Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende avacopan som tillægs-behandling til ANCA-associeret vaskulitis

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. avacopan
2. Forhandlingsnotat fra Amgros vedr. avacopan
3. Ansøgers endelige ansøgning vedr. avacopan

Medicinrådet
Ved Formandskabet
Jørgen Schøler Kristensen og Steen Werner Hansen

25. juni 2023

Høringssvar til Udkast: Medicinrådets anbefaling vedr. avacopan som tillægsbehandling til ANCA-associeret vaskulitis, juni 2023.

Den 14. juni fremsendte Medicinrådet (MR) "Udkast til MR anbefaling vedr. avacopan som tillægsbehandling til ANCA-associeret vaskulitis". Til høring hos Vifor Pharma Nordiska (Vifor). Vifor har 2 bemærkninger til udkastet til MR-anbefaling vedr. avacopan:

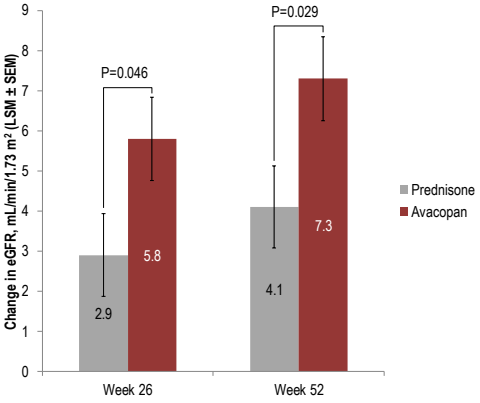
1. ***MR vurderer i pkt. 2.4.5 at effekten af avacopan ikke er dårligere end effekten af prednison målt på nyrefunktion (eGFR).***

Ved vurdering af patienter med nyrepåvirkning viste ADVOCATE-studiet en signifikant klinisk stigning i gennemsnitlige eGFR-værdier for avacopan-gruppen fra baseline til uge 26 (LSM +5,8±1,0) og uge 52 (LSM +7,3±1,0) sammenlignet med prednison-gruppen (LSM +2,9±1,0 henholdsvis LSM +4,1±1,0) (jf. Ansøgningens pkt. 7.1.1.1 [1] og figur 1 nedenfor). Forbedring af nyrefunktionen var mere udtalt hos patienter med mere alvorlig nyresygdom i en subgruppeanalyse af patienter med stadium CKD 4 (dvs. baseline eGFR <30ml/min/1,73 m^2), der viste klinisk signifikant forbedring i eGFR i avacopan-gruppen efter 26 uger (LSM) +10,5) og 52 uger (LSM+13,7) sammenlignet med prednison (henholdsvis LSM +6,4 og LSM +8,2) (ref. 2). Avacopan flyttede patienter med kronisk nyrefunktionsstadie fra CKD 4 til CKD 3B i både uge 26 og 52 (figur 2).

Table 1 Baseline eGFR values in ITT population (DMC assessment report) and kidney involvement population (Jayne et al 2021) in prednisone and avacopan ADVOCATE study arms.

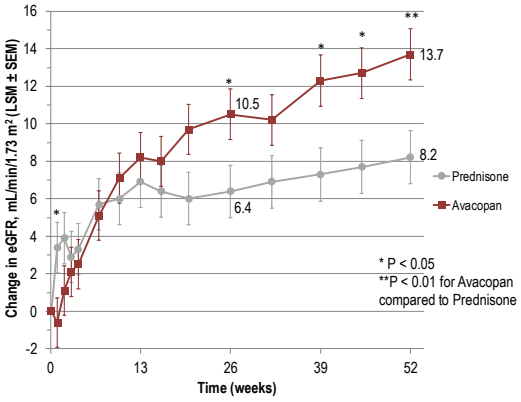
	Baseline eGFR (ml/min/1.73m²), average ± SD	
	Prednisone arm	**Avacopan arm**
DMC assessment report (Pg. 20)	N=164	N=166
	52.9 ± 32.67	50.7 ± 39.96
Jayne et al. 2021 (NEJM)	N= 134	N=131
	45.6 ± 2.4	44.6 ± 2.4

Figur 1 Change from baseline in eGFR during the study period in subjects with renal disease at baseline.



Patient numbers:
Avacopan: Week 26=121; week 52=119.
Prednisone: week 26=127; week 52=125

Figur 2 Change from baseline in eGFR during the study period in subjects with renal disease at baseline and baseline eGFR < 30ml/min/1,73m².



Patient numbers:
Avacopan: baseline=52; week 13=49; week 26=46; week 39=46; week 52=45
Prednisone: baseline=48; week 13=45; week 26=42; week 39=41; week 52=42

I forbindelse med den klinisk signifikante forbedring i nyrefunktionen, sås et hurtigere fald i proteinuri i avacopan-gruppen på 40 % ved uge 4 sammenlignet med 0 % i prednison-gruppen (-40% vs. 0%, P =<0,0001), [1,2].

På denne baggrund finder Vifor, at der ikke er belæg for MRs konklusion om, at forbedringen af nyrefunktionen ikke er klinisk relevant for nogen af behandlingerne. Derfor er det Vifors opfattelse, at den nuværende tekst i anbefalingen bør slettes, og at følgende bør tilføjes: *"Patienter med ANCA-associeret vaskulitis med nedsat nyrefunktion har fordele ved avacopan som følge af en signifikant forbedring i eGFR".*

2. MR vurderer i pkt. 2.3.3 at patienter, som fik rituximab som en del af induktions- behandlingen, var underbehandlet efter studiets første 26 uger.

Vifor er uenig i MRs konklusion om, at patienter, som fik rituximab som en del af induktionsbehandlingen, var underbehandlet efter studiets første 26 uger, og at MR ved uge 52 derfor kun har inddraget resultater for subgruppen af patienter, som modtog cyclophosphamid som en del af induktionsbehandlingen.

ADVOCATE studiedesign:

• På det tidspunkt, hvor ADVOCATE-studiet blev designet, var rituximab endnu ikke godkendt til vedligeholdelse behandling, og der var ingen konsensus om vedligeholdelsesbehandling hver 6. måned med rituximab. Brugen af avacopan i induktionsterapi op til 1 år er siden blevet anbefalet ved 2022-opdateringen af EULAR-konsensusanbefalinger (5), som implementeres i dansk klinisk praksis. Således var ADVOCATE-studiets design helt i overensstemmelse med klinisk praksis på daværende tidspunktet for design og gennemførelse af studiet.

• 2022-opdateringen af EULAR-konsensus (5) anbefaler, at overveje avacopan i kombination med rituximab eller cyclophosphamid til induktion af remission i GPA eller MPA, som en del af en strategi om væsentligt at reducere eksponeringen for glukokortikoider (evidensniveau grad 1b).

Vifor betragter metoden anvendt af MR som kritisabel

•, fordi MR anvender hele ITT-populationen til at vurdere resultaterne i uge 26, og efterfølgende ser MR bort fra 65 % af studiepopulationen (den del der modtog rituximab som induktionsbehandling) ved vurdering af resultaterne i uge 52. At se bort fra en signifikant del af de pivotale effektdata er en væsentlig afvigelse fra analyseplanen beskrevet i forsøgsprotokollen og derfor udgør en risiko for en bias i fortolkningen af resultaterne.

• Da flertallet af patienter med svær og aktiv ANCA-associeret vaskulitis i ADVOCATE-studiet og i klinisk praksis i Danmark behandles med rituximab som induktionsbehandling, tilsidesætter MR det fulde effektpotentiale efter 52 uger for denne subpopulation (hvis behandlingsvarigheden er i overensstemmelse med Markedsføringstilladelse), og det vil føre til en ufuldstændig vurdering af avacopans kliniske effekt.

• MR ser bort fra, at patienter i avacopan-armen ikke behandles med andre lægemidler efter uge 26, hvilket betyder, at reduktionen i tilbagefald og forbedring af vedvarende remission efter uge 26 alene kan tilskrives avacopan. Desuden viste ADVOCATE-studiets resultater en adskillelse af Kaplan-Meier-kurverne for relaps efter dag 40 i studiet, hvilket betyder, at avacopan er effektivt til at forhindre relaps selv ved tilstedeværelse af rituximab-behandling (Ansøgningen, figur 18).

Med venlig hilsen

Yvonne Thomsen
Head market Access & External Affairs

Referencer

1 Vifor Pharma Nordiska. Application for the assessment of Tavneos®(avacopan) for the treatment of ANCA-associated vasculitis

2 European Medicines Agency. Assessment Report Tavneos. 11. November 2021

3 Jayne, D.R.W., et al., *Avacopan for the Treatment of ANCA-Associated Vasculitis.* N Engl J Med 2021;384:599-609. DOI: 10.1056/NEJMoa2023386 https://doi.org/10.1056/NEJMoa2023386, 2021.

4 Supplementary Appendix. Supplement to Jayne DRW, Merkel PA, Schall TJ, Bekker P. Avacopan for the treatment of ANCA-associated vasculitis. N Engl J Med 2021;384:599-609. DOI: 10.1056/NEJMoa2023386 https://doi.org/10.1056/NEJMoa2023386, 2021.

5 Bernhard H, Beatriz S-A, Jan HS, Alvise B, Daniel B, Maria CC, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Annals of the Rheumatic Diseases. 2023:ard-2022-223764.

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Forhandlingsnotat

03.08.2023

BMC

BMC/CAF

Dato for behandling i Medicinrådet	23.08.2023
Leverandør	Vifor Pharma Nordiska
Lægemiddel	Tavneos (avacopan)
Ansøgt indikation	Behandling af voksne med svær, aktiv granulomatose med polyangiitis (GPA) eller mikroskopisk polyangiit (MPA)
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Tavneos (avacopan):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Tavneos	10 mg	180 stk.	52.879,00	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

[redacted]

[redacted]

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	SAIP (DKK) pr. 01.09.2023	Rabatprocent ift. AIP
Tavneos	10 mg	180 stk.	52.879,00	[redacted]	[redacted]

Aftaleforhold

[redacted]

Konkurrencesituationen

Tavneos indgår ikke i et udbud og er ikke i en behandlingsvejledning.
Tabel 3 viser lægemiddeludgifter for Tavneos for 12 måneders behandling.

