or organ-threatening disease is rituximab or cyclophosphamide in combination with corticosteroids as standard of care. Mycophenolate is not routinely used as standard induction therapy for severe disease; the MYCYC trial showed similar remission rates later relapse rates were higher and the trial excluded patients with rapidly progressive renal disease. It has not been adopted as routine standard of care induction therapy in the UK for those with severe disease. Methotrexate is used only for patients with limited disease and cannot be used for patients with renal disease.

	The narrower list of comparators is not likely to impact on the efficacy, safety and cost of avacopan.
4. The model assumes only azathioprine is used during the maintenance phase of the treatment. However, BSR/BHPR guidelines specify that rituximab may be used for maintenance treatment for patients achieving remission after rituximab induction.	Maintenance therapy following induction of remission is recommended by guidelines for at least 24 months. The standard of care for maintenance therapy in the UK at present is azathioprine plus low dose corticosteroids, although increasingly rituximab maintenance is being used. Current specialist commissioning guidance supports rituximab maintenance in those who have had previous rituximab induced remission requiring re-induction and in those who are cyclophosphamide refractory who require induction with rituximab and there is risk of organ damage if a future relapse was to occur. Despite this not being included in the original trial the submission has agreed to include an exploratory analysis of using rituximab as maintenance therapy. This is to be encouraged. It is stated that the treatment effect of rituximab maintenance will cancel out if the model assumes it is applied to both avacopan and standard of care, this is a reasonable assumption. However, it is likely that the absolute number of relapses will reduce significantly in both treatments. The impact of the COVID pandemic may affect future use of rituximab as a maintenance agent. Rituximab severely inhibits response to the SARS-CoV2 vaccine due to the prolonged impact on B cells and their depletion. This is likely to push routine maintenance back to azathioprine focused regimens. This is potentially important in the modelling as an agent that maintains remission without impacting vaccine response rates would be highly beneficial. Methotrexate maybe used as maintenance therapy in those without renal involvement however there is no evidence that methotrexate is any safer or more effective than azathioprine at maintaining remission (Pagnoux C NEJM 2008). It is acceptable not to include this in the comparator of maintenance therapy.
5. The estimated hazard ratio (pooled	The risk of ESRD is very dependent on the population studied in clinical practice and includes renal function at diagnosis and remission, disease type, degree of persistent proteinuria and other risk factors known to increase

estimate versus single study) of developing ESRD has a large impact on the cost effectiveness results.	risk of CKD progressing. The assumptions made will impact on the risk of ESRD development and cost-effectiveness. It is not unreasonable to use a pooled estimate rather than a single study as most single studies limit the inclusion criteria for the trial, for example NORAM limited inclusion to patients with Creatinine<150umol/l and had no incidence of ESRD at 1 year and 1 patient in longterm followup over 7 years CYCLOPS and CYCAZERAM limited inclusion to patients with renal involvement with creatinine 150-500umol/l and had moderate rates of ESRD, approximately 20% after achieving remission MEPEX included patients with creatinine >500umol/l and had high rates of ESRD varying between 40-60% PEXIVAS, which recruited those with GFR<50ml/min had a probability of 20% death or ESRD at 1 year
6. The company explored two different approaches to estimate the probability to transition the ESRD leading to very different results.	Both approaches require significant assumptions to be made and there are challenges with the quality of the data available. If using CPRD data, it is likely to miss a large number of patients with MPA due to coding (ICD 10 code not good for MPA, which registers it as polyarteritis nodosa). Most studies that report CPRD data only identify GPA patients due to the coding issue. This means that CPRD may under-estimate the number of patients who progress to develop ESRD. Patients with MPA are more likely to progress to ESKD than patients with GPA (10.7% versus 3.5% in Robson se al) and MPA patients frequently present with worse renal function than GPA patients and have worse outcomes. The GPA data included will not differentiate between those with sever/organ-threatening disease and limited disease. Those with limited disease have a much lower probability of progression to ESRD, as reflected in the NORAM trial. There may also be significant data quality issues around GC dosing. The use of advocate data and literature may give a more realistic assessment of risk of ESRD for the population, although this does depend on the population included from the literature. This opinion is based on my previous use of CPRD data for research purposes. I am not a health economist

7. Validity of costing approach used for hospitalisation costs	This is outside my area of expertise
8. Representativeness of modelled annual health care costs	This is outside my area of expertise
Are there any important issues that have been missed in ERG report?	Not that I am aware of

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Avacopan for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report in Table 1.1. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Clinical expert statement

Avacopan for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Friday, 4 March 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

Avacopan for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating anti-neutrophil cytoplasmic antibody-associated vasculitis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Peter Lanyon
2. Name of organisation	NHS England Specialised Rheumatology Clinical Reference Group
3. Job title or position	Consultant Rheumatologist and National Clinical Co-Lead for Rheumatology, Getting It Right First Time (GIRFT), NHS England and NHS Improvement
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with this condition? ☒ A specialist in the clinical evidence base for this condition or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☒ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for anti-neutrophil cytoplasmic antibody-associated vasculitis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The aims of treatment are to • induce clinical remission (e.g., to obtain rapid resolution of clinical manifestations of active vasculitis, to prevent active disease progressing to organ damage/death, and to minimise the risk of treatment related toxicity whilst minimising morbidity associated with active disease) • maintain remission (e.g., the avoidance of disease relapse which has a risk of both organ damage and toxicity associated with remission induction agents) • reduce long term morbidity associated with vascular inflammation and the risk associated with immunosuppression treatment including steroids • reduce the negative impact of treatment on health protection strategies e.g., vaccine effectiveness
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Achieving remission defined by BVAS score (zero) Sustaining relapse-free remission Avoidance of organ damage accrual assessed by VDI score Avoidance of Adverse Events including glucocorticoid toxicity
10. In your view, is there an unmet need for patients and healthcare professionals in anti-neutrophil cytoplasmic antibody-associated vasculitis?	Yes. There are several facets of unmet need, specific to ANCA – associated vasculitis but which also reflect the wider needs of people living with rare diseases Prior to the point of accessing the pathway of care, many people may have had diagnostic delays (the diagnostic “odyssey”) reflecting the difficulties and unmet needs faced by people with rare diseases in general, and ANCA - associated vasculitis specifically, to obtain more timely diagnosis. These needs have been highlighted in the England Rare Diseases Action Plan (DHSC February 2022) and in publications using lived experience data by Vasculitis UK and the Rare Autoimmune Rheumatic Disease Alliance, RAIRDA, https://rairdaorg.files.wordpress.com/2020/06/rairda-survey-report-2018.pdf and using routinely collected healthcare data https://doi.org/10.1093/qjmed/hcx194 https://doi.org/10.3310/nihropenres.1115171.1

	Despite current treatment pathways, this condition has the highest mortality of any of the autoimmune rheumatic diseases at approximately (13.6% in first year), indicating the unmet need for new therapeutic agents https://doi.org/10.1093/rheumatology/kew413 There is also an unmet need for pathways of care and treatments that reduce the susceptibility to infection in general (of which corticosteroids are a significant risk factor). And in the current NHS context, of reducing the risks associated with COVID-19 infection and other novel viruses. For example, during the first wave of the COVID-19 pandemic, people with rare autoimmune diseases including ANCA-associated vasculitis, had a 54% increased risk of COVID-19 infection and more than twice the risk of COVID-19-related death compared with the general population, despite shielding policies. https://doi.org/10.1093/rheumatology/keab794 In addition to reducing infection risks, there are also unmet needs to reduce relapse rates, as each relapse brings with it a risk of organ damage and treatment toxicity. There is also an unmet need to improve care by reducing variation in care pathways and access to treatment, as highlighted in audit data. 10.1093/rap/rky025
11. How is anti-neutrophil cytoplasmic antibody-associated vasculitis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis (currently being revised but last published 2014) https://academic.oup.com/rheumatology/article/53/12/2306/1802843

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis https://www.rheumatology.org/Portals/0/Files/Guideline-Management-ANCA-Associated-Vasculitis-2021.pdf Rituximab for maintenance of remission in ANCA-associated vasculitis: expert consensus guidelines https://doi.org/10.1093/rheumatology/kez632 The pathways are in general well defined and facilitated by previous NHS England commissioning policies related to the treatment of ANCA-associated vasculitis. There will be some variation in care pathways according to both the presenting (organ) features of the disease and according to which specialties leads on the management of these condition in each NHS Trust. For example, in HES data (Hospital Episode Statistics), the specialty treatment function codes (TFC) that associate with an ICD code for ANCA-associated vasculitis combined with an OPCS code for an intravenous cytokine inhibitors band 1 (which includes rituximab) are predominately rheumatology and nephrology, indicative of the main specialties involved in the pathway of care (source: GIRFT National Specialty Report for rheumatology) There may also be variation in access to specialised MDT care when needed, and in whether an NHS Trust needs to seek external approval for the use of rituximab as maintenance therapy depending on whether that Trust is a recognised specialised centre on the Provider Eligibility List. These arrangements have been facilitated by the development of NHS England regional networks for autoimmune diseases/specialised rheumatology and the existence of informally recognised major tertiary/national centres of expertise for complex or refractory cases.

• What impact would the technology have on the current pathway of care?	There is likely to be no significant increase in resources required to implement the technology into current pathways of care. The ability of the technology to reduce steroid use and steroid associated toxicity and hence adverse events is likely to lead to less healthcare interaction related to assessing and treating these events. The ability to reduce relapse risk to week 52 (e.g., an increase in the proportion of people who have a sustained remission) would also be anticipated to lead to a reduction in the healthcare usage related to relapse.
12. Will avacopan be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	In terms of resource use associated with serious adverse events, comparison between the avacopan and steroid groups indicates higher risk in the prednisone group than in the avacopan group. There were more deaths, life-threatening or serious adverse events, and infections in the prednisone group than in the avacopan group. This is consistent with the higher glucocorticoid exposure. The resource use associated with this would therefore be anticipated to be lower with avacopan use. It is worth noting that although the Advocate trial did not include maintenance rituximab after the initial treatment course, at week 52 the magnitude of the treatment difference between avacopan and prednisolone arms is greater for the patients who receive rituximab induction compared to cyclophosphamide and subsequently azathioprine. This is an important consideration and should be interpreted in light of the current NHS landscape that the clinical community is trying where possible if clinically appropriate to reduce exposure to rituximab during the COVID-10 pandemic. This is because ongoing B cell depletion risks a poor response to vaccination, leading to this exposure (rituximab) being included as a high priority group in the community roll-out of nMABs and antivirals for people with COVID-19 who remain vulnerable to infection. In other words, a drug

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	that may have any rituximab-sparing potential or a relapse-prevention potential may have additional beneficial implications for the NHS that might not be captured in existing economic models. There is likely to be discussion about implementation models for this treatment and whether this technology will require to be given at or in discussion with a specialised centre. However, it will be important to note that patients with this condition are likely to present acutely for remission induction treatment to any NHS Trust, and for example, the NHS England Commissioning Policy for use of rituximab in ANCA-associated vasculitis does not mandate specialised centre involvement for initiation of treatment, to avoid delays. Given that the most important aspect of care is rapid initiation of the best treatment and given that the comparative mortality risks are highest in the early months from diagnosis, it may be more appropriate not to limit initiation by requiring involvement of a specialised centre MDT, as the frequency at which these are held varies according to geography, unless these networks are strengthened and operate consistently. Education for health professionals and patients. Strengthening of existing specialised networks depending on commissioning model
13. Do you expect avacopan to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care?	Yes, this is difficult to quantitate in terms of specific benefit but a reduction in steroid related toxicity and the associated morbidity associated with this is likely to have a beneficial effect on life expectancy. Each relapse of disease potentially comes with a risk of mortality from active disease and therefore any reduction in relapse risk is likely to influence life expectancy. The main drivers of mortality are infection and active disease.

• Do you expect the technology to increase health-related quality of life more than current care?	Yes via the same mechanisms
14. Are there any groups of people for whom avacopan would be more or less effective (or appropriate) than the general population?	The only data I am aware of is from the appraisal documents which would appear to indicate greater benefit in rituximab treated patients, relapsing patients and those with MPO/MPA antibodies and renal disease, although there may be limitations to the power of subgroup analysis and would need biologic explanation. Remission rates at week 26 appears higher in relapsing than in new patients, although it is possible that this is an effect of the fact that the relapsing patients have already demonstrated an ability to go into remission (at their initial remission induction). The ability to reduce relapse rates in a population who have already been identified to be at risk of relapse (because they have relapsed already) is significant
15. Will avacopan be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Likely neutral effect, no barriers to practical implementation due to oral route
16. Will any rules (informal or formal) be used to start or stop treatment with avacopan? Do these include any additional testing?	I would anticipate that stopping criteria will be for attributable adverse events, likely to be detected because of the existing current close monitoring arrangements for this patient group in routine care
17. Do you consider that the use of avacopan will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The ability to reduce the risk of relapse and by doing so reduce the risk of needing further rituximab may, in the context of COVID-19 associated with steroids and rituximab, may have additional benefits that may not be captured in a cost-effectiveness analysis.
18. Do you consider avacopan to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is avacopan a 'step-change' in the management of the condition? • Does the use of avacopan address any particular unmet need of the patient population?	The data from the advocate trial of the ability of avacopan to substantially reduce the use of glucocorticoids and also reduce relapse risk in the first year is a ground-breaking innovation. Yes, addresses unmet need of to reduce steroid burden, and reduce risk of relapse
19. How do any side effects or adverse effects avacopan affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on avacopan reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes Outcome measures in the trials were appropriate including use of BVAS to define initial and sustained remission and GC related toxicity Not aware of any

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA308?	No
23. How do data on real-world experience compare with the trial data?	Not aware of any real-world use
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	Not aware of any

• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

1. The narrower population in the company submission may impact generalisability of the findings.	The CS is narrower than the Scope, by virtue of the fact that the 3rd (and least common) subtype of AAV, EGPA was not included in the Advocate clinical trial. It would therefore be appropriate for this trial population to be the scope i.e., all people with newly diagnosed or relapsed AAV subtypes GPA or MPA for whom remission induction with rituximab or cyclophosphamide is required (although it should be noted that there is precedence of an NHS England commissioning policy for ANCA-associated vasculitis to extend to all 3 subtypes despite the clinical trials only being GPA and MPA)
2. The inclusion of glucocorticoids in the intervention group may have generated biased effect estimates of the intervention.	Clinically, I think this would be unlikely to introduce a significant bias in the outcome if the “as required” e.g., non protocolised steroid use was the same in both treatment arms. These would appear to be broadly similar, noting slightly higher in the avacopan arm 1265mg vs 1348mg for the avacopan arm

Clinical expert statement

3. The list of comparators differs from the list in the final scope issued by NICE, potentially affecting the relative apparent efficacy, safety, and cost of avacopan.	I would suggest that Azathioprine is not an appropriate comparator for remission induction.
4. The model assumes only azathioprine is used during the maintenance phase of the treatment. However, BSR/BHPR guidelines specify that rituximab may be used for maintenance treatment for patients achieving remission after rituximab induction.	Maintenance rituximab would not routinely be used for remission maintenance, and not in new patients receiving their first remission induction unless they have been refractory to cyclophosphamide. A small subset of relapsing patients will also eligible for maintenance rituximab as per the NHS England commissioning policy (note that the original NHS England commissioning policy predates the NICE TA) “NHS England will commission the use of rituximab as maintenance therapy only when one of the following three clinical criteria, and all three additional centre criteria, is met. 1. The person is enrolled in a randomised trial that includes B cell suppression as maintenance therapy (e.g. RITAZAREM); OR. 2. Relapse requiring re-induction therapy has occurred after a previous rituximab induced remission; OR 3. Rituximab has been required to induce remission in Cyclophosphamide-refractory disease and future relapse would have a high risk of organ damage. In addition • The decision regarding rituximab maintenance has been made at, or in conjunction with, a specialised centre AND • The person has been provided with the opportunity to be considered for any suitable clinical trials AND • The person is registered on the UKIVAS database, to enable identification of use and outcome of treatment” In general, since COVID-19 pandemic, the clinical community is attempting where clinically appropriate to reduce the use of rituximab

5. The estimated hazard ratio (pooled estimate versus single study) of developing ESRD has a large impact on the cost effectiveness results.	Comments on point 5 and 6 It would be helpful to have additional scientific review of the CPRD report. These difference in risk of ESRD would potentially be influenced by different populations in this compared to other studies. The CPRD study reports on an AAV population that would appear to be have a potential bias in case ascertainment towards containing a much higher proportion of cases who have a GPA subgroup (who are known to have less risk of renal disease) compared to MPA. The ratio in the CPRD study between these 2 subgroups is very different to that which would be expected from other epidemiology studies in England which do not have an ascertainment bias. This bias will have been introduced because of the difficulties in identify cases of MPA in the CPRD, and this is also linked to potentially inconsistent coding of MPA in HES. The CPRD paper does not report how many patients had GPA compared to MPA but appears to have 567 cases of which a maximum 73 had MPA. Epidemiology studies would suggest the expected ratio to be GPA:MPA:EGPA of 35.5% vs 57.9% vs 6.5% https://doi.org/10.1093/rheumatology/kew232 One approach to investigating this might be to establish the risk of ESRD between the 2 subgroups (MPA and GPA) in the CPRDR cohort and adjusting this for the expected ratio.
6. The company explored two different approaches to estimate the probability to transition the ESRD leading to very different results.	See above

7. Validity of costing approach used for hospitalisation costs	The resource use end points in the CPRD study appear, in terms of in patient resource use, to only capture Rheumatology inpatient admissions, Nephrology inpatient admissions and ENT inpatient admissions.? The majority of hospitals in England do not have rheumatology in-patient beds and so restricting to the 410 TFC will not detect the majority of admissions for diagnosis, relapse and infection. It is likely that the majority will be admitted under general medicine, and this may affect the costs identified
8. Representativeness of modelled annual health care costs	The CPRD study may not have adequately been able to detect remission and relapse due to the inability to detect secondary care prescribed medication for remission induction including steroids. In addition, some patients will be treated for early relapse with a dose of prednisolone below 30mg and have their shorter treatment course prescribed exclusively in secondary care.
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Avacopan for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

NICE National Institute for Health and Care Excellence

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Friday, 4 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Renal Pharmacy Group
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. The narrower population in the company submission may impact generalisability of the findings	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
2. The inclusion of glucocorticoids in the intervention group may have generated biased effect estimates of the intervention	Yes	Prednisolone tapering dose included is higher than in the PEXIVAS trial so that may have more side effects than a regimen aimed at in more recent practice. Was this looked at as part of the review?
3. The list of comparators differs from the list in the final scope issued by NICE, potentially affecting the relative apparent efficacy, safety, and cost of avacopan	No	If renal involvement methotrexate is never used
4. The model assumes only azathioprine is used during the maintenance phase of the treatment. However, BSR/BHPR guidelines specify that rituximab	Yes	Rituximab may be used for maintenance therapy and is commissioned for this use. Also I accept that the trial stopped at 52 weeks, however following rituximab induction a maintenance therapy is standard of care – further rituximab or azathioprine. KDIGO guidelines are not referenced.

may be used for maintenance treatment for patients achieving remission after rituximab induction		
5. The estimated hazard ratio (pooled estimate versus single study) of developing ESRD has a large impact on the cost effectiveness results	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
6. The company explored two different approaches to estimate the probability to transition the ESRD leading to very different results	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
7. Validity of costing approach used for hospitalisation costs	No	The cost of rituximab is significantly less than in the evaluation page 107. The table states a cost of rituximab per mg. This should be 1g using the prices in the document, however there is a much cheaper generic product available. Page 109, you would need LFT tests if the patient was having cyclophosphamide.
8. Representativeness of modelled annual health care costs	No	Little discussion around cardiovascular mortality and morbidity and diabetes from GC

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Centres ability to prescribe	Please indicate the section(s) of the ERG report that discuss this issue	No	If approved for use, Avacopan should be available both in Rheumatology and Renal specialist centres. Tertiary renal centres may not be the same as tertiary Rheumatology centres. Should also be available for shared care with primary care
Additional issue 2: practice varies slightly if renal involvement or only rheumatology, ie if renal then no methotrexate used	Please indicate the section(s) of the ERG report that discuss this issue	No	Should not include in the requirements for avacopan that methotrexate has been tried first
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

NICE National Institute for Health and Care Excellence

Technical engagement response form

Avacopan for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

NICE National Institute for Health and Care Excellence

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Friday, 4 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	UKIVAS (United Kingdom and Ireland Vasculitis Society)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. The narrower population in the company submission may impact generalisability of the findings	No	***The population defined in the NICE scope is people with newly diagnosed or relapsed anti-neutrophil cytoplasmic autoantibody-associated vasculitis (AAV). The population studied by the company is people with severe microscopic polyangiitis (MPA) or granulomatosis with polyangiitis (GPA) variant of newly diagnosed or relapsed AAV. The population studied by the company is therefore narrower than the population defined in the final NICE scope.*** **Our response** *Disease scope:* the Phase III ADVOCATE study included patients with MPA and GPA and excluded patients with EPGA. ANCA vasculitis includes all three diagnoses. We would agree with the scope of the Company Submission – that is, that Avacopan is considered as a treatment for MPA and GPA, and not for patients with EGPA. *Disease severity*: We support access to avacopan for all patients with MPA and GPA where avoidance of glucocorticoids is deemed to be clinically important.

2. The inclusion of glucocorticoids in the intervention group may have generated biased effect estimates of the intervention	No	***The intervention is described as avacopan in contrast to the comparator, which is described as the "prednisone-based regimen" in the clinical effectiveness section and "glucocorticoid" (GC) in the cost effectiveness section. This is potentially misleading given that GCs were given in addition to avacopan, and GCs given in addition to the randomised dose of prednisolone as required during the trial would form part of standard of care (SoC) on this basis. Whether the level prescribed is as would be expected in clinical practice is uncertain.*** **Our response** We agree with the ERG (Evidence Review Group) suggestion that GC be added to the description of both the intervention and comparator. However, we would also like to highlight that, in the Phase III ADVOCATE study, the addition of avacopan resulted in a significant and clinically meaningful reduction in cumulative GC dose and related toxicity.
3. The list of comparators differs from the list in the final scope issued by NICE, potentially affecting the relative apparent efficacy, safety, and cost of avacopan	No	***Whereas the company considers treatment including azathioprine (AZA) as a comparator treatment for inducing remission, the final NICE scope does not. Also, the company uses methotrexate (MTX) and MMR* [sic] *as alternatives to cyclophosphamide (CYC), whereas the final NICE scope does not. The different comparators could have affected the relative apparent efficacy, safety, and cost of avacopan.*** **Our response** Clinical trial data for avacopan only included induction treatment with either cyclophosphamide or rituximab, which are current standard of care. Thus, the scope of the STA should focus on this patient population.