Tabel 2: Lægemiddeludgift for 12 måneders behandling

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Tavneos	10 mg	180 stk.	30 mg to gange dagligt	[redacted]	[redacted]

Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering		Link til status
Sverige	Ikke anbefalet	[redacted]	
England	Anbefalet		Link til anbefaling

Konklusion

[redacted]

APPLICATION FOR THE ASSESSMENT OF

TAVNEOS® (AVACOPAN)

FOR THE TREATMENT OF ANCA-ASSOCIATED VASCULITIS

Date: June 2022
Vifor Pharma Nordiska AB

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1. BASIS INFORMATION

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1.2 Overview of the pharmaceutical

Propietary name	Tavneos®
Generic name	Avacopan, (CCX168). Danish: Avakopan
Marketing authorization holder in Denmark	Vifor Fresenius Medical Care Renal Pharma France 100-101 Terrasse Boieldieu Tour Franklin La Défense 8 92042 Paris La Défense Cedex France
ATC code	New ATC-code will be assigned
Pharmacotherapeutic group	New group will be assigned
Active substance	Avacopan; (2R,3S)-2-(4-cyclopentylaminophenyl)-1-(2-fluoro-6-methylbenzoyl)piperidine-3 carboxylic acid(4-methyl-3-trifluoromethylphenyl)amide

Pharmaceutical form	Hard capsule
Mechanism of action	Avacopan is a selective antagonist of the human complement 5a receptor (C5aR1 or CD88) and competitively inhibits the interaction between C5aR1 and the anaphylatoxin C5a. The specific and selective blockade of C5aR1 by avacopan reduces the pro-inflammatory effects of C5a, which include neutrophil activation, migration, and adherence to sites of small blood vessel inflammation, vascular endothelial cell retraction and permeability [154].
Dosage regimen	30 mg Tavneos (3 hard capsule of 10 mg each) taken orally twice daily, morning and evening, with food [154].
Therapeutic indication relevant for Assessment (as defined by the (European Medicines Agency, EMA)	Tavneos, in combination with rituximab or cyclophosphamide regimen, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) [154].
Other approved therapeutic indications	No
Will dispensing be restricted to Hospitals	Yes, we expect the dispensing will be restricted to hospitals, because: • Avacopan is an immunosuppressants (L04AA59) • According to the Danish guidelines, patients with suspected AAV must be referred for assessment in a highly specialized setting. Assessment and treatment of AAV usually presupposes a multidisciplinary collaboration between different highly specialized medical and surgical departments, a the diagnosis should be supported by a biopsy from affected organ [188,189]. • Treatment should be initiated and monitored by healthcare professionals experienced in the diagnosis and treatment of GPA and MPA [154].
Combination therapy and/or Comedication	Yes, Tavneos should be administered in combination with a rituximab or cyclophosphamide regimen [154].
Packaging – types, Sizes/number of units, and concentrations	Tavneos®, hard capsule contains 10 mg avacopan, 180 hard capsules [154]
Orphan drug designation	The 19th. November 2014 European Commission graded orphan designation for treatment of: • granulomatosis with polyangiitis (EU/3/14/1373) [157] • microscopic polyangiitis (EU/3/14/1372) [183]

2. ABBREVIATIONS AND GLOSSARY OF TERMS

ANCA-AV	Antineutrophil cytoplasmic autoantibodies (ANCA)-associated vasculitis
AE(s)	Adverse event(s)
ACR	American College of Rheumatology
ANCA	Antineutrophil cytoplasmic autoantibodies
ASMR	Age-standardized global and sex-specific mortality rates
AZA	Azathioprine
BHPR	British Health Professionals in Rheumatology
BSR	British society for rheumatology
BVAS	Birmingham Vasculitis Activity Score
CAF	Concerns about the future
CEM	Cost effective model
CPRD	Clinical practice research datalink
CI	Confidence interval
CKD	Chronic kidney disease
CRP	c-reactive protein
CSR	Clinical study report
CVD	Cardiovascular disease
CYC	Cyclophosphamide
DNPR	The Danish National Patient Register (Landspatientregistret)
DRS	Danish Society of Rheumatology (Dansk Reumatologisk Selskab)
DNS	Danish Society of Nephrology (Dansk Nefrologisk Selskab)
DNSL	Danish Society of Nephrology National register (Dansk Nefrologisk Selskabs Landsregister)
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EGPA	Eosinophilic granulomatosis with polyangiitis
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimension questionnaire
ERA-EDTA	European Renal Association-European Dialysis and Transplant Association
ESRD	End-stage renal disease
EU	European Union
EULAR	European League Against Rheumatism
EUVAS	European vasculitis society
FDA	Food and Drug Administration
GC(s)	Glucocorticoid(s)
GFR/eGFR	Estimated glomerular filtration rate
GMR	Geometric mean ratio

GPA	Granulomatosis with polyangiitis
GTI	Glucose AEs and complications index
GVD	Global value dossier
GVS	Global value story
GWASs	Genome-wide association studies
hpf	High-power field
HR	Hazard ratio
HRQol	Health-related quality of life
hsCRP	High-sensitivity c-reactive protein
HSZ	Herpes Zoster
HSUV	Health state utility values
ICER	Incremental cost effectiveness ratio
ICD10	International Classification of Diseases Version 10
IQR	Interquartile range
ITT	Intent-to-treat
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
MCP-1	Monocyte chemoattractant protein-1
MCS	Mental component summary
MDRD	Modification of diet in renal disease study
MMF	Mycophenolate mofetil
MMRM	Mixed models for repeated measures
MoA	Mechanism of action
MPA	Microscopic polyangiitis
MPO	Myeloperoxidase
MTX	Methotrexate
NICE	National Institute for Health and Clinical Excellence
NMSC	Non-melanoma skin cancer
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
OSS	Organ symptoms severity
PBO	Placebo
PCS	Physical component summary
PF	Physical function
PLEX	Plasma exchange
PR3	Leukocyte proteinase 3
PROs	Patient reported outcomes
QoL	Quality of life
RBC	Red blood cells
RCT(s)	Randomized controlled trial(s)
RTX	Rituximab

SAE(s)	Serious adverse event(s)
SD	Standard deviation
SD	Statistic Denmark (Danmarks Statistik)
SE	Standard error
SEI	Social and emotional impact
SLR	Systematic literature review
SMR	Standardized mortality ratio
SF-36	Short-form 36 Health Survey Questionnaire
SI	Serious infection
SOC	Standard of care
SSS	Systemic symptoms severity
TSE	Treatment side effects
UACR	Urine albumin-to-creatine ratio
VAS	Visual analogue scale
VDI	Vascular damage index
Antineutrophil cytoplasmic autoantibodies associated vasculitis (ANCA-AV)	A group of diseases (GPA: granulomatosis with polyangiitis, EGPA: eosinophilic granulomatosis with polyangiitis, and MPA: microscopic polyangiitis), characterised by destruction and inflammation of small vessels.
Antineutrophil cytoplasmic autoantibodies (ANCA)	Autoantibodies directed against antigens found in the cytoplasmic granules of neutrophils and monocytes
Azathioprine (AZA)	Azathioprine is a commonly used immunosuppressant in the maintenance phase of ANCA-AV in order to maintain remission after induction therapy- For further guidance on use see http://bnf.nice.org.dk/drug/ azathioprine.html
Birmingham Vasculitis Activity Score (BVAS)	BVAS is a robust and validated clinical tool for the assessment of systematic vasculitis. It is used as a checklist of parameters to examine in daily practice, to assess disease activity (identify remission major and minor relapses) and to assess response to treatment. It is calculated from a checklist of 56 items/descriptors of vasculitis manifestation across 9 organ-based systems. Each item is weighted, and each organ-system has a maximum score to reflect major or minor vasculitis disease activity, BVAS 0 = no disease and BVAS ≥ active disease.
Chronic Kidney Disease (CKD)	CKD is present if there are abnormalities of kidney function or structure present for more than 3 months. The definition of CKD includes any patient with markers of kidney damage or with an eGFR of less than 60 ml/min/1.73m2 on at least 2 occasions 90 days apart (with or without markers of kidney damage). Kidney disease markers may include: albuminuria, haematuria, electrolyte abnormalities due to tubular disorders, renal histological abnormalities, structural abnormalities on imaging or a history of kidney transplantation. CKD graded by eGFR result is given as a stage of 1 of 5: • Stage 1 – a normal eGFR above 90ml/min, but other tests have detected signs of kidney damage

	• Stage 2 – a slightly reduced eGFR of 60 to 89ml/min, with other signs of kidney damage • Stage 3a – an eGFR of 45 to 59 ml/min • Stage 3b – an eGFR of 30 to 44 ml/min • Stage 4 – an eGFR of 15 to 29 ml/min • Stage 5 – an eGFR below 15ml/min, kidneys have lost almost all function
C-reactive protein (CRP)	A substance produced by the liver in response to inflammation. A high level of CRP in the blood is a marker of inflammation. It can be caused by a wide variety of conditions, from infection to cancer.
Cyclophosphamide (CYC)	A chemotherapy medication used to suppress the immune system in the induction and maintenance of ANCA-AV remission. For more information see http://bnf.nice.org.uk/drug/cyclophosphamide. html
Eosinophilic granulomatosis with polyangiitis (EGPA)	An inflammatory disease of small and medium sized blood vessels, previously known as a Churg-Strauss Syndrome. The lungs and skin are commonly affected but it can affect other organs including the heart, kidneys, nerves and bowels.
Estimated glomerular filtration rate (eGFR)	A calculation of how many milliliters of waste a patient's kidneys should be able to filter in a minute, based on blood test results, age, size, gender, and ethnic group. Healthy kidneys should be able to filter more then 90ml/min.
End-stage renal disease (ESRD)	ESRD is the final, permanent stage of chronic kidney disease, where kidney function has declined to the point that the kidneys can no longer function independently (eGFR < 15 ml/min/1.73m^2)
Genome-wide association studies (QWAS)	A term to refer to hypothesis-free methods for identifying associations between genetic regions (loci) and traits (including diseases)
Glomerulonephritis	Damage of the glomeruli, the filtering units within the kidneys
Granulomatosis with polyangiitis (GPA)	A rare disorder that causes inflammation of the blood vessels in the nose, sinuses, throat, lungs and kidneys. Formerly called Wegener's granulomatosis, this condition is one of a group of blood vessel disorders called ANCA-AV, which slows blood flow to some organs.
High-sensitivity C-reactive Protein (CRP)	A blood test that finds lower levels of C-reactive protein (CRP). This protein measures general levels of inflammation in your body.
Leukocyte proteinase 3	A trypsin-like serine protease that degrades extracellular matrix proteins.
Methotrexate (MTX)	An immunosuppressant which suppresses the body's immune system and helps reduce inflammation. It is used to treat inflammatory conditions, including rheumatoid arthritis and psoriasis. For further information see http://bnf.nice.org.uk/drug/methotrexate.html
Mixed models for repeated measures (MMRM)	Mixed models explicitly account for the correlations between repeated measurements within each patient, considering both fixed (assumed to have the same effect) and random effects (likely to vary substantially between patients)
Microscopic polyangiitis (MPA)	An ill-defined autoimmune disease characterized by a systemic, pauci-immune, necrotizing, small-vessel vasculitis without clinical or pathological evidence of necrotizing granulomatous inflammation.
Mycophenolate mofetil (MMF)	An immunosuppressant that is mainly used to stop the body from rejecting a transplanted organ (e.g., kidney, heart, liver). MMF can also be used to treat skin