4. The model assumes only azathioprine is used during the maintenance phase of the treatment. However, BSR/BHPR guidelines specify that rituximab may be used for maintenance treatment for patients achieving remission after rituximab induction	No	***The model assumes that only azathioprine is used during the maintenance phase of the treatment. However, British Society of Rheumatology/British Health Professionals in Rheumatology guidelines specify that rituximab may be used for maintenance treatment for patients achieving remission after rituximab induction. The company included (as exploratory analysis) the option to model rituximab as maintenance treatment (in line with the) instead of azathioprine but had to use a non-adjusted naïve comparison to do so.*** **Our response** We agree that using rituximab as maintenance therapy after rituximab-based induction may reduce the cost-effectiveness of avacopan. Although emerging data are highlighting higher cost implications of rituximab including secondary immunodeficiency and impairment of vaccine responses.
5. The estimated hazard ratio (pooled estimate versus single study) of developing ESRD has a large impact on the cost effectiveness results	No	***The estimated hazard ratio (pooled estimate versus single study) of developing ESRD has a large impact on the cost effectiveness results.*** **Our response** Please see response to Point 6 below.
6. The company explored two different approaches to estimate the probability to transition the ESRD leading to very different results	Yes	***The company explored two different approaches to estimate the probability of transition to ESRD. Both these approaches have merit but lead to very different results. When the transition probabilities are based on literature and ADVOCATE, they are about six times higher than when they are based on CPRD data.*** **Our response**

		CPRD data rely on accurate coding of vasculitis as a diagnosis and will include patients with all severity of disease. Although coding in CPRD for GPA has been considered reliable [Pearce F, Rheumatology 2017], coding for MPA has not, and patients with renal-limited MPA may be missed yet have the highest kidney failure risk. CPRD data have also shown much lower mortality than HES data [Pearce F 2017]. Other studies comparing data from ANCA vasculitis clinical trials to cohort registry data have also reported better outcomes with registry data, yet patients in RCTs are typically managed in expert centres [Pagnoux C, Experimental Rheumatology, 2015]. Further, there is insufficient detail in the CPRD database to assess severity, for example, frequency of kidney involvement, to permit any comparison with clinical trial eligibility. Thus, CPRD database estimates for kidney failure risk are not appropriate for a severe GPA/MPA population defined by the ADVOCATE trial. The ADVOCATE study only included patients with severe disease. Thus, it is unsurprising that progression to kidney failure was more frequent when analysing the trial data compared to CPRD data. Baseline risk of progression to kidney failure at diagnosis of ANCA vasculitis or at flare varies between patients, and there are recognised predictors of long-term kidney risk. A recent meta-analysis, for example, demonstrates the relationship between initial serum creatinine and the risk of kidney failure at 1 year (https://doi.org/10.1136/bmj-2021-064597). We suggest that subgroups of patients at greatest risk of kidney failure (those with eGFR <30 ml/min/1.73m^2 at diagnosis / flare) should be the main focus of the STA. This approach would increase the cost effectiveness of avacopan.
7. Validity of costing approach used for hospitalisation costs	No	***The ERG has concerns regarding the validity of including costs for excess bed days, which were sourced from the 2017/2018 NHS Reference costs, in combination with unit costs for hospitalisations from the NHS Reference costs 2019/2020. The ERG prefers to use the unit cost for hospitalisations from the NHS Reference costs 2019/2020 as such, without additional costs for excess bed days.***

		Our response We have no specific comments.
8. Representativeness of modelled annual health care costs	No	***The modelled annual health care costs (approximately £13,400 for CYC/RTX+GC) were considerably lower than those that were estimated in the CPRD study (approximately £25,000).*** **Our response** We refer to our comments regarding ADVOCATE and CPRD data in response to Points 5 & 6***.***

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Identifying sub-groups of patients most likely to benefit from avacopan treatment		No	In our expert opinion, patients most likely to benefit from avacopan include: (i) Those at high risk of kidney failure (see Response to Point 6 above). Also, in the ADVOCATE study patients with an initial eGFR <30 ml/min/1.73m^2 showed the greatest improvement in eGFR with avacopan treatment. (ii) Those at the greatest risk of GC-related toxicity, for example those with diabetes, those with previous steroid-induced psychosis, those with sever hypertension and those with osteoporosis. (iii) Those with refractory disease who have failed to respond to conventional treatment including GC. By narrowing the target population, one might expect the cost effectiveness of avacopan to increase.

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

NICE National Institute for Health and Care Excellence

Technical engagement response form

Avacopan for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

NICE National Institute for Health and Care Excellence

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Friday, 4 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	NHS England Specialised commissioning: Specialised Rheumatology Clinical Reference Group
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No disclosure**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. The narrower population in the company submission may impact generalisability of the findings	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
2. The inclusion of glucocorticoids in the intervention group may have generated biased effect estimates of the intervention	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
3. The list of comparators differs from the list in the final scope issued by NICE, potentially affecting the relative apparent efficacy, safety, and cost of avacopan	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
4. The model assumes only azathioprine is used during the maintenance phase of the treatment. However, BSR/BHPR guidelines specify that rituximab	Yes/No	NHS England commissions rituximab for maintenance under specific criteria – 'NHS England will commission the use of rituximab as maintenance therapy only when one of the following three clinical criteria, and all three additional centre criteria, is met.

may be used for maintenance treatment for patients achieving remission after rituximab induction		1. The person is enrolled in a randomised trial that includes B cell suppression as maintenance therapy (e.g. RITAZAREM); OR. 2. Relapse requiring re-induction therapy has occurred after a previous rituximab induced remission; OR 3. Rituximab has been required to induce remission in Cyclophosphamide**[1]**refractory disease and future relapse would have a high risk of organ damage. **In addition** • The decision regarding rituximab maintenance has been made at, or in conjunction with, a specialised centre AND • The person has been provided with the opportunity to be considered for any suitable clinical trials AND • The person is registered on the UKIVAS database, to enable identification of use and outcome of treatment. Maintenance therapy will be stopped after 2 years, or earlier if either treatment intolerance, a contraindication, or a major relapse occurs' Link to the Clinical Commissioning Policy: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/a13-ritux-anca-vascul.pdf
5. The estimated hazard ratio (pooled estimate versus single study) of developing ESRD has a large impact on the cost effectiveness results	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
6. The company explored two different approaches to estimate	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

the probability to transition the ESRD leading to very different results		
7. Validity of costing approach used for hospitalisation costs	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
8. Representativeness of modelled annual health care costs	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Cost of rituximab	e.g. table 4.13	No	The drug cost for rituximab in the company submission and the ERG report is higher than the current cost of rituximab. The cost has reduced significantly with the use of biosimilar drug instead of the more expensive originator drug. This will affect the cost effectiveness of avacopan versus the comparator and presumably the ICER.
Additional issue 2: Dose frequency of rituximab	e.g. table 4.13 in ERG report	No	Rituximab is usually administered as 1g x 2 pulses for the first course and then 1g x 1 for maintenance and not the 4 weekly doses as outlined in the company submission. This reduces the infusion costs and may affect the cost effectiveness for both arms and the ICER
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

NICE National Institute for Health and Care Excellence

Technical engagement response form

Avacopan for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1581]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Friday, 4 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Vifor Pharma
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG critique
1. The narrower population in the company submission may impact generalisability of the findings	No	Avacopan was only studied (ADVOCATE, CLASSIC and CLEAR) in patients with severe, active GPA or MPA and, therefore, is only indicated, in combination with a RTX or CYC regimen, for the treatment of adult patients with severe, active GPA or MPA; EGPA is not part of the marketing authorisation for avacopan. In the company submission, severe GPA and MPA (also referred to as 'organ-threatening' disease) is defined as disease activity that threatens the function of the affected organ and has the potential to cause permanent organ damage or to threaten the patient's life unless effective therapy is implemented quickly. Non–organ-threatening disease describes patients with no evidence of organ damage. The population in the decision	The ERG comment that population studied by the company is therefore narrower than the population studied in the final NICE scope stands.

		problem did not include patients with localised disease at low risk of suffering organ damage.	
2. The inclusion of glucocorticoids in the intervention group may have generated biased effect estimates of the intervention	No	The ADVOCATE study protocol envisioned the use of some GCs in both groups as a function of administration during screening and prior to randomisation; as co-administration with RTX (to prevent hypersensitivity reactions per the RTX prescribing information), and, for example, to manage adrenal insufficiency. During the trial, extra IV and/or oral GC treatment was administered to subjects who experienced a relapse of their AAV, tapered according to the subject's condition, which is in line with the anticipated use of avacopan in clinical practice. Such GC use was reasonably well balanced between the two groups; therefore, the benefits can be ascribed to the avacopan treatment arm and compared to the tapered GC dosing regimen in the comparator arm. The cost and adverse event consequences of GCs are included in the model for both intervention and comparator.	The ERG concerns regarding the inclusion of glucocorticoids in the intervention group remain (see ERG report, especially section 3.2.5.6).
3. The list of comparators differs from the list in the final scope issued by NICE, potentially affecting the relative apparent efficacy, safety, and cost of avacopan	No	The comparators considered in the company submission scope are aligned with the current SoC and NICE recommendations for treatment of severe, active AAV in England [1-3]. The relevant comparators considered for the scope of this submission are:	The ERG reiterates the differences between the comparators listed in the final NICE scope and those considered by the company (see section 2.3 of the ERG report).

		• CYC in combination with GCs (induction), followed by AZA in combination with low-dose GCs as maintenance treatment • RTX in combination with GCs (induction), followed by RTX in combination with low-dose GCs as maintenance treatment The use of avacopan, in combination with a CYC or RTX regimen, is indicated for severe, active GPA or MPA; the population in the decision problem did not include patients with localised disease at low risk of suffering organ damage. MTX and MMF are recommended as alternatives to CYC or RTX for remission induction in patients with localised disease at low risk of suffering organ damage; as such, they were not considered as relevant comparator treatments.	
4. The model assumes only azathioprine is used during the maintenance phase of the treatment. However, BSR/BHPR guidelines specify that rituximab may be used for maintenance treatment for patients achieving remission after rituximab induction	No	The company have provided an amended cost-effectiveness model in response to the clarification questions by the ERG before the technical engagement meeting with NICE. The revised model included a full list of options for maintenance treatment, including rituximab, which can be used in scenario analysis.	The ERG did indeed present a scenario with rituximab in their report (Table 6.2 ERG report). The reason why the ERG included the issue of rituximab for maintenance treatment was the warning of the company that a non-adjusted naïve comparison was used for this analysis and that the results of this scenario should be seen as purely explorative. Thus, in

			formulating key issue 4, the ERG suggested that, to improve the evidence regarding rituximab for maintenance, observational data might be available to create a network including RTX maintenance.
5. The estimated hazard ratio (pooled estimate versus single study) of developing ESRD has a large impact on the cost effectiveness results	Yes	**ERG comment:** Wherever the hazard ratio of developing ESRD was adjusted based on an increase or decrease in eGFR a hazard ratio (HR=0.90) estimated from the Gercik et al. study was used by the company [4]. Though not mentioned in report, the model shows that three other studies have estimated the same hazard ratio. The ERG considers the studies by Gercik et al. in addition to two other studies to be equally relevant The ERG derived a pooled estimate (based on inverse variance approach) for these three studies, yielding a HR of 0.955 (95% CI 0.926 – 0.985). This estimate will be used in an ERG preferred base case. **Company response:** We do not believe that it is appropriate to combine the estimated GFR hazard ratios of developing ESRD across multiple studies. This is due to the fact that parameter estimates obtained from Cox proportional hazards regression models are, in fact, conditional on the other covariates that are included in the model. The estimated coefficients obtained from multiple Cox proportional hazards models that each adjust for a different set of covariates are, therefore,	The ERG thanks the company for providing the reference to the interesting paper on model inconsistency with Cox proportional hazard models. We understand that one should be careful in combining HRs from different studies with different sets of covariates. However, in the studies from Brix and Ford, the coefficient for eGFR remained approximately the same for various model specification. The Gercik study however only included eGFR as variable in 1 of the 3 model specifications explored. So it is unclear if their coefficient for eGFR is also robust against variation in the included covariates. The ERG compared the study by Gopaluni to the other studies in the meta-analysis. An important difference between Gopaluni and the other 3 is that in the former eGFR at 6 months was included as explanatory variable whereas in the other 3 studies this was eGFR at baseline.

		inconsistent [5]. We did consider a pooled approach but abandoned it for this reason. Instead, we selected the single most appropriate estimate from the available sources. The Gercik et al. study [4] was chosen on the basis of it being the most recent work and having a large sample size. Moreover, the same HR as in Gercik et al. study is also reported in a study based on trial and registry data from the EUVAS studies with the largest sample size. (Gopaluni et al.)[6]. The patient population ("All patients diagnosed with AAV according to biopsy and/or antineutrophil cytoplasmic antibody (ANCA) serology") and the treatments received ("Cyclophosphamide or rituximab in conjunction with high-dose GCs for induction or major relapses, and maintenance treatment combination of oral methylprednisolone and azathioprine, rituximab or mycophenolate mofetil for at least 24 months") were also most closely aligned with the modelled patient population for avacopan.	During the re-assessment of all studies, the ERG also realized that in the study by Ford the independent variable is not ESRD but ESRD or death. Based on the way the HR will be used in the model, the ERG decided that it would be better to combine only Gercik and Brix, leading to a HR of 0.947 (95% CI 0.904,0.996) per unit eGFR.
6. The company explored two different approaches to estimate the probability to transition the ESRD leading to very different results	Yes	**Issue:** The ERG pointed out that there are important differences in the modelled incidence of ESRD depending on the source used for the baseline probability. It was stated that both the approach based on the Robson et al. study [7] and based on the CPRD were considered plausible. The ERG then selected the CPRD approach for their	The ERG is happy with the new approach implemented by the company.

		base case on the basis that this produced an incidence of ESRD that reflected real-world incidence from CPRD. **Company response:** i) Is it appropriate to assume that the CPRD provides a standard for validating model outputs? The company agrees with the ERG statement that the probability of ESRD is sensitive to the choice of data source to inform the baseline probability. However, we would question the use of the CPRD study as the gold-standard with which to judge the validity of methods for modelling ESRD incidence. Estimation of event rates from CPRD linked data is not necessarily free from bias. The means through which bias can emerge when using CPRD linked data is discussed in Padmanabhan et al [8]. For a specific example of how different approaches to the construction of linked data can lead to substantial differences in estimated event rates, see Gallagher et al [9]. Although from a very different disease area this study does demonstrate the complexity of estimating event rates from linked data. ii) An updated approach calibrated to multiple published sources	

		In order to examine the external validity of the ESRD estimates produced in the model, the cumulative incidence of ESRD based on Robson et al. and CPRD was compared against the cumulative incidence reported in published studies carried out in AAV. The company carried out a targeted literature search to identify relevant studies, which are reported in Table 1. The estimated proportion of patients reported with ESRD ranged from 19.7% to 28.0% across the studies. However, it was difficult to draw a comparison between studies due to differences in the median length of follow-up. An approach using a pooled estimate was not considered to be appropriate due to the differences in the study design and length of follow-up. Instead, the cumulative incidence reported in each study was plotted against the estimated cumulative incidence in our model based on the alternative approaches considered by the ERG (Robson et al. and CPRD) in Figure 1. Based on the estimates reported in the studies identified in the targeted literature search, the plausible range for the rate of ESRD lies between the projected estimates in the company base case and the ERG's preferred base case informed by CPRD. In order to ensure that the estimates produced in the model maintain external validity compared to previously published evidence,	

		the baseline rates of ESRD in the model were calibrated in order to reflect the rate of ESRD expected in real-world practice. The calibrated company base case is represented using the dotted line in Figure 1. The company identified an error in the application of CPRD ESRD rates in the model. Patients who are in the sustained remission health state (cycle 7+) for both avacopan and GC SoC were erroneously applied the rate associated with relapse, which corresponds to the overall rate of ESRD reported in CPRD ([redacted] per 1000 patient-years). The correct probability for this health state corresponds to the rate for patients with no GC prescription ([redacted] per 1000 patient-years). The company corrected this error in the updated model. Changing this transition probability had no impact on the company base case, as it uses Robson et al. as the source of ESRD probabilities. However, this change has an impact on the scenario analysis which uses CPRD as the source of ESRD probabilities, which was the ERG's preferred base case (Table 4). **Key issue 6: further detail on the population in CPRD in comparison to published studies** Within their response to the technical engagement questions from the company,	

		the ERG have asked for additional information regarding the population of the CPRD study, and how it compares against the target population for avacopan. The inclusion criteria in the CPRD study includes diagnosis codes for Wegener's granulomatosis and microscopic polyangiitis. The target population of avacopan, as described in the SmPC, is severe, active GPA or MPA. It is therefore likely that the CPRD study population included patients with less severe GPA and MPA compared to the target population for avacopan, and thus the population in the economic model. This may explain the considerably lower rate of ESRD observed in CPRD compared to other published studies as reported in the validation section above.	
7. Validity of costing approach used for hospitalisation costs	Yes	**Issue:** The ERG had concerns about the chosen approach to estimate the cost of hospitalisation using data from ADVOCATE. Using the unit cost from NHS Reference Costs 2019/20 combined with excess bed days and cost from NHS Reference Costs 2017/18 may produce incorrect estimates due to differences in the way these two versions estimate the cost of inpatient care. **Company response:** The ERG provide three reasons for excluding the cost of excess bed days in their preferred base case:	No evidence was provided to demonstrate that lengths of stay in clinical practice will be longer than the mean length of stay associated with the unit cost for hospitalization as provided by the 2019/2020 NHS Reference costs. Indeed, the latter is likely more consistent with actual clinical practice than the avacopan trial.

		1. **ERG:** Firstly, it is not clear that a difference in length of stay should imply an excess bed day at all. **Company response:** we disagree that a longer hospital length of stay may not represent additional bed days associated with extra cost. Ignoring differences in length of stay is likely to underestimate the cost of hospital care and thus produce biased estimates in the model 2. **ERG:** Secondly, the most recent 2019/2020 version of the NHS Reference costs no longer includes the cost of an excess bed day. This suggest a difference in the way the unit costs were calculated between the 2017/2018 version and the 2019/2020 version of the NHS Reference cost. **Company response:** the company acknowledge that there may be a difference in the way that costs were calculated in the two versions of NHS Reference Costs. However, there is no evidence to suggest that excess bed days have been incorporated into the cost estimates in the 2019/20 version. The unit costs reported in the NHS Reference Costs represent a weighted average across all episodes	

		reported, and thus is representative of a hospital spell with an average length of stay. The length of stay reported in the ADVOCATE trial is likely to be longer than the average length of stay in clinical practice in the UK, based on the most recent version of NHS Reference Costs which reported mean length of stay for this category of hospital spell. This means that an adjustment is required in order to ensure that the cost estimate in the model reflects the true cost of hospital care for this population. 3. **ERG:** Thirdly, the unit cost for all but Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, with Interventions (i.e., for Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with CC Score 5+; Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with CC Score 2-4; and Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with CC Score 0-1) decreased substantially. **Company response:** The ERG statement contains an error: in addition to Granulomatous, Allergic	

		Alveolitis or Autoimmune Lung Disease, with Interventions (DZ29G), the costs associated with Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with CC Score 5+ (DZ29H) also increased for both elective and non-elective episodes, in addition to Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with CC Score 0-1 (DZ29K) for non-elective episodes. The various unit costs for AAV hospital episodes both increased and decreased, which is expected given the high levels of uncertainty and low episode counts recorded in NHS Reference Costs for this rare disease. A modest increase in the weighted average unit cost across all relevant HRG codes was observed between 2017/18 and 2019/20 (Table 2). The company disagrees with the ERG preferred approach of excluding excess bed day costs as this will underestimate the cost of hospital care and ignore the differences in the length of stay between the avacopan and comparator arms observed in the ADVOCATE trial. The company has revised the approach for the estimation of hospital cost in the model. NHS Reference Costs	

		2017/18 will be used as the source of both the base unit costs and excess bed day cost. The final cost which is adjusted for excess bed days will be inflated to 2020 prices using the NHS cost inflation index. The cost of hospitalisation estimated in the model was compared against the estimates in the CPRD study to verify their external validity. The total per-member cost reported in the first five years associated with rheumatology, nephrology, and ENT visits in the CPRD study was [redacted]. The undiscounted 5-year cost estimated in the CYC+GC comparator of the model (patient group which most closely matches the population in the CPRD study) was £11,848. The total hospital cost estimated in the model was therefore reflective of the cost observed in clinical practice in the UK and may in fact be an under-estimate.	
8. Representativeness of modelled annual health care costs	Yes/No	**Issue:** the ERG raised its concern that the total healthcare cost estimated in the model is substantially lower compared to the cost reported in the CPRD study. **Company response:** the company acknowledge that there is a substantial difference in the total undiscounted cost estimated in the SoC arm of the model and the cost reported in the CPRD study. This difference may be explained by the fact that the total cost estimate in CPRD included the	The company argue that any underestimate of cost is likely to be conservative because that cost is associated with current standard care. However, this does not explain the fact that, if the CPRD is used to estimate the cost of AEs then the ICER goes up, even if total cost seems to be lower than that based on the CPRD.