	conditions. For further information see http://bnf.nice.org.uk/mycophenolate-mofetil. html
Myeloperoxidase (MPO)	A heme-containing peroxidase expressed mainly in neutrophils and to a lesser degree in monocytes. MPO has been demonstrated to be a local mediator of tissue damage and the resulting inflammation in various inflammatory diseases. These findings have implicated MPO as an important therapeutic target in the treatment of inflammatory conditions, and MPO antibodies, evaluated alongside other factors, are used to diagnose immune-medicated vasculitis, especially MPA.
Glucocorticoids (GCs)	GCs are immunosuppressants used to achieve and sustain remission in organ or life-threatening ANCA-AV. A high-dose GC regimen usually consists of prednisone at 1 mg/kg/day (to a maximum daily dose of 80 mg), gradually increased to a target dose of 7.5-10 mg prednisolone (or equivalent) where the disease is controlled, after 3 months of treatment.
Rituximab (RTX)	A biological therapy, that can reduce inflammation and damage to the joints. It is also known by the trade names MabThera, Rixathon, Ruxience, and Truxima. Indications for use include rheumatoid arthritis, non-Hodgkin's lymphoma, Chronic lymphocytic leukaemia, pemphigus vulgaris as well as GPA and MPA. For further information see http://www.rituxan.com/gpa-mpa.html
Standard of Care (SOC)	All guidelines recommend induction therapy (up to 6 month) of high-dose GCs, plus either CYC or RTX. For maintenance of remission, administration of low-dose GCs, as well as AZA if CYC was used for remission induction, or a continuation of RTX if used for remission induction, is recommended.
Vascular damage index (VDI)	A tool to distinguish vasculitis-induced chronic damage from active inflammation or persistent disease. It was developed by consensus by a group of vasculitis experts and is widely used in clinical trials. The VDI comprises 64 items of damaged grouped into 11 organ systems. Damage is defined as the presence of non-healing scars during or present within the previous 3 months. Each item of damage is assigned 1 point and the point from alle 11 categories are totalled to provide a VDI total score. New patients usually have a VDI score of 0.

3. TABLES AND FIGURES

3.1 Tables

3.2 Figure

4. SUMMARY

Overview

An Avacopan-based regimen has a unique and targeted approach that is, at week 52, superior in controlling active severe GPA and MPA compared with current GC-based regimens. It also reduces relapses and improves kidney function in patients with prior renal involvement, without the considerable complications of long-term GC therapy. The clinical benefits, together with improved quality of life, a simpler dosing regimen vs GCs, and cost savings for the health system in terms of relapse reduction, offer prescribers, patients, and payers a significant advance in the treatment of GPA and MPA.

Historically, GCs have been a foundation of ANCA-AV management, but their usage is associated with several issues. Most importantly, 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 comply accurately with treatment. An Avacopan-based regimen reduces, and in some cases eliminates, the need for GC therapy, thereby greatly benefiting patients by positively impacting quality of life while also providing a simpler fixed-dosing regimen.

An avacopan-based regimen reduces the overall number of relapses

An Avacopan-based regimen sustains more patients in remission than is possible with the current SOC, with the potential to save the additional costs of relapses. At Week 52 of the ADVOCATE trial, 65.7% subjects achieved sustained remission with an Avacopan-based regimen compared with 54.9% with SOC (p=0.0066) [155, 156]. An Avacopan-based regimen also reduced the relative risk of relapse by 54% compared with SOC in patients who achieved BVAS = 0 (regardless of GC use in prior 4 weeks) at any point during the trial (p< 0.01) [155, 156].

An avacopan-based regimen reduces the hospitalizations

In the ADVOCATE trial, hospitalization was captured and analysed as part of safety monitoring. The data demonstrated that an Avacopan-based regimen could decrease both the number of hospitalisations and the duration of hospital stay by approximately one third compared to SOC, (GC-based regimen) in the treatment of ANCA-AV see the table below [155, 156].

Post-hoc analysis Hospitalisation length of stay (days) at day 1-Week 52in the ITT population [155, Appendix L]

	No pts	**No. hospitalisations**	**Duration of hospitalisation (days)**					**Shapiro-Wilk test p value**	**2 sample T-test p value**	**Wilcoxon Mann Whitney U test p value**
			Min	Max	Mean	Median	Total			

Avacopan-based regimen	57	78	2	80	13.8	8	786	0.000	0.142	0.204
SOC, GC-based regimen	69	111	1	208	19.6	12	1354			

Post-hoc analysis from ADVOCATE study, Appendix L

An avacopan-based regimen reduces the cost of treating ESRD

Renal involvement occurs in up to 78% of ANCA-AV patients [56], with 15-38% progressing to ESRD within 5 years of diagnosis[48-50].

An Avacopan-based regimen may reduce the 5-year relative risk of ESRD by 15% in all patients with renal involvement and by 28% in patients with CKD stage 4, thereby potentially substantially reducing treatment costs [155, 156].

An avacopan-based regimen may reduce the cost of treating the AEs associated with GCs

The use of GCs as SOC for ANCA-AV patients has been linked to an increase in GC-related AEs [133, 134]. A UK study found a greater incidence of adverse effects in those on higher doses of GCs compared with those on lower doses. AAV patients on high dose GCs experienced a 2.15 time higher infection rate and a 2.75 times higher rate of new onset renal disease compared with those on low dose GCs [142]. An increased risk of infection has been demonstrated in Germany, where a study found a 42% higher risk of infections in GPA or MPA patients over a 4-year period after diagnosis of ANCA-AV compared with the period before [162].

An Italian study also found that 9.1% of hospital admissions in ANCA-AV patients are due to infections [39].

Avacopan-based regimen reduces the cumulative dose of GCs in ANCA-AV patients and thereby directly reduce the steroid related adverse event rate and overall toxicity. Avacopan-based regimen can even potentially eliminate the usage of GCs, for some patients. In addition, Avacopan-based regimen has a favourable safety profile, with lower AEs, GC-related AEs, and infection rates seen in the Avacopan compared with the SOC group.

5. THE PATIENT POPULATION, THE INTERVENTION AND CHOICE OF COMPARATOR

5.1 The medical condition and patient population

The cause of ANCA-AV is not fully understood with numerous genetic and environmental factors affecting an individual's risk of developing the disease; the global prevalence of ANCA-AV has increased significantly in the past 25 years [7,155].

ANCA-AV affects <5 out of every 10.000 people, meeting the definition of a rare disease. The prevalence is between 46-184 cases per million and the annual incidence rates are 2,1 -14,4 per million for GPA and 2,4-10,1 per million for MPA [1].

Patients are classified by antibody status or clinical phenotype, which are associated with different disease courses [2,3,189].

In ANCA-AV there is immune system mediated blood-vessel inflammation leading to organ damage [2].

5.1.1 Medical condition - ANCA-AV disease characteristics

5.1.1.1 Clinical phenotypes

Patients are classified by antibody status or clinical phenotype, which are associated with different disease courses.

The three major clinicopathologic variants are:

- Granulomatosis with polyangiitis (GPA), formerly known as Wegener granulomatosis (WG)
- Microscopic polyangiitis (MPA)
- Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg–Strauss syndrome (CSS) (EGPA is not an approved indication for Avacopan)

GPA and MPA are the two main forms of the disease that carry the most severe complications. The definitions of these are presented in table 2.

Table 1 Capel Hill Consensus definition (2012) for GPA and MPA [11]

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.	

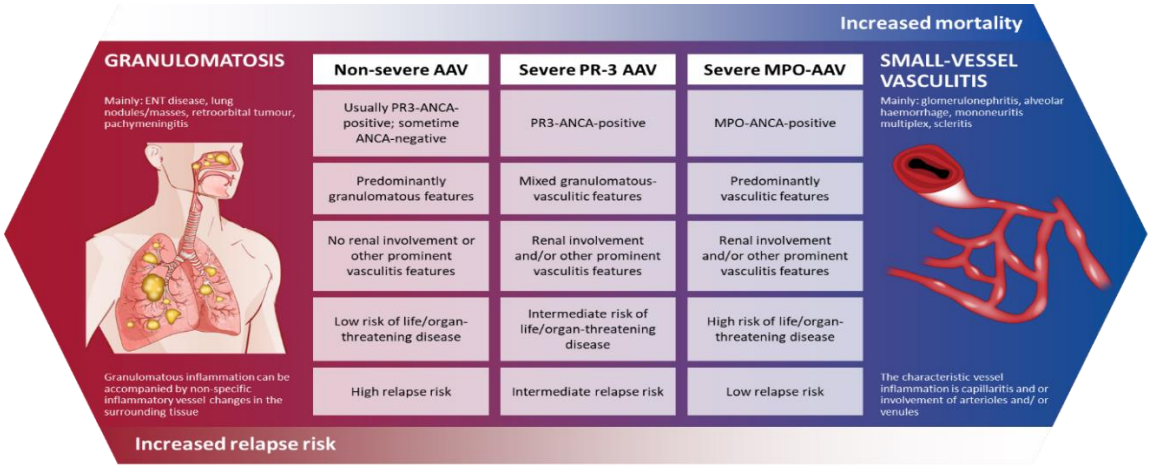
GPA and MPA are distinguished by their clinical phenotype and antibody profile but are managed in the same treatment paradigm as they share the same pathophysiology, involving complement pathways and neutrophils [8].