		aggregate cost of all healthcare episodes, which included treatment of comorbidities unrelated to AAV. The total costs of specific episodes which were likely to be related to AAV (inpatient and outpatient episodes for rheumatology, nephrology and ENT) and drug treatments for AAV were similar to the corresponding costs in the model. It is possible that the total cost in the model did not account for hidden costs of AAV which were not considered within the parametrisation of the model. Given that a larger cost associated with worsening AAV (i.e. relapse and ESRD) would favour avacopan, it is reasonable to consider the current cost assumptions in the model to be conservative.	
Abbreviations: AAV, anti-neutrophil cytoplasmic antibody–associated vasculitis; AZA, azathioprine; CYC, cyclophosphamide; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MTX, methotrexate; RTX, rituximab			

Table 1. Summary of studies reporting the cumulative incidence of ESRD in AAV

Study	Country	Recruitment period	N	Median follow-up	Cumulative incidence
Booth et al.[10]	UK	1995-2000	246	5.0	28.0%
Huang et al.[11]	China	2003-2017	141	5.3	25.5%
Lionaki et al. [12]	USA	1986-2007	523	5.3	26.0%
Mohammad et al. [13]	Sweden	1997-2009	183	4.6	20.2%
Scott et al. [14]	Ireland	2012-2020	332	3.4	22.0%

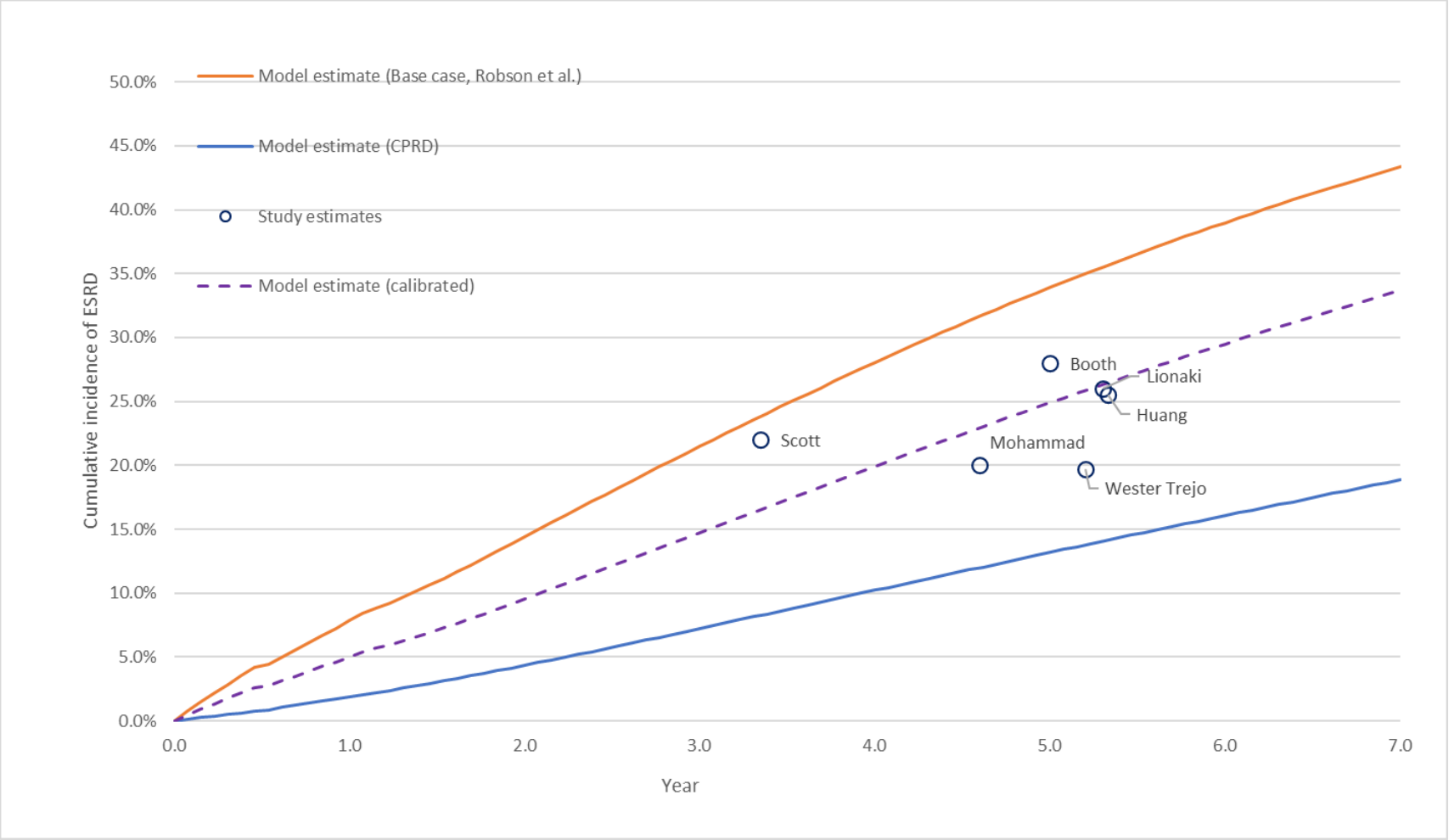
Wester Trejo et al. [15]	Multiple	1995-2002	535	5.2	19.7%

Table 2. Comparison of unit costs for granulomatous, allergic alveolitis or autoimmune lung disease from NHS Reference Costs 2017/18 and 2019/20

HRG	Cost (£) from NHS Reference Costs 2017/18	Cost (£) from NHS Reference Costs 2019/20	% change from 2017/18 to 2019/20
Elective			
DZ29G	5,232	5,900	13%
DZ29H	3,054	3,489	14%
DZ29J	2,069	1,955	-6%
DZ29K	1,450	1,012	-30%
Weighted average	2,692	2,724	1%
Non-elective			
DZ29G	5,292	5,511	4%
DZ29H	2,621	2,962	13%
DZ29J	2,076	1,930	-7%
DZ29K	1,506	1,714	14%
Weighted average	2,748	2,887	5%

DZ29G: Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, with Interventions;
DZ29H: Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with CC Score 5+
DZ29J: Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with CC Score 2-4
DZ29K: Granulomatous, Allergic Alveolitis or Autoimmune Lung Disease, without Interventions, with CC Score 0-1

Figure 1. Comparison of cumulative incidence of ESRD reported in published studies in AAV and the model



Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response	ERG critique
Additional issue 1: Transition probabilities from active disease and remission into relapse	Section 4.2.6.2	Yes	**Issue:** the ERG raised its concerns regarding the company's assumption that remission rates are the same for patients in the active disease and relapsed disease health states. The ERG noted that analyses of pre-specified subgroup analyses from the ADVOCATE trial submitted by the company showed that the difference in remission rates between the two treatment arms were reported for relapsed patients, but not for newly diagnosed patients. Given that the ADVOCATE ITT population consisted of a mixed population of relapsed and newly diagnosed patients, it may not be reasonable to assume that remission rates are the same in the active disease and relapsed health states. **Company response:** the company agree with the ERG that remission rates may be different in the active disease and relapsed health states. In the technical engagement meeting, the company noted that relapse rates in 'remission 1' and 'remission 2' health states should not be assumed to be the same, given the difference in relapse rates in the newly diagnosed and relapsed subgroups from ADVOCATE. Therefore, the company updated the transition probabilities in the model to ensure that both the rates of remission and relapse reflect the correct patient population.	The ERG is happy with the new approach implemented by the company.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Company response: The company agree with the following model changes reported in the ERG report:

1. Model errors corrected by ERG
2. Corrected ESRD HR for mortality of 6.6
3. Treatment independent health state utility values (HSUV)

The changes above have been incorporated before calculating the starting ICER in "corrected company BC + accepted ERG changes" below. The incremental impact of each model change implemented by the company in response to the technical engagement, as well as the aggregate impact on the model results are shown in the table below.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Corrected company BC + accepted ERG changes (base case before additional company changes)	N/A	N/A	£15,043
Key issue 6	ESRD transition probabilities based on Robson et al. adjusted	Calibrated transition probabilities in line with previously published	£23,215

	for decreasing eGFR due to relapse	estimates of cumulative incidence of ESRD in AAV	
Key issue 7	Hospital costs based on unit costs from NHS Reference Costs 2019/20 and excess bed day costs from NHS Reference Costs 2017/18	Both base and excess bed day costs derived from NHS Reference Costs 2017/18 and inflated to 2020 using the NHS cost inflation index	£15,035
Additional issue 1	Probability of remission and relapse after first relapsed in the model informed by ADVOCATE ITT population	Probability of remission and relapse after first relapsed in the model informed by ADVOCATE relapsed subgroup	£13,273
All company changes combined (new company base case)	**N/A**	**N/A**	**£19,441**

Sensitivity analyses around revised base case

Deterministic sensitivity analysis: Tornado diagram

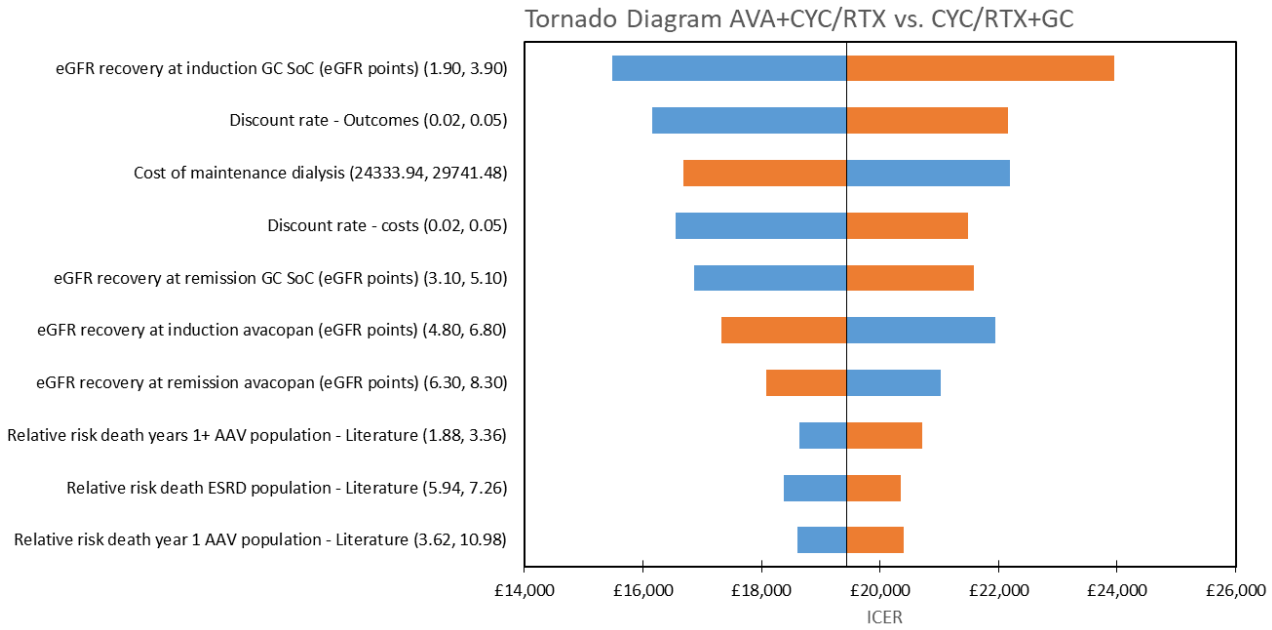


Table 3. Probabilistic sensitivity analysis results

Comparison	Incr. cost	Incr. QALYs	ICER per QALY
AVA+CYC/RTX vs. CYC/RTX+GC	[redacted]	[redacted]	£20,635