GPA is characterized by extravascular granulomatous inflammation, most often in the respiratory tract. Clinical manifestations of GPA can be heterogeneous, often affecting the upper and lower respiratory tract, with characteristic destructive lesions in the nasal septum, lung infiltrates and cavities but renal disease is also common.

Glomerulonephritis is more frequently detected, and can be more severe, in patients with MPA. In some MPA cases vasculitis is limited only to the kidney [9]. Relapse is more commonly seen in patients with GPA, compared to MPA [10].

Patients with MPA and GPA may be further subcategorized into clinically relevant subtypes with different clinical features [12], by the target of the ANCA, either leukocyte proteinase 3 (PR3)-ANCA positive (more often associated with a GPA phenotype) or MPO-ANCA positive (more often associated with a MPA phenotype) (See Figure 1). These antibody defined subtypes share greater homogeneity in genetics, disease pathogenesis, organ involvement, and potentially response to treatment [12].

Figure 1 Patients with MPA and GPA may be further subcategorized by PR3 and MPO titres into clinically relevant subtypes with different clinical features [12].



5.1.1.2 Etiology and risk factors

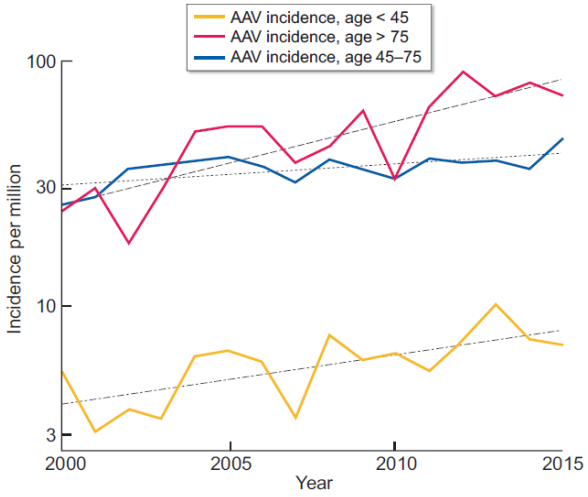
The cause of ANCA-AV is not fully understood, with genetic factors, environmental exposures, medication history, and infection all contributing to the disease aetiology and initial loss of immune tolerance [27-31]. To date, two different genome-wide association studies (GWASs) have been performed in ANCA-AV, both showing that ANCA-AV is a polygenic disease with approximately 20% of the disease risk due to genetic factors, which also differ between patients who are PR3-ANCA positive or MPO-ANCA positive. 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 ANCA-AV [32].

Incident GPA and MPA patients often have symptoms for a long time before diagnosis , a factor associated with worse long-term clinical outcomes [33]. Although ANCA-AV 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 [9, 34].

In a Danish retrospective cohort study Nelveg-Kristensen et al identified 1.631 incident patients with ANCA-associated vasculitis (AAV) from the Danish National Patient Register (DNPR) diagnosed with at least two consecutive hospital encounters registered as GPA or MPA (International Classification of Diseases Version 10 (ICD10): DM31.3 and DM31.7) between 2000-2015 corresponding to an incidence of 18,5 [185].

In this study Nelveg-Kristensen et al also found an increasing incidence with age. The average age of diagnosis was mean (SD) 60,2 (16,9) years and the frequency of incidence increased with age, with incidence for the total study period of 6,0 (SD 1,9); 36,6 (SD 5,3) and 51,0 (SD 21,2) for patients <45; 45-75 and >75 years, respectively. The highest increase in incidence over time was seen among patients > 75 years old **Fejl! Henvisningskilde ikke fundet.** [185].

Figuren 2 Age stratified incidence of AAV in Denmark during 2000-15 [185]



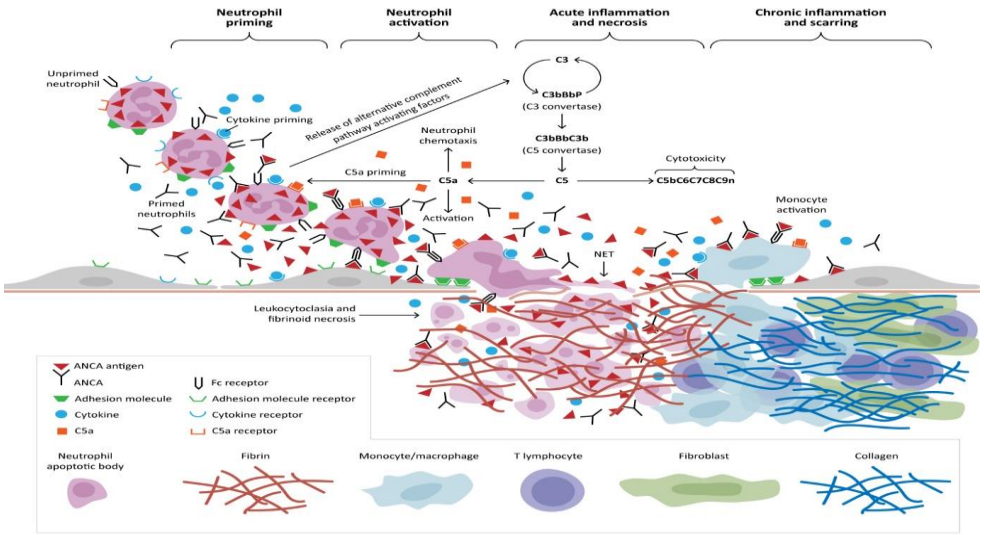
Seasonal variations in GPA and peaks in ANCA-AV in general every 4 years have suggested an infectious ethology. There are inconsistencies in the data however, with a UK study suggesting higher incidence in winter, a seasonality that was not seen in the US. Environmental exposure to silicon has been associated with the development of chronic renal failure and vasculitis, with MPO-ANCA described in patients with pulmonary silicosis and nephropathy [32].

5.1.1.3 Vasculitis pathophysiology

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

In addition, neutrophils release several mediators, including properdin, which 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 ANCA-AV [35-37]. The heart of the vasculitis process in ANCA-AV 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 [37].

Figure 3 Initiation of vasculitis lesions in small vessels by activated neutrophils: C5a generated from the alternative pathway attracts more neutrophils which adhere to vessel walls and release inflammatory mediators. The events from left to right occur sequentially and amplify at each site of injury and are repeatedly initiated at multiple sites until induction of remission [38].



5.1.2 Medical Condition - The clinical burden of ANCA-Associated Vasculitis

ANCA-Associated Vasculitis (ANCA-AV) can affect multiple organs, causing debilitating and life-threatening damage [1,2,39]

72 % of patients diagnosed with ANCA-AV are hospitalized or die over a 5-year period [39]

Patients with GPA have a 9-fold increased mortality risk in the first year of disease compared to healthy controls, attributed to infections, vasculitis, and renal disease [40]

Almost 3 times as many ANCA-AV patients die over a period of 5,2 years vs. general population (p<0,0001) [3]

If left untreated, 93 % of patients with GPA die within 2 years of disease onset [4].

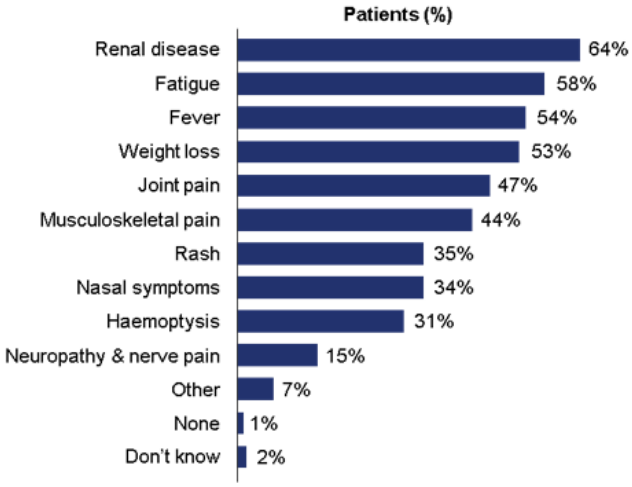
5.1.2.1 Disease introduction

ANCA-AV presents with severe organ and life-threatening, and non-severe, manifestations, with the latter still causing major adverse impact to patients. It can involve many organs, with the kidneys, respiratory tract, nose/sinuses, eyes, skin, and nervous system the most commonly affected [41].

Patients with ANCA-AV may have a wide range of specific signs and symptoms reflecting particular organ involvement, as well as systemic symptoms such as fatigue and weight loss (**Fejl! Henvisningskilde ikke fundet.**). The range of symptoms include [41]:
Fatigue
Renal symptoms
Coughing
Nasal symptoms

Rash (such as purpura and urticaria, resulting from blood from small vessels leaking under the skin).

Figure 4 Symptoms at GPA/MPA diagnosis: real-world EU data (retrospective clinical audit of healthcare records from 929 incident ANCA-AV patients (GPA: 54 %; MPA: 46 %) who initiated remission induction therapy between November 2014 and February 2017 and were followed for 1 year [41].



ANCA-AV can be broadly differentiated into three levels of severity depending on the potential impact on vital organs [41]:
Mild
Organ/life threatening
Organ/life threatening with rapid progression.

ANCA-AV is commonly a chronic, relapsing condition [1,2,39] and the majority of patients have evidence of organ- or life-threatening disease [11].

GPA more commonly involves nasal crusting, stuffiness and epistaxis, uveitis, upper respiratory tract and nervous system involvement, while MPA patients presenting with renal and gastrointestinal involvement [42]. Renal disease is a typical observation in both GPA and MPA patients, with haematuria, proteinuria or reduced eGFR common signs [11] (Table 2).

Table 2 A comparison of GPA and MPA characteristics, demonstrating significant differences

	GPA*[1]	MPA*[1]	P-value
PR3-ANCA+	79%	23%	Not available
MPO-ANCA+	21%	77%	Not available
Relapse	50%	18%	<0.001
Renal involvement	64%	89%	<0.001
Lung involvement	78%	61%	0.03
Rheumatologic involvement	61%	41%	0.003
Ear, nose or throat involvement	74%	9%	<0.001

*1 Retrospective study of 94 GPA patients and 56 MPA patients, in which demographic, clinical and laboratory data were collected from patient files [43].