Figure 2. Probabilistic sensitivity analysis scatter diagram

Figure 3. Probabilistic sensitivity analysis cost-effectiveness acceptability plane

Table 4. Scenario analysis

Scenario	Incr. cost	Incr. QALYs	ICER per QALY
Updated company base case	[redacted]	[redacted]	£19,441
CPRD as the source of ESRD transition probabilities	[redacted]	[redacted]	£44,523

References

1. Chalisey, A. and M. Karim, *Guidelines for the management of ANCA-associated vasculitis with renal involvement*. 2021: NNUH.
2. NICE. *Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis.* 2014 [cited 2021 9th September]; Available from: https://www.nice.org.uk/guidance/ta308.
3. Ntatsaki, E., et al., *BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis.* Rheumatology (Oxford), 2014. **53**(12): p. 2306-9.
4. Gercik, O., et al., *Histopathological subgrouping versus renal risk score for the prediction of end-stage renal disease in ANCA-associated vasculitis.* Ann Rheum Dis, 2020. **79**(5): p. 675-676.
5. Ford, I., J. Norrie, and S. Ahmadi, *Model inconsistency, illustrated by the Cox proportional hazards model.* Stat Med, 1995. **14**(8): p. 735-46.
6. Gopaluni, S., et al., *Effect of Disease Activity at Three and Six Months After Diagnosis on Long-Term Outcomes in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis.* Arthritis Rheumatol, 2019. **71**(5): p. 784-791.
7. Robson, J., et al., *Damage in the anca-associated vasculitides: long-term data from the European vasculitis study group (EUVAS) therapeutic trials.* Ann Rheum Dis, 2015. **74**(1): p. 177-84.
8. Padmanabhan, S., et al., *Approach to record linkage of primary care data from Clinical Practice Research Datalink to other health-related patient data: overview and implications.* Eur J Epidemiol, 2019. **34**(1): p. 91-99.
9. Gallagher, A.M., et al., *The Impact of the Choice of Data Source in Record Linkage Studies Estimating Mortality in Venous Thromboembolism.* PLoS One, 2016. **11**(2): p. e0148349.
10. Booth, A.D., et al., *Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study.* Am J Kidney Dis, 2003. **41**(4): p. 776-84.
11. Huang, X., et al., *Antineutrophil Cytoplasmic Antibody-Associated Vasculitis With Acute Kidney Injury: Short-Term Recovery Predicts Long-Term Outcome.* Front Immunol, 2021. **12**: p. 641655.
12. Lionaki, S., et al., *The clinical course of ANCA small-vessel vasculitis on chronic dialysis.* Kidney Int, 2009. **76**(6): p. 644-51.
13. Mohammad, A.J. and M. Segelmark, *A population-based study showing better renal prognosis for proteinase 3 antineutrophil cytoplasmic antibody (ANCA)-associated nephritis versus myeloperoxidase ANCA-associated nephritis.* J Rheumatol, 2014. **41**(7): p. 1366-73.
14. Scott, J., et al., *A cohort study to investigate sex-specific differences in ANCA-associated glomerulonephritis outcomes.* Sci Rep, 2021. **11**(1): p. 13080.
15. Wester Trejo, M.A.C., et al., *Renal relapse in antineutrophil cytoplasmic autoantibody-associated vasculitis: unpredictable, but predictive of renal outcome.* Rheumatology (Oxford), 2019. **58**(1): p. 103-109.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Avacopan for treating anti-neutrophil cytoplasmic autoantibody-associated vasculitis [ID1581]

Addendum Technical Engagement

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

Authors

Jeremy Howick, Reviews Manager, KSR Ltd, UK
Maiwenn Al, Health Economic Researcher, Erasmus School of Health Policy & Management (ESHPM), EUR, the Netherlands
Nigel Armstrong, Health Economics Manager, KSR Ltd, UK
Charlotte Ahmadu, Health Economist, KSR Ltd, UK
Pim Wetzelaer, Health Economic Researcher, ESHPM, EUR, the Netherlands
Pawel Posadzki, Reviews Manager, KSR Ltd, UK
Hannah Penton, Health Economist, ESHPM, EUR, the Netherlands
Lisa Stirk, Information Specialist, KSR Ltd, UK
Robert Wolff, Managing Director, KSR Ltd, UK
Jos Kleijnen, Founder and Owner, KSR Ltd, UK

Correspondence to Jeremy Howick, Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, YO19 6FD
United Kingdom

Date completed 18/03/2022

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number STA 13/53/71.

.**Declared competing interests of the authors**

None.

Acknowledgements
None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report

Introduction

This addendum contains the ERGs critique of the company's new evidence provided in the company's response to technical engagement. The company's updated cost effectiveness results and scenarios are provided in Section 2, followed by the ERG's updated cost effectiveness results and scenarios in Section 3.

1. Suggested changes for model input including key issues 6 and 7

Key Issue 6 - Which hazard ratio of developing ESRD should be used?

In the ERG report, the company's choice for the hazard ratio of developing ESRD based on an increase or decrease in eGFR was critiqued. The company used the hazard ratio (HR=0.90) estimated from a study by Gercik et al.(1) In the Excel model, the ERG found 3 alternative hazard ratio estimates. The ERG considered the studies by Gercik et al.,(1) Brix et al,(2) and Ford and al.(3) to be equally relevant. Thus, the ERG derived a pooled estimate (based on inverse variance approach) for these three studies, yielding a HR of 0.955 (95% CI 0.926 – 0.985). This estimate was be used in an ERG preferred base case.

In their Technical engagement (TE) response the company explained that they considered it not appropriate to combine the estimated eGFR hazard ratios of developing ESRD across multiple studies. This is due to the fact that parameter estimates obtained from Cox proportional hazards regression models are, in fact, conditional on the other covariates that are included in the model. The estimated coefficients obtained from multiple Cox proportional hazards models that each adjust for a different set of covariates are, therefore, inconsistent.(4) They did consider a pooled approach but abandoned it for this reason.

Instead, the company selected what they considered the single most appropriate estimate from the available sources. The Gercik et al. study was chosen on the basis of it being the most recent work and having a large sample size. Moreover, the same HR as in Gercik et al. study is also reported in a study based on trial and registry data from the EUVAS studies with the largest sample size. (Gopaluni et al.).(5) The patient population ("All patients diagnosed with AAV according to biopsy and/or antineutrophil cytoplasmic antibody (ANCA) serology") and the treatments received ("Cyclophosphamide or rituximab in conjunction with high-dose GCs for induction or major relapses, and maintenance treatment combination of oral methylprednisolone and azathioprine, rituximab or mycophenolate mofetil for at least 24 months") were also most closely aligned with the modelled patient population for avacopan.

ERG comment:

We understand that one should be careful in combining HRs from different studies with different sets of covariates. However, in the studies from Brix and Ford, the coefficient for eGFR remained approximately the same for various model specification. The Gercik study(1) however only included eGFR as variable in 1 of the 3 model specifications explored. So, it is unclear if their coefficient for eGFR is also robust against variation in the included covariates.

The ERG compared the study by Gopaluni(5) to the other studies in the meta-analysis. An important difference between Gopaluni and the other 3 is that in the former eGFR at 6 months was included as explanatory variable whereas in the other 3 studies this was eGFR at baseline. During the re-assessment of all studies, the ERG also realized that in the study by Ford the independent variable is not ESRD but (ESRD

or death). Based on the above the ERG decided that it would be better to combine only Gercik and Brix, leading to a HR of 0.947 (95% CI 0.904,0.996) per unit eGFR.

Key issue 7: Choosing between two methods to estimate the probability of developing ESRD

In the ERG report the ERG pointed out that there are important differences in the modelled incidence of ESRD depending on the source used for the baseline probability. The company used for its base case an approach based on a study by Robson et al. and provided an approach based on the CPRD data as a scenario. The ERG considered both approaches plausible, but selected the CPRD approach for the ERG preferred base case on the basis that this produced an incidence of ESRD that reflected real-world incidence from CPRD.

In their Technical engagement (TE) response the company questioned the use of the CPRD study as the gold-standard with which to judge the validity of methods for modelling ESRD incidence. Estimation of event rates from CPRD linked data is not necessarily free from bias. The company clarified that the means through which bias can emerge when using CPRD linked data is discussed in Padmanabhan et al.(6)

In light of the uncertainty about which method would produce the most valid results, the company provided an updated approach.

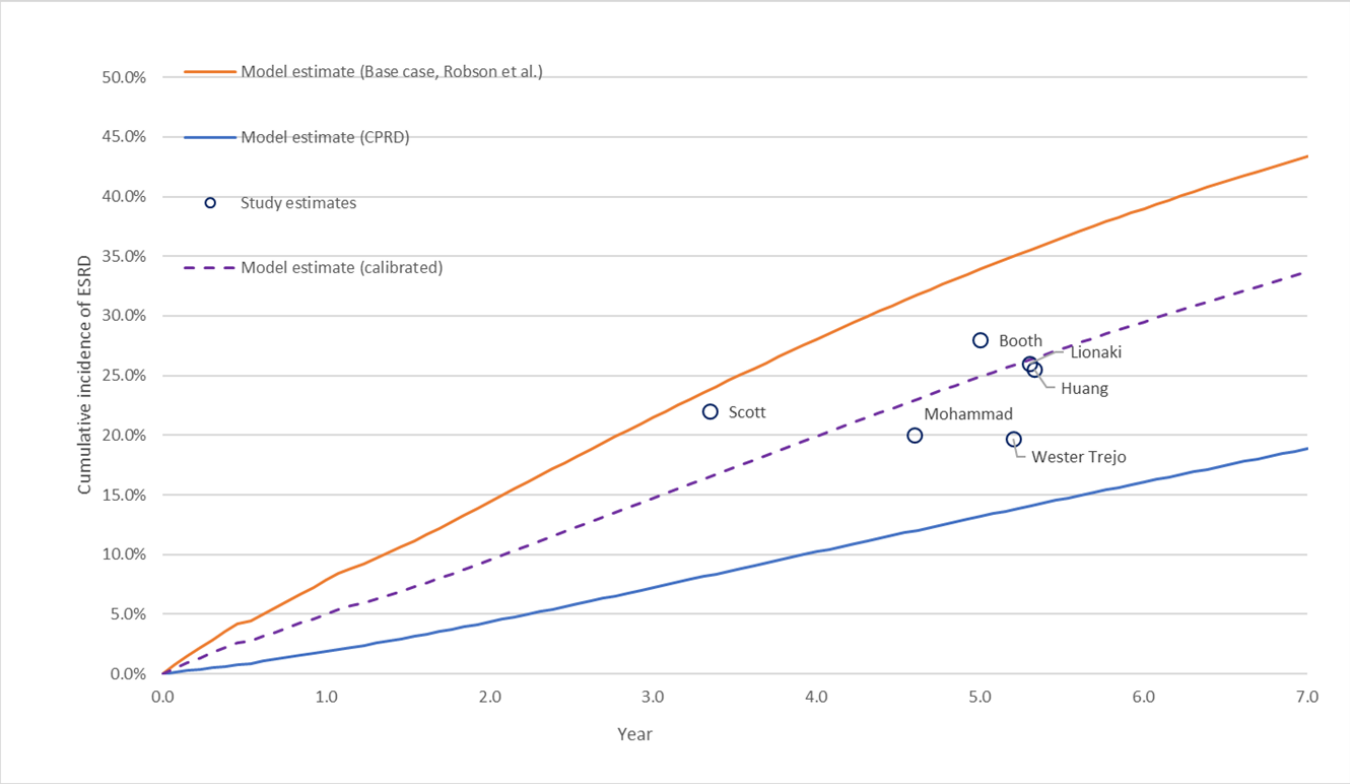
In order to examine the external validity of the ESRD estimates produced in the model, the cumulative incidence of ESRD based on Robson et al.(7) and CPRD was compared against the cumulative incidence reported in published studies carried out in AAV. The company carried out a targeted literature search to identify relevant studies, which are reported in Table 1.

Table 1. Summary of studies reporting the cumulative incidence of ESRD in AAV

Study	Country	Recruitment period	N	Median follow-up	Cumulative incidence
Booth et al. (8)	UK	1995-2000	246	5.0	28.0%
Huang et al. (9)	China	2003-2017	141	5.3	25.5%
Lionaki et al. (10)	USA	1986-2007	523	5.3	26.0%
Mohammad et al. (11)	Sweden	1997-2009	183	4.6	20.2%
Scott et al. (12)	Ireland	2012-2020	332	3.4	22.0%
Wester Trejo et al. (13)	Multiple	1995-2002	535	5.2	19.7%

The estimated proportion of patients reported with ESRD ranged from 19.7% to 28.0% across the studies. However, it was difficult to draw a comparison between studies due to differences in the median length of follow-up. An approach using a pooled estimate was not considered to be appropriate due to the differences in the study design and length of follow-up. Instead, the cumulative incidence reported in each study was plotted against the estimated cumulative incidence in our model based on the alternative approaches considered by the ERG (Robson et al. and CPRD) in **Error! Reference source not found.**.

Figure 1 Comparison of cumulative incidence of ESRD reported in published studies in AAV and the model



Based on the estimates reported in the studies identified in the targeted literature search, the plausible range for the rate of ESRD lies between the projected estimates in the company base case and the ERG's preferred base case informed by CPRD. In order to ensure that the estimates produced in the model maintain external validity compared to previously published evidence, the baseline rates of ESRD in the model were calibrated in order to reflect the rate of ESRD expected in real-world practice. The calibrated company base case is represented using the dotted line in **Error! Reference source not found.**.

In addition, the company identified an error in the application of CPRD ESRD rates in the model. Patients who are in the sustained remission health state (cycle 7+) for both avacopan and GC SoC were erroneously applied the rate associated with relapse, which corresponds to the overall rate of ESRD reported in CPRD ([redacted] per 1000 patient-years). The correct probability for this health state corresponds to the rate for patients with no GC prescription ([redacted] per 1000 patient-years). The company corrected this error in the updated model.

Key issue 9: Validity of costing approach used for hospitalisation costs

In the ERG report, concerns were expressed about the chosen approach to estimate the cost of hospitalisation using data from ADVOCATE. Using the unit cost from NHS Reference Costs 2019/20 combined with excess bed days and cost from NHS Reference Costs 2017/18 might produce incorrect estimates due to differences in the way these two versions estimate the cost of inpatient care. The ERG pointed out that the most recent 2019/2020 version of the NHS Reference costs no longer includes the cost of an excess bed

day. This suggest a difference in the way the unit costs were calculated between the 2017/2018 version and the 2019/2020 version of the NHS Reference cost.

In their Technical engagement (TE) response the company acknowledged that there might be a difference in the way that costs were calculated in the two versions of NHS Reference Costs. However, there is no evidence to suggest that excess bed days have been incorporated into the cost estimates in the 2019/20 version. The unit costs reported in the NHS Reference Costs represent a weighted average across all episodes reported, and thus is representative of a hospital spell with an average length of stay. The length of stay reported in the ADVOCATE trial is likely to be longer than the average length of stay in clinical practice in the UK, based on the most recent version of NHS Reference Costs which reported mean length of stay for this category of hospital spell. This means that an adjustment is required in order to ensure that the cost estimate in the model reflects the true cost of hospital care for this population.

The company indicated to disagree with the ERG preferred approach of excluding excess bed day costs as this will underestimate the cost of hospital care and ignore the differences in the length of stay between the avacopan and comparator arms observed in the ADVOCATE trial. Thus, the company has revised the approach for the estimation of hospital cost in the model. NHS Reference Costs 2017/18 are now used as the source of both the base unit costs and excess bed day cost. The final cost which is adjusted for excess bed days will be inflated to 2020 prices using the NHS cost inflation index.

ERG comment:

No evidence was provided to demonstrate that lengths of stay in clinical practice will be longer than the mean length of stay associated with the unit cost for hospitalization as provided by the 2019/2020 NHS Reference costs. Indeed, the latter is likely more consistent with actual clinical practice than the avacopan trial.

Additional issue 1: Transition probabilities from active disease and remission into relapse

In the ERG report the ERG expressed concerns regarding the company's assumption that remission rates are the same for patients in the active disease and relapsed disease health states. The ERG noted that analyses of pre-specified subgroup analyses from the ADVOCATE trial submitted by the company showed that when comparing the proportions of patients in remission between newly diagnosed and relapsed patients, the data suggest that the differences in remission between the two treatments arms in the ITT population are primarily driven by the difference in proportions for relapsed patients. In contrast, the differences in remission between treatment arms for newly diagnosed patients are relatively small. Given that the ADVOCATE ITT population consisted of a mixed population of relapsed and newly diagnosed patients, it may not be reasonable to assume that remission rates are the same in the active disease and relapsed health states.

The company indicated in their Technical engagement (TE) response that they agree with the ERG that remission rates may be different in the active disease and relapsed health states. In the technical engagement meeting, the company noted that relapse rates in 'remission 1' and 'remission 2' health states should not be assumed to be the same, and therefore the company updated the transition probabilities in the model to ensure that both the rates of remission and relapse reflect the correct patient population.

2. Company's updated cost effectiveness results

The company provided updated cost effectiveness results. Of all the ERG preferred model changes as discussed in the ERG report, the company agreed with the following:

1. Model errors corrected by ERG
2. Corrected ESRD HR for mortality of 6.6
3. Treatment independent health state utility values (HSUV)

Table 2 presents the incremental impact of each model change implemented by the company in response to the technical engagement, as well as the aggregate impact on the model results. Table 3 shows the full results for the new company base case, and table 4 shows the probabilistic results for the new company base case.

Table 2 Changes to the company's cost-effectiveness estimate

(Key) issue	ICER per QALY
Corrected company BC + accepted ERG changes (base case before additional company changes)	£15,043
Key issue 7: Alternative approach to estimate the probability of developing ESRD	£23,215
Key issue 8: Alternative approach to hospitalisation costs	£15,035
Additional issue 1: Alternative approach to estimation transition probabilities from active disease and remission into relapse	£13,273
All company changes combined (new company base case)	£19,441

Table 3 New deterministic company base case

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
CYC/RTX+GC	£[redacted]	10.17	[redacted]				
AVA+CYC/RTX	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£19,441

Based on the model provided with the company's Technical Engagement Response.
ICER = incremental cost effectiveness ratio; Incr. = incremental; LYG = life years gained; PAS = patient access scheme; QALY(s) = quality-adjusted life year(s).

In figure 2 we see that parameters relating to eGFR recovery at induction and remission in both treatment groups had the largest impact on the ICER. Cost of maintenance dialysis, as the main cost component of ESRD, also had a substantial impact on results.

Figure 2 Tornado diagram

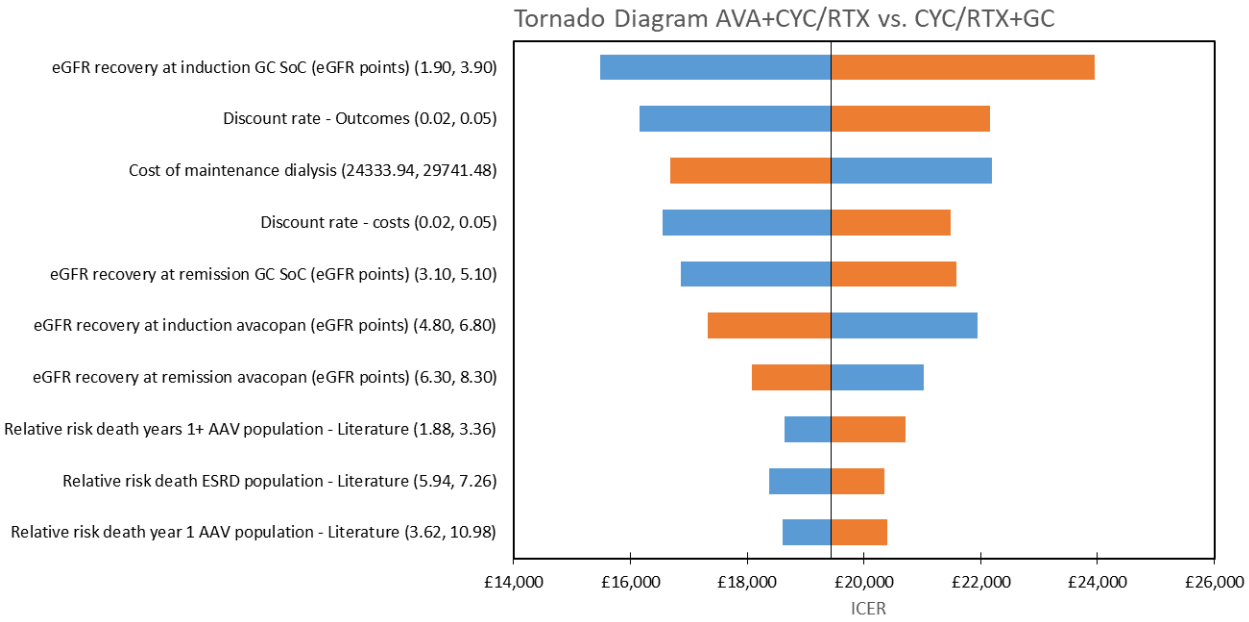


Table 4 New probabilistic company base case

Comparison	Incr. cost	Incr. QALYs	ICER per QALY
AVA+CYC/RTX vs. CYC/RTX+GC	£[redacted]	[redacted]	£20,635

The cost effectiveness plane in Figure 2 shows that the vast majority of the PSA simulations fell in the north-east quadrant. Based on the cost effectiveness acceptability curve in Figure 3, the probability that avacopan is cost-effective at thresholds of £20,000 and £30,000 per QALY gained is 48% and 70% using the company new base-case assumptions.

Figure 3. Probabilistic sensitivity analysis scatter diagram

Figure 4. Probabilistic sensitivity analysis cost-effectiveness acceptability plane

Table 5 shows what the ICER would be if the source of ESRD transition probabilities would be set to CPRD instead of the current calibrated version.