5.1.2.2. Cause of disease

Summary:

Renal involvement is the most common severe manifestation of ANCA-AV: 78% of patients have renal involvement [2,56]

CKD has one of the most significant impacts on patient survival and is present in 90% of MPA patients and 80% of GPA patients [57]

Mortality risk is higher in patients with renal involvement (HR 2.4 in wide-extent extra-renal disease, p=0.05; HR 3.31 in low-extent extra-renal disease p=0.005), particularly if PR3-ANCA were not present (HR 5.87, p <0.0005) [58]

Approximately 5–29% of ANCA-AV patients experience major relapses each year [71-73].

ANCA-AV patients are at particularly high risk of mortality within the first year of diagnosis, and most deaths (59%) are attributable to the medications used [64].

Almost 3 times as many ANCA-AV patients die over a period of 5.2 years vs. general population (p<0.0001) [3].

5.1.2.2.1 Course of disease - overview

Morbidity in ANCA-AV results due to a complex interaction of evolving factors: active vasculitis; chronic multi-organ damage from both ANCA-AV (including disease relapse) and its associated treatments; comorbidities; and adverse effects associated with ANCA-AV therapies [44, 45], and there is often difficulty in disentangling disease- and treatment-related morbidities [46].

ANCA-AV patients have renal involvement and as such may require renal replacement therapy (RRT) [47]. 15% of ANCA-AV patients require RRT at remission induction rising in some cases up to 38% within 5 years of diagnosis [2, 48-50]. Other common comorbidities, seen in >5% of patients at both diagnosis and relapse, are hypertension, Type 2 diabetes, COPD/asthma, coronary artery disease, arthritis, osteoporosis, BMI >35, and cardiac failure [47]. Up to 70% of patients also develop severe fatigue, which is associated with altered perception of exertion and reduced cardiovascular capacity [51].

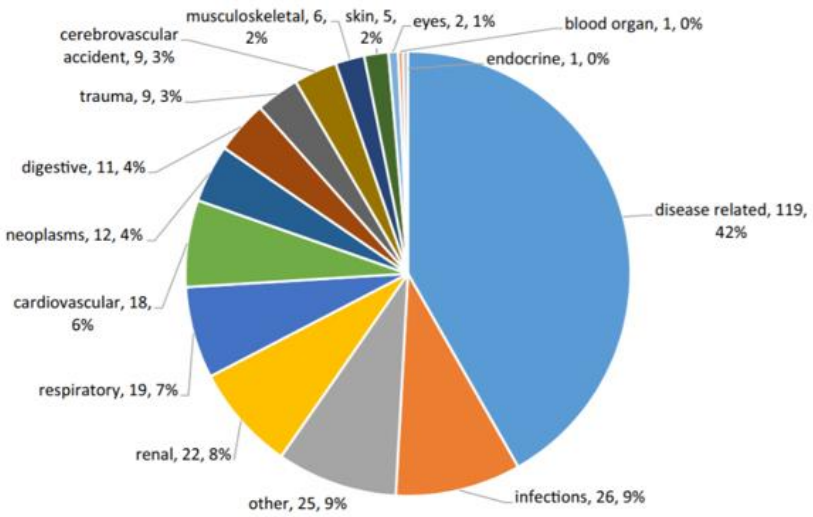
If left untreated, 93% of patients with GPA die within 2 years of disease onset [4]. 72% of patients diagnosed with ANCA-AV are hospitalised or die over a 5-year period [39]. Hospitalisations are generally due to lung and/or renal involvement, infection, cardiovascular or gastro-intestinal complications [39]. Most GPA and MPA patients have comorbidities at both diagnosis and relapse [34, 41] ; only 32% of incident patients at diagnosis have no comorbidities [41].

Ear, nose and throat disease in GPA has a high risk of causing irreversible damage and chronic symptoms, including damage of the nasal mucosa. This is associated with nasal crusting, which causes nasal obstruction and increases susceptibility to infection [42]. Furthermore, some GPA patients may experience hearing loss due to eustachian tube obstruction, recurrent otitis, or damage to the eighth cranial nerve [52]. Vasculitis damage of the airways may cause fibrotic subglottic, and tracheal or bronchial stenoses [53, 54].

Cardiovascular events have also been shown to be a significant source of morbidity among ANCA-AV patients, a cohort of cases diagnosed from 2002 to 2017 indicated a standardized mortality rate of 2.3 fold higher for cardiovascular mortality, with a significant association of MPO-ANCA vasculitis with cardiovascular death [55].

Quartuccio et al. [39] reported that the main cause of the 285 hospitalisations recorded from 2013-2018 in a cohort of Italian ANCA-AV patients were disease-related factors (42%), followed by infections (26.9%) (**Fejl! Henvisningskilde ikke fundet.**).

Figure 5 Distribution of the categories of main discharge diagnosis for 285 hospitalizations in 103 Italian ANCA-AV patients [44]



5.1.2.2.2 Cause of Disease - Renal Involvement in ANCA-AV

Renal involvement is the most common severe manifestation. Renal disease is usually due to a challenging combination of factors: active renal vasculitis, CKD as a comorbidity [59], and risk factors exacerbated by both vasculitis and GC use [56]. CKD occurs in up to 90% of MPA patients and 80% of GPA patients [57].

Deterioration of renal function carries a poor prognosis [59], with a high rate of end stage renal disease (ESRD) seen in the ANCA-AV population: 14-38% of ANCA-AV patients develop ESRD within

5 years [4, 48-50, 60-62]. Although patients can recover renal function, 26% reach ESRD after 3 years, which is associated with active vasculitis with incident disease in 51% of patients, progressive CKD without active vasculitis in 43% of patients, and renal relapse in 6% of patients [59].

In a follow-up of the EUVAS study in 535 patients, 19.7% developed ESRD, 11% in the first year following diagnosis, and experience of renal relapse led to a 9-fold increased risk of developing ESRD [63, 64]. Real-world data from a cohort study reviewing 1755 GPA and 756 MPA patients from 12 EU renal registries highlights the significant burden of renal disease in real-world practice, with 22.2% of patients requiring kidney transplantation, and a 10-year probability of survival on RRT after day 91 of 32.5% (95% CI, 29.9%-35.1%) [65].

At disease presentation, renal disease is more prevalent in MPO- compared to PR3-ANCA positive patients (85% vs. 68%, $p<0.05$) [50]. Compared to PR3-ANCA positive patients, MPO-ANCA positive patients are three times more likely to develop ESRD (HR 2.98; 95% CI 1.44–6.18; $p<0.01$) and have lower renal survival (77.1% vs. 90.8%) [50]. Studies also document an association between the development of ESRD and older age, and when renal insufficiency (i.e. proteinuria) is present at time of diagnosis [66].

A population-based study involving 186 patients with ANCA-AV (92 GPA, 83 MPA, 11 EGPA) and 744 matched controls in Sweden aimed to investigate comorbidities associated with ANCA-AV, and reported that the highest rate ratios (defined as ANCA-AV: matched controls) were reported for osteoporosis (4.6, 95% CI 3.0–7.0; $p<0.001$), venous thromboembolism (4.0, 95% CI 1.9–8.3; $p=0.003$), thyroid diseases (2.1, 95% CI 1.3–3.3; $p=0.009$), and diabetes mellitus (2.0, 95% CI 1.3–2.9; $p=0.003$) [46].

In a retrospective clinical audit of healthcare records from 929 incident ANCA-AV patients (GPA: 54%; MPA: 46%, who initiated remission induction therapy between November 2014 and February 2017 and were followed for 1 year), nearly two-thirds of patients had renal disease at diagnosis (Figure 5) [41]. A retrospective analysis in incident GPA patients (n=757) also showed that up to one year prior to diagnosis, GPA patients experience a significantly higher incidence of chronic renal impairment, as well as type 1 diabetes, thyroid disease, rheumatoid arthritis, inflammatory bowel disease, pulmonary fibrosis, and bronchiectasis (all $p<0.02$) [67]. Longitudinal data from the German insurance database (inGEF) showed that the development of severe kidney damage (chronic kidney disease stages III–IV) in GPA/MPA patients was highest during the induction period, and higher in MPA compared to GPA patients [68].

5.1.2.2.3 Cause of Disease - Relapsing ANCA-AV

Identified risk factors for ANCA-AV relapse include GPA diagnosis, better renal function (creatinine level <200 µmol/L) at diagnosis, ENT involvement, PR3-ANCA at presentation, ANCA positive after induction or rise in ANCA during treatment, GC/immunosuppressive withdrawal, lower cumulative CYC exposure [11] and history of previous relapse [69] oral prednisolone dose after the initiation of remission induction therapy [74], and persistent haematuria [75].

Approximately 5–29% of ANCA-AV patients experience major relapses each year [71-73]. Successful disease management is required to lower relapse rates, and subsequently reduce cumulative organ damage and exposure to GC therapy [69-72]. Therefore, reduction of relapse is a major unmet need with current treatment in ANCA-AV.

5.1.2.2.4 Cause of Disease - Mortality in ANCA-AV

With the advent of cyclophosphamide or rituximab plus high dose glucocorticoid treatment, the mortality rate of ANCA-AV has decreased, but remains higher than that of the general population [3, 76-80]. Despite current standard of care treatment, patients with GPA have an increased mortality risk in the first year of disease compared to healthy controls, with mortality attributed to infection, vasculitis, and renal disease [40]. Almost 3 times as many ANCA-AV patients die over a period of 5.2 years vs. general population ($p<0.0001$) [3].

The effect of ANCA-AV on mortality is two-fold. Longer-term mortality is increased due to disease-related complications, development of CVD, renal disease and GC-induced diseases [3, 64], whereas short-term mortality within one year of diagnosis is attributed to infections related to treatments, in particular GCs, as well as disease complications [64].

GPA patients have been shown to have a nine-fold greater risk of death than healthy controls within the first year of their diagnosis ($p<0.001$), with mortality in the first year after GPA diagnosis 11%, compared to 1.2% in control patients ($p<0.001$) [45].