Table 5. Scenario analysis

Scenario	Incr. cost	Incr. QALYs	ICER per QALY
Updated company base case	[redacted]	[redacted]	£19,441
CPRD as the source of ESRD transition probabilities	[redacted]	[redacted]	£44,523

3. Exploratory and scenario analyses undertaken by the ERG

The ERG made the following amendments to the company's updated base-case in line with the ERG's original base-case:

- The ERG prefers to use the most recent (i.e., 2019/2020) unit cost for hospitalisation, with no adjustment for excess bed days, as described in Section 4.2.8.3 of the ERG report.
- A hazard ratio of developing ESRD per unit change in eGFR was used to adjust the probability of developing ESRD for avacopan patients (higher eGFR than comparator) and after a relapse (decrease in eGFR). The ERG prefers to use a pooled estimate (0.947) based on two similar studies identified by the company, rather than selecting one of these studies for the base-case (0.90).

The deterministic results of the ERG base-case are displayed in Table 6. The ERG base-case results in higher incremental costs and lower incremental QALYs than the company base-case, resulting in a higher ICER of £40,516 per QALY gained versus the company's ICER of £19,441 per QALY gained.

Table 7 shows the separate impact of the two ERG preferred assumptions.

Table 6 New deterministic ERG base case

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
CYC/RTX+GC	[redacted]	10.42	[redacted]				
AVA+CYC/RTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,516
Based on the model provided with the company's Technical Engagement Response. ICER = incremental cost effectiveness ratio; Incr. = incremental; LYG = life years gained; PAS = patient access scheme; QALY(s) = quality-adjusted life year(s).							

Table 7 Incremental impact of ERG preferred assumptions

Preferred assumption	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
Company base-case (original)	[redacted]	[redacted]	£18,537
Updated company base case	[redacted]	[redacted]	£19,441
Updated company BC + Exclude excess bed days for hospitalisation costs	[redacted]	[redacted]	£26,297
Updated company BC + HR eGFR based on pooled estimate	[redacted]	[redacted]	£30,888
ERG BC (including all ERG changes)	[redacted]	[redacted]	£40,516
ICER = incremental cost effectiveness ratio; Incr. = incremental; QALY(s) = quality-adjusted life year(s); HR = hazard ratio; ERG = evidence review group; eGFR = estimated glomerular filtration			

The ERGs probabilistic sensitivity analysis (PSA) results in an ICER of £42,541 when comparing AVA+CYC/RTX to CYC/RTX+GC which is close to the deterministic ICER of £40,516 per QALY gained (Table 6). The cost effectiveness plane in Figure 5 shows that the majority of simulations fall above the threshold line of £20,000 per QALY shown in the figure. Based on the cost effectiveness acceptability curve in Figure 6, the probability that avacopan is cost effective at thresholds of £20,000 and £30,000 per QALY gained is 6% and 25%, using the ERG base-case assumptions.

Table 8 New probabilistic ERG base case

Technologies	Incr. costs	Incr. QALYs	ICER (£/QALY)
AVA+CYC/RTX vs CYC/RTX+GC	[redacted]	[redacted]	£42,541

Figure 5: ERG base-case cost effectiveness plane

[redacted]

Based on the model provided with the company's Technical Engagement Response.
ERG = Evidence Review Group; QALY = quality-adjusted life year.

Figure 6: ERG base-case CEAC

Based on the model provided with the company's Technical Engagement Response.

References

1. Gercik O, Bilgin E, Solmaz D, Cakalagaoglu F, Saglam A, Aybi O, et al. Histopathological subgrouping versus renal risk score for the prediction of end-stage renal disease in ANCA-associated vasculitis. Ann Rheum Dis. 2020 May 1;79(5):675–6.

2. Brix SR, Noriega M, Tennstedt P, Vettorazzi E, Busch M, Nitschke M, et al. Development and validation of a renal risk score in ANCA-associated glomerulonephritis. Kidney Int. 2018 Dec 1;94(6):1177–88.

3. Ford SL, Polkinghorne KR, Longano A, Dowling J, Dayan S, Kerr PG, et al. Histopathologic and clinical predictors of kidney outcomes in ANCA-associated vasculitis. Am J Kidney Dis Off J Natl Kidney Found. 2014 Feb;63(2):227–35.

4. Ford I, Norrie J, Ahmadi S. Model inconsistency, illustrated by the Cox proportional hazards model. Stat Med. 1995 Apr 30;14(8):735–46.

5. Gopaluni S, Flossmann O, Little MA, O'Hara P, Bekker P, Jayne D, et al. Effect of Disease Activity at Three and Six Months After Diagnosis on Long-Term Outcomes in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis. Arthritis Rheumatol. 2019;71(5):784–91.

6. Padmanabhan S, Carty L, Cameron E, Ghosh RE, Williams R, Strongman H. Approach to record linkage of primary care data from Clinical Practice Research Datalink to other health-related patient data: overview and implications. Eur J Epidemiol. 2019 Jan;34(1):91–9.

7. Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Höglund P, et al. Damage in the anca-associated vasculitides: long-term data from the European vasculitis study group (EUVAS) therapeutic trials. Ann Rheum Dis. 2015 Jan;74(1):177–84.

8. Booth AD, Almond MK, Burns A, Ellis P, Gaskin G, Neild GH, et al. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. Am J Kidney Dis Off J Natl Kidney Found. 2003 Apr;41(4):776–84.

9. Huang X, Chen L, Lan L, Ren P, Ni A, Ma Y, et al. Antineutrophil Cytoplasmic Antibody-Associated Vasculitis With Acute Kidney Injury: Short-Term Recovery Predicts Long-Term Outcome. Front Immunol. 2021;12:641655.

10. Lionaki S, Hogan SL, Jennette CE, Hu Y, Hamra JB, Jennette JC, et al. The clinical course of ANCA small-vessel vasculitis on chronic dialysis. Kidney Int. 2009 Sep;76(6):644–51.

11. Mohammad AJ, Segelmark M. A population-based study showing better renal prognosis for proteinase 3 antineutrophil cytoplasmic antibody (ANCA)-associated nephritis versus myeloperoxidase ANCA-associated nephritis. J Rheumatol. 2014 Jul;41(7):1366–73.

12. Scott J, Canepa C, Buettner A, Ryan L, Moloney B, Cormican S, et al. A cohort study to investigate sex-specific differences in ANCA-associated glomerulonephritis outcomes. Sci Rep. 2021 Jun 22;11(1):13080.

13. Wester Trejo MAC, Floßmann O, Westman KW, Höglund P, Hagen EC, Walsh M, et al. Renal relapse in antineutrophil cytoplasmic autoantibody-associated vasculitis: unpredictable, but predictive of renal outcome. Rheumatol Oxf Engl. 2019 Jan 1;58(1):103–9.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Avacopan for treating anti-neutrophil cytoplasmic autoantibody-associated vasculitis [ID1581]

Addendum after PMB

Produced by Maiwenn Al, EUR

On behalf of
Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

Date completed 26/04/2022

Introduction

This addendum contains various additional scenarios that were requested after the pre-meeting brief of 20 April 2022.

The following scenarios were requested:

1. Rituximab as maintenance therapy for people who had rituximab as induction therapy, with the company's other base case assumptions
2. Rituximab as maintenance therapy for people who had rituximab as induction therapy, with the ERG's other base case assumptions
3. Subgroup analyses using the company's and ERG's preferred assumptions for subgroups considered in original ERG report:
    - Newly diagnosed AAV
    - Relapsed AAV
    - GPA
    - MPA
    - RTX background therapy
    - CYC background therapy
    - MPO positive
    - PR3 positive

Results

For scenario 1 and 2, where we assume rituximab as maintenance therapy for people who had rituximab as induction therapy, we used the model settings:

- Population = RTX background therapy
- Combination maintenance treatment = rituximab

Table 1 shows the results when imposing the above scenario settings on the company base case. Compared to the company base case ICER, £19,441, the ICER of this scenario is substantially higher at £43,554.

Table 1 Scenario with rituximab maintenance therapy for people who had rituximab as induction therapy (company's preferred assumptions)

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
RTX+GC	[redacted]	10.77	[redacted]				
AVA+RTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,554

Based on the model provided with the company's Technical Engagement Response.
ICER = incremental cost effectiveness ratio; Incr. = incremental; LYG = life years gained; QALY(s) = quality-adjusted life year(s).

Table 2 shows the results of the same scenario, this time applied to model with the ERG's preferred assumptions. The ERG base case ICER is £40,516, and with this RTX scenario the ICER becomes £69,364.

Table 2 Scenario with rituximab maintenance therapy for people who had rituximab as induction therapy (company's preferred assumptions)

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
RTX+GC	[redacted]	10.92	[redacted]				
AVA+RTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£69,364
Based on the model provided with the company's Technical Engagement Response. ICER = incremental cost effectiveness ratio; Incr. = incremental; LYG = life years gained; PAS = patient access scheme; QALY(s) = quality-adjusted life year(s).							

Tables 3 and 4 show the results of the subgroup analyses that the company included in the cost-effectiveness assessment. These subgroups had been pre-specified for the ADVOCATE study and the trial population was stratified for these subgroups. Table 3 presents the subgroup analyses based on the model with the company's preferred assumptions, whereas table 4 present the results based on the model with the ERG's preferred assumptions.

Table 3 Subgroup analysis with company's preferred assumptions

	N 26w	N 52w	Δ Costs	Δ QALYs	ICER
ADVOCATE ITT population	[redacted]	[redacted]	[redacted]	[redacted]	£19,441
Newly diagnosed AAV	[redacted]	[redacted]	[redacted]	[redacted]	£44,387
Relapsed AAV	[redacted]	[redacted]	[redacted]	[redacted]	£17,019
GPA	[redacted]	[redacted]	[redacted]	[redacted]	£64,198
MPA	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
RTX background	[redacted]	[redacted]	[redacted]	[redacted]	£17,867
CYC background	[redacted]	[redacted]	[redacted]	[redacted]	£40,414
MPO positive	[redacted]	[redacted]	[redacted]	[redacted]	£13,085
PR3 positive	[redacted]	[redacted]	[redacted]	[redacted]	£76,102

Table 4 Subgroup analysis with ERG's preferred assumptions

	N 26w	N 52w	Δ Costs	Δ QALYs	ICER
ADVOCATE ITT population	[redacted]	[redacted]	[redacted]	[redacted]	£40,516
Newly diagnosed AAV	[redacted]	[redacted]	[redacted]	[redacted]	£80,652
Relapsed AAV	[redacted]	[redacted]	[redacted]	[redacted]	£27,696
GPA	[redacted]	[redacted]	[redacted]	[redacted]	£87,583
MPA	[redacted]	[redacted]	[redacted]	[redacted]	£16,586
RTX background	[redacted]	[redacted]	[redacted]	[redacted]	£34,666
CYC background	[redacted]	[redacted]	[redacted]	[redacted]	£77,225
MPO positive	[redacted]	[redacted]	[redacted]	[redacted]	£25,455
PR3 positive	[redacted]	[redacted]	[redacted]	[redacted]	£102,444