Long-term mortality in newly-diagnosed GPA patients (n=255) in the UK between 1989-2004 was 20.8% vs 7.8% in control patients (n=2546) ($p<0.001$; mean follow-up, 6.4 years) [40]. Although population-based data suggest the all-cause mortality risk in GPA patients has improved over time, since a report from 1958 stating that many GPA patients did not survive longer than 1 year after diagnosis [81], it is significantly higher compared with matched controls (GPA: 72.0 vs 35.7 cases/1000 person years; controls: 19.8 vs 17.0 cases/1000 person years) [82]. European vasculitis society (EUVAS) data has demonstrated that over a median 5.2 years after diagnosis, the mortality rate of ANCA-AV patients is 2,6 times higher than the general population ($p<0,0001$), with survival rates at 2-5 years after diagnosis 85 % and 78 %, respectively [3].

<u>Risk factors for mortality within the first year</u>

Mortality risk is increased with MPA compared to GPA, often due to renal involvement and the increasing age of MPA patients [25]. For ANCA-AV patients with renal involvement, the high risk of mortality and of progression to long-term renal replacement therapy (RRT) has not improved in the last 30 years [83], and the risk of frequent renal relapse has also remained constant [62].

A population-based study by Tan et al. (2018), demonstrated that patients with GPA (following age, sex, and entry time-adjustment) have a 3-fold higher risk of death than those without ANCA-AV [84]. An investigation of a dataset including 715 recently diagnosed ANCA-AV patients enrolled in five clinical trials showed that 5-year and 10-year survival rates were 80.9% (95% CI 77.6-84.3) and 67.8% (95% CI 62.4-73.7) respectively, with patients with renal involvement identified as being at particular risk [58]. In this cluster analysis of 673 ANCA-AV patients the risk of death was significantly higher in ANCA-AV patients with renal involvement (HR 2.4 in wide-extent extra-renal disease, $p=0.05$; HR 3.31 in low-extent extra-renal disease $p=0.005$), particularly if PR3-ANCA were present (HR 5.87, $p < 0.0005$) [58]. Similarly, in a study of 273 ANCA-AV patients, survival rates were shown to be higher among ANCA-AV patients without renal involvement than those with renal issues (HR 0.55; 95% CI 0.33-0.92; $p=0.02$) [85].

In addition, the MPO antibody subtype is associated with worse survival than PR3 subtype, (5-year survival 87% PR3 vs 68% MPO) [3]. In a 2019 study by Wallace et al. a standardised mortality rate of

2.3-fold higher for cardiovascular mortality was reported in ANCA-AV patients, with a significant association of MPO-ANCA-AV with cardiovascular death, while a non-significantly increased mortality rate was reported for PR3-ANCA positive disease. Following adjustment for sex, age and baseline creatinine, cases with MPO-ANCA vasculitis maintained a significantly higher risk of fatal cardiovascular events (p=0.03) [86].

Comorbidities

Comorbidities present at diagnosis are a significant predictor for early mortality (HR: 1.7 95% CI: 1.2-2.5; p=0.005), even after adjusting for age, BVAS, serum albumin, ANCA type and haemodialysis dependency on admission (p=0.047) [87]. The most significant factor in longer term risk of mortality (i.e. after the first year of disease) is cardiovascular disease (CVD), followed by malignancy, and infection [3, 76, 86]. GPA and MPA patients are at high risk of vascular disease, which contributes to the elevated long-term mortality risk [76]. Incidence of both CVD and ischaemic stroke is four times higher in ANCA-AV patients compared to the general population [76].

Amongst the EUVAS cohort, after the first year of diagnosis, cardiovascular events (26%), malignancy (22%), and infection (20%) were the leading causes of death with only 8% of patients dying of active vasculitis [3], and it was estimated that CVD mortality rate ratio in GPA and MPA patients in the EUVAS cohort was greater than three-fold compared to the general population (age-standardised mortality rate ratio: 3.68) [79]. Tan et al. (2018) determined that GPA patients, following age, sex, and entry time-adjustment, had an approximate two-fold increased CVD mortality risk (HR 2.41, 95% CI 1.35 -4.29) [84].

In addition, advanced age, higher disease activity, and severely impaired kidney function have been identified as negative prognostic factors for patient survival [3, 66, 87, 88]. Organ damage [88], and heart failure [89] are among the factors associated with poor prognosis. Multivariable analysis of EUVAS data demonstrated that an estimated glomerular filtration rate <15 ml/min, advancing age, higher BVAS, lower haemoglobin and higher white cell count were significant negative prognostic factors for patients' survival, with age and CKD stage shown to have the most significant impact [3, 66,87,88].

5.1.3 Medical condition – Quality of Life of ANCA-AV patients

Summery:

- QoL is already significantly impaired (vs. population norms) at the time of diagnosis, both physically (OR 7.0, 95% CI, 4.4–11.1) and mentally (OR 2.5, 95% CI, 1.7–3.6)[90, 91]
- Fatigue is a major issue for ANCA-AV patients, with up to 56% developing severe fatigue [56]
- 25% of ANCA-AV patients attribute fatigue to poor physical QoL and 47% attribute fatigue to poor mental QoL [91]
- Up to 40% ANCA-AV patients have work disability, 50% feel their disease has hindered their careers and 43% suggest the disease has led to a salary reduction [92]
- In ANCA-AV fatigue is independently associated with loss of employment (OR 7.1 95%; CI 1.5-33.1) [93]

5.1.2.3.1 Overview

ANCA-AV is a debilitating disease that substantially impairs patients' physical and emotional well-being, reducing their quality of life (QoL) compared to population norms at diagnosis both physically (OR 7.0, 95% CI, 4.4–11.1) and mentally (OR 2.5, 95% CI, 1.7–3.6) [91]. The chronic relapsing and remitting nature of ANCA-AV, and requirement for prolonged treatment, significantly impacts patients' physical and emotional well-being, reducing their QoL [91, 92, 94-100]. ANCA-AV impacts all aspects of patient's QoL, with patients reporting significantly worse QoL than population controls [92, 96]. Benarous et al. assessed QoL using the SF-36 (36 item Short Form Survey) in a French cohort of 189 ANCA-AV patients, and reported altered physical health in 19% of patients, and altered mental health in 14% of the study population [92]. In another study, sleep impairment, assessed using the Pittsburg Sleep Quality Index, was significantly worse in ANCA-AV patients (p=<0.001). Anxiety and depression, assessed using the Hospital Anxiety and Depression Scale, was present in significantly more patients with AAV than healthy controls (anxiety, p=0.001 and depression, p=0.003) [101].

5.1.2.3.2 Physical and mental health dimensions

Poor scores for the physical health QoL domains, as measured using the SF-36, are associated with BVAS >0, raised C-reactive protein (CRP) levels, anaemia, and nervous system involvement [91] as well as higher prednisolone dose, and higher VDI score [96].

Poor scores for mental health are associated with hypalbuminaemia, raised CRP, and exposure to mycophenolate mofetil (MMF) [91]. In addition, bio-psychosocial factors, i.e. unemployment, anxiety, depression, pain, sleep disturbance, and fatigue, have all shown strong association with SF-36 scores for both physical and mental health, with ANCA-AV patients experiencing an increase in general and physical fatigue, comparable to that of patients with other chronic diseases [91].

5.1.2.3.3 Fatigue

Fatigue is a major issue for ANCA-AV patients, with up to 58% developing severe fatigue [56]. EUVAS data shows that whilst fatigue improves after induction remission, it still remains higher than that measured in controls (p<0.001) [102]. Group-based trajectory modelling (GBTM) also identified varying trajectories of fatigue following treatment initiation: low fatigue stable (n=23); moderate baseline fatigue improver (n=29); high baseline fatigue improver (n=61); and stable baseline high fatigue (n=37) [102]. A 2011 study found that 25% of ANCA-AV patients attribute fatigue to poor physical QoL and 47% attribute fatigue to poor mental QoL [90].

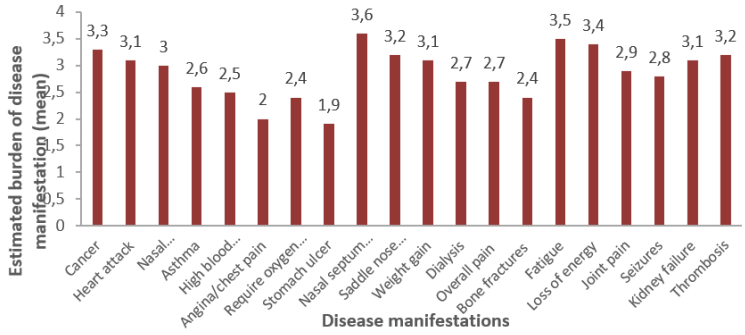
Fatigue in ANCA-AV is significantly associated with numerous biopsychosocial and clinical factors, such as an altered perception of exertion and reduced cardiovascular capacity [101], with the strongest independent associations being sleep disturbance (OR: 5.3; 95% CI: 2.7–10.5) and pain (OR: 3.8; 95% CI: 2.0–7.3) [103].

5.1.2.3.4 Patient perception of disease

In a study by Herlyn et al., 264 ANCA-AV patients across three countries, the US, Germany, and the UK, were assessed for their perspective of the burden of disease using a validated questionnaire. Patients ranked the severity of their symptoms on a scale from zero to five, with five 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 (**Fejl!**

Henvisningskilde ikke fundet.) [6]. Ninety-five percent (95%) 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 (figure 6) 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 [6].

Figure 6 Mean estimates of burden (range 1-5) of specific ANCA-AV disease manifestations. (Adopted from [6])



5.1.2.4. Economic burden of ANCA-AV

Summery

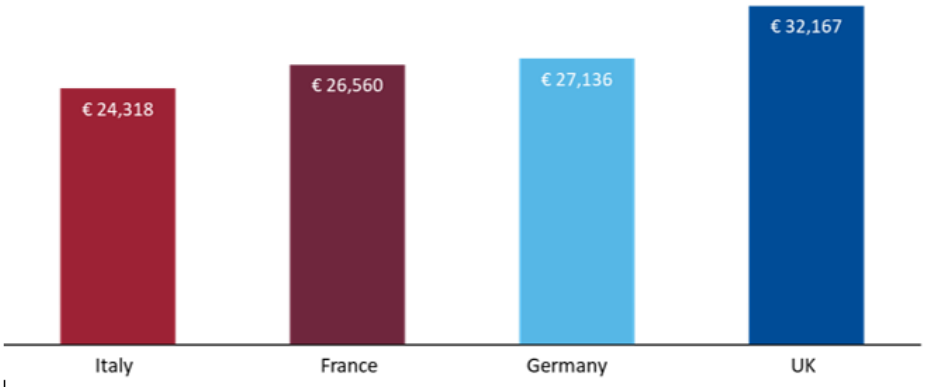
- In Europe, the average annual cost per GPA/MPA patient ranges from €24,318 in Italy to €32,167 in UK. [160] [163, 164]
- In-patient costs of treating ANCA-AV represent 61%, 60% and 55% of annual total cost-per-patient in France, Italy and the UK, respectively. [39, 163, 164]
- ANCA-AV is associated with 9-11 days of hospitalisation per year in the US for primary AAV (GPA and MPA) diagnoses, and with 6-13 days of hospitalisation per year in Germany, depending upon the existence of comorbidities. [170, 169]
- Infection is an important cause of hospitalisation of ANCA-AV patients. [171, 176, 162]
- Up to 40% ANCA-AV patients have work disability, 50% feel their disease has hindered their careers and 43% suggest the disease has led to a salary reduction. [92]

5.1.2.4.1 Overview – economic burden of ANCA-AV

ANCA-AV is a long-term condition with the potential for organ damage and high morbidity. Therefore, it is associated with considerable health costs. Due to the rarity of ANCA-AV and its variable clinical picture, few data are available in the literature on the health economic burden resulting from the direct and indirect costs of managing this family of diseases.

In Europe, the estimated average annual cost per GPA/MPA patient is set out in table 7.

Figure 7 The average annual cost of treatment for GPA/MPA patients in four European countries [163]



Regional analysis (Friuli Venezia Giulia (FVG), Italy). The analysis in France, Germany and the UK were national analyses.

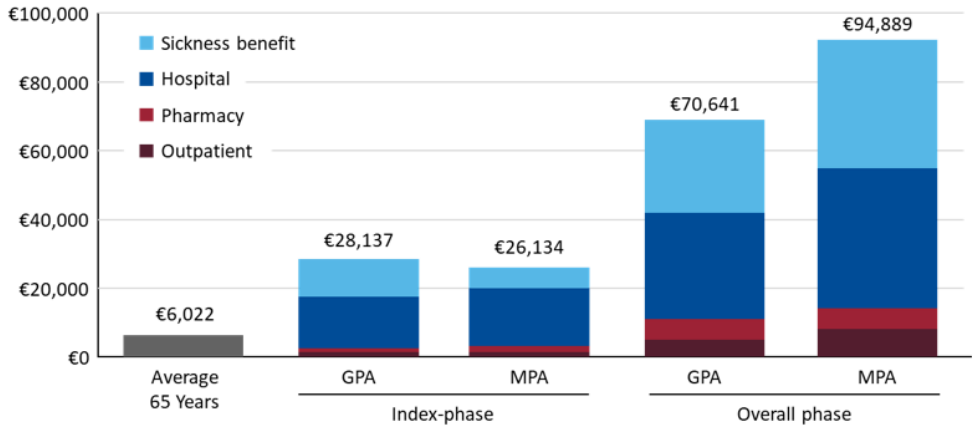
In the United States, the average annual cost per GPA patient is estimated to range from $18,478 to $32,005 [165, 166].

The highest costs are associated with the remission induction period and development of ESRD. Hospitalisation due to disease-related complications, particularly development of ESRD and the associated need for dialysis or transplantation; is a significant economic burden, while drug costs are also important [170].

A recent longitudinal German study of an insurance dataset (inGEF) showed that the treatment costs for ANCA-AV patients are an economic burden for the German healthcare system. These were found to be significantly higher than those for the general population at the age of 65 [170].

Cumulative costs for induction and three years of follow-up, in Germany, of €70,641 for GPA and €94,889 for MPA patients respectively are shown in **Fejl! Henvisningskilde ikke fundet.**.

Figure 8 Annual costs of of GPA and MPA patients to the German healthcare system (induction and total phases) in addition to those for an average 65-year-old (translated from [170]



A retrospective analysis of data from the UK Clinical Practice Research Datalink (CPRD) - Hospital Episode Statistics (HES) linked database provides insight into the extent and cause of additional costs for ANCA-AV patients. The total inpatient costs in the year of diagnosis are double those observed in subsequent years: £12,995 in year 1 versus £6,896 in the year following diagnosis. A decrease from £5,966 to £5,057 was seen over the subsequent four years. Total outpatient (range £1,650 -

£3,123) and general practitioner (GP) visit (range £2,377 - £3,632) costs were slightly higher and lower, respectively, in the first 5 years than in subsequent years. Mean total GP prescription costs were considerably lower in the year of diagnosis (£8,335) than in the subsequent 14 years (range £15,043 - £25,575) in the overall population. This difference in prescribing costs offsets the increase in inpatient costs in the year of diagnosis, leading to total mean healthcare costs in the overall ANCA-AV population remaining relatively stable over the first 15 years (range £23,274 - £36,988), with variation in mean cost per year after the first 15 years resulting from low patient numbers [167].

Excluding the first year, the mean cost of prescribing GCs by GPs decreased over time: £1,966, £1,096, and £830 at 1-, 5- and 10-years post diagnosis respectively. Similarly, the mean cost of GP prescribed non-GC drugs decreased over time [167].

5.1.2.4.2 Hospitalisation a considerable burden of ANCA-AV

ANCA-AV is associated with 9-11 days of hospitalisation per year in the US for primary ANCA-AV (GPA and MPA) diagnoses [169], and with 6-13 days of hospitalisation per year in Germany, depending upon the existence of comorbidities [170].

In-patient costs associated with ANCA-AV have been shown to represent 61%, 60% and 55% of annual total cost per patient in France [164], Italy [39], and the UK [163], respectively. In Canada, these prove to be 76% of total cost [168]. In the US, overall annual costs for MPA patients were almost a third higher than for GPA patients ($145,766 vs. $107,529 respectively), with longer hospital stays for MPA patients compared with GPA patients (11.3 and 9.2 days, respectively) contributing to the higher costs [169].

Hospitalisation may also be required for treatment-related complications such as severe infection and due to relapses. Hospitalization costs in the longitudinal German study of the insurance dataset (inGEF) were shown to be the main contributor: costs for GPA and MPA during induction over the first 6 months of treatment were €28,137 and €26,137 respectively [171].

The observation of higher average costs for MPA versus GPA patients can be attributed in part to higher hospitalisation rates in the former group.

In a 2015 study of US GPA patients, Raimundo et al. reported 25% had ≥1 hospitalisation in the post-index period, of which 22% were GPA-related [172]. On average, 58.7% of all-cause costs per GPA patient was associated with GPA, with a mean total GPA-related annual cost of $24,319, in comparison to a total all-cause annual cost of $41,400 [172]. In addition, receiving an MPA diagnosis was associated with a nearly 2-fold increase in all-cause healthcare resource utilisation and costs ($30,166 vs $56,642), primarily attributable to an increase in costs of inpatient admissions ($15,344 vs $34,776) [173].

Reinhold-Keller et al. showed that more than half of GPA patients were hospitalised in the year preceding their study [174], with Wallace et al. estimating that the hospitalisation rate for ANCA-AV in the US between 1993 to 2011 increased from 1.9/100,000 persons to 4.5/100,000 persons [175].

In the largest reported GPA related cohort to date (n=5,566), hospitalisation rates for working-age adult patients were reported as 463 hospitalisations per 1000 person-years [176]. Between 2006 and 2014, GPA patients underwent 5,522 hospitalisation events in the US, with a median stay of 5 days [176]

A study of a German dataset demonstrated that a third of patients develop a serious infection requiring hospital treatment during the induction period of ANCA-AV therapy [171], with 42% patients at risk of infection over a 4-year period after diagnosis of GPA or MPA [162].

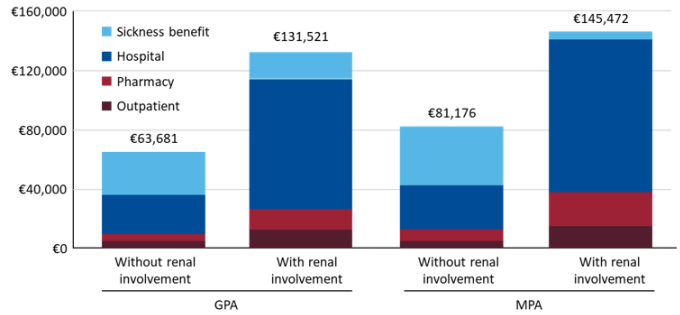
An increase in the hospitalisation rate among those with a secondary discharge diagnosis of ANCA-AV (1.4/100,000 persons to 3.9/100,000 persons) was most commonly due to infection [175].

5.1.2.4.3 ESRD a driver of ANCA-AV treatment costs

Severe kidney disease is a significant factor for increased healthcare costs, with total annual costs for patients without renal involvement at €63,681 and €81,176 for GPA and MPA patients respectively, compared with €131,521 and €145,472 for patients with kidney disease.

The long-term treatment of MPA has been shown to be more expensive both with and without severe kidney disease than the treatment of GPA; (Figure 9) [164].

Figure 9 Annual costs for GPA and MPA patients with and without renal involvement, (translated from [164]



5.1.2.4.4 Major relapse in ANCA-AV increase healthcare resource use

Kong et al. 2018 assessed two groups of US patients with GPA and MPA and reported total GPA related costs over 12-months were $88,631 in patients who experienced a relapse, versus $32,005 in relapse-free patients with a similar trend seen for MPA patients ($61,044 for MPA patients who did not experience a relapse, vs. $111,691 for those who relapsed) [165].

A 2018 study of US GPA patients found that patients re-admitted to hospital within 30 days had direct costs approximately $1,000 higher than patients who did not need to be re-admitted ($19,538 vs $18,478) [177].

Renal relapses were the main drivers of relapse-related costs, with total associated costs substantially higher than those of other types of relapse; inpatient admissions and outpatient procedures, including renal dialysis, were the largest contributors to the cost of relapse management [165]. Over one-third of GPA patients , and 23% of MPA patients, with renal relapse had ≥1 claim for dialysis in the 4-month follow-up period [165].

For GPA and MPA patients with renal relapses, dialysis accounted for 36% and 18% of all-cause total costs, respectively. Among patients requiring dialysis, the average cost of dialysis alone was $51,734 for GPA patients and $32,143 for MPA patients [165].

5.1.2.4.5 Work Disability in ANCA-AV patients

In ANCA-AV fatigue is independently associated with loss of employment (OR 7.1 95%; CI 1.5-33.1) [93]. A 2017 study by Benarous et al. of 94 working-age (<60 years) ANCA-AV patients in France, found that only 56% worked. Nearly a quarter (23%) of this group felt that their disease qualitatively limited the nature of their work, while 43% felt it limited the quantity of work they could do. Half of the workers felt that ANCA-AV had hindered their careers, and 43% that it had led to a salary reduction [92].

Work disability, defined by receiving disability living allowance or disability pension, or recognition as disabled worker status, is also very common in ANCA-AV patients. 26% of ANCA-AV patients in the EUVAS

cohort have been reported to have work disability [98], and 40% of patients reported work disability in the EXPOVAS study [92].

In addition, over 25% caregivers reported having lost income due to caregiving for an ANCA-AV patient. Caregivers reported spending a median of 19 weekly hours on various caregiving tasks, including a median 17 weekly hours on household activities [104].

5.1.4 Patient population

ANCA-AV affects fewer than 5 out of every 10,000 people, meeting common definitions of a rare disease, for example that of the European Commission which designates a rare disease as one that affects no more than 1 person in 2,000 [13, 14]. As such, assessing the epidemiology of ANCA-AV can be challenging, and current data available are relatively limited. The incidence and prevalence of MPA and GPA from global epidemiological studies are summarised in Table 3.

Table 3 Epidemiology of MPA and GPA from studies conducted globally

Geographic area	Period	MPA		GPA		Reference
		Incidence	Prevalence	Incidence	Prevalence	
		per 1,000,000				
Finland	1996–2000	–	–	9.3	–	[21]
Germany	1998-2014	2.4	28	7.9	98	[19] [20, 22]
Greece	1995–2003	10.2	–	6.6	–	[23]
Italy	1995–2009	–	–	2.4	34.3	[24]
Norway	1999-2013	6.5	58.2	15.6	261	[7]
Spain	1994–2010	3.4	23.8	2.1	15.8	[17]
Sweden	1997–2006	10.1	–	9.8	160	[20, 25]
UK	1988–2014	5.9-13.4	63.1	8.2-14.3	145.9	[17, 26]
USA	1996–2015	16*	184*	13*	218*	[16]

Abbreviations: GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis
*Reported as incidence per 100,000
Images: Icons made by Roundicons from Flaticon.com

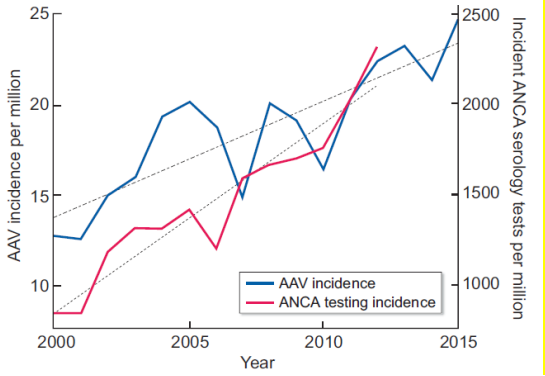
Incidence

Overall, the incidence of ANCA-AV has increased since the 1980s but remained stable in the last 20 years, likely due to an increase in physician awareness and the introduction of ANCA testing [9,185].

Important geographic differences have been observed among subsets of ANCA-AV, with a higher incidence of GPA in Northern Europe and Australia, and a higher incidence of MPA in Asia (especially Japan) than in Europe [15], se table 3 Although information on geographical variation in GPA is scarce, prevalence studies suggest that GPA is less common in the US (26 per million) as opposed to Europe (40–60 per million).

In the Danish retrospective cohort study Nelveg-Kristensen et al grouped the identified 1.631 patients ANCA-AV according to year of inclusion (Period 1: 2000-04, Period 2: 2005-09, Period 3: 2010-15). The head-to-head comparison of the three consecutive time period showed an increasing incidence Period 1: 15,1, Period 2: 18,5, Period 3: 21,4 patients/million/year. The study showed increasing incident ANCA testing was associated with increasing incident AAV diagnoses in the test period [185] and **Fejl! Henvisningskilde ikke fundet.**0.

Figure 10 Incident AAV and ANCA testing (North Region) in Denmark during 2000-15



Y axis to the left denotes incidence of the incident AAV diagnoses. **Y-axis to the right** denotes incident ANCA serology test.

A data extract from LPR3 including 2019-21 performed for Vifor Pharma Nordiska shows an incidence for GPA and/or MPA on 34/million in 2020 and 29/millions in 2021. The documentation for the data-extract is descripted in detail in Appendix K, "Documentation for a data-extract on incidence and prevalence of ANCA-associated vasculitis in Denmark".

The incidence seems higher in the data-extract from 2020 and 2021 than the extracts from 2000 to 2015. There may be several reasons for this difference one could be differences in the identification strategy: Nelveg-Kristensen included all patients diagnosed with at least two consecutive hospital encounter registered LPR2 2000-2015, while in the data-extract from LPR3 (2019-2021) was patients with one discharge diagnoses included in the dataset.

Dansk Reumatologisk Selskab (DRS), refers to an incidence of GPA 8-11/million/year and of MPA 2-6/million/year. Approximately 90 % of GPA patients are ANCA-positive. The main part of the antineutrophil antibodies exhibit reactivity against proteinase-3 (PR3-ANCA) and a smaller number against myeloperoxidase (MPO-ANCA) [186].

In the data-extract from LPR3 the incidence for GPA was 29/million/year and 23/million/year in 2020 and 2021, respectively. The incidence for MPA was 5/million in 2020 and 4/million in 2021, 4, Appendix K.

Prevalence

The prevalence of ANCA-AV has progressively increased over the last 25 years due to improved diagnosis, survival and the overall ageing of the population increasing risk of disease initiation [7]. The global prevalence is between 46-184 cases per million [1]. The highest prevalence of MPA was observed in the USA, at 184 per million [15, 16], with highest prevalence of GPA in Norway, at 261 per million [7]. The lowest prevalence was reported in Spain (23.8 per million for MPA and 15.8 per million for GPA [17], with the UK prevalence of MPA at 63.1 per million and GPA at 145.9 per million [18], and lower figures of 28 per million for MPA and 98 per million for GPA seen in Germany [19] (Table 3). The prevalence in Denmark of MPA is almost 30/million and GPA approximately 200/ million in 2020-2021, (Table 4).

Table 4 Summery from literature of Danish Incidence and prevalence per 1.000.000 persons/year

	<2014*2	2010-2015*3	2016	2017	2018	2019*1	2020*1	2021*1
Number Danish Population, 1, January each year*4	5.627.235	5.659.715	5.707.251	5.748.769	5.781.190	5.806.081	5.822.763	5.840.045
Incidens in Denmark								
DM313 Granulomatosis with polyangiitis (GPA)	(8-11)					na	29	23
DM317 Mikroskopisk polyangiitis (MPA)	(2-6)					na	5	4
DM313 and/or DM317		21,4				na	34	29
Prevalens in Denmark								
DM313 Granulomatosis with polyangiitis (GPA)						171	194	210
DM317 Mikroskopisk polyangiitis (MPA)						20	24	28
DM313 and/or DM317						191	219	240
*1 Data-extract LPR3 2019-2021								
*2 Dansk Rheumatologisk Selskab 2014								
*3 Nelveg et all 2022. Incidens/1.000.000 Average 21,4; stigende fra 2010 ca 17 til ca 24,4 i 2015								
*4 Statistic Danmark, www.statistikbanken.dk/FOLK1A								

The incidence in Denmark of GPA and/or MPA are increased from an incidence 21,4/million/year in 2015 to approximately 30/million/year in 2020-21, it looks like the increase mainly is driven by the incidence of GPA. The shown increasing incident ANCA testing was associated with increasing incident AAV diagnoses in the test period [185].

Extracts from registers for calculating incidence and prevalence are highly dependent on the quality and practice of registrations (input) to the registries, which may change over time. The extraction method also has a great influence on the extracted data.

The estimated incident patient-populations (2022-2027) are based on the data-extract from LPR3 (2019-2021). The estimated incidence in a year is based on the average of the available past years.

The Population projection (average 23.297 persons/year) are included in the calculation of the incidence and prevalence estimates for the coming six year (2022-2027) [187].

Table 5 Incidence in Denmark (number of patients) in the past 3 years and estimated number of patients the next five years

	2019*1	2020*1	2021*1	2022*2	2023*3	2024*3	2025*3	2026*3	2027*3
Number Danish Population, 1. January each year*2,3	5.806.081	5.822.763	5.840.045	5.857.847	5.881.144	5.904.441	5.927.738	5.951.035	5.974.332
Befolknings increace in procent*2				1,003048	1,003977	1,003961	1,003946	1,00393	1,003915
Incidens in Denmark									
DM313 Granulomatosis with polyangiitis (GPA)	na	168	136	152	153	153	153	153	153
DM317 Mikroskopisk polyangiitis (MPA)	na	28	26	27	27	27	27	27	27
DM313 and/or DM317*4	na	200	167	184	184	185	185	185	185
*1 Data-extract LPR3 2019-2021. The method to extract the data is described in more details in Appendix K.									
*2 Statistic Danmark, www.statistikbanken.dk/FOLK1A									
*3 Statistic Denmark, www.statistikbanken.dk Befolkningsfremskrivning for hele landet (FRDK 121) in average 23.297/year									
*4 due to discretion, all rows do not add up correctly									

The estimated prevalent patient-populations (2022-2027) are based on the data-extract from LPR3 (2019-2021). Example on the prevalence calculation year 2022: the number of prevalent patients from the year before (2021) minus number of deaths during the year before (2021) plus number of incident patients the year before (2021), e.g.: 1.228-44+136=1.320, cf. Table 6.

The Population projection has been included in the estimate of the incidence and prevalence the coming six year (2022-2027) and it is increasing with average 23.297 persons/year [187].

The proportion of patients who die during the year is assumed (approximately 3,58 %) to be constant.

Table 6 Prevalence in Denmark (number of patients) in the past 3 years and estimated number of patients the next five years.

	2019*2	2020*2	2021*2	2022*2	2023*3	2024*3	2025*3	2026*3	2027*3
Population at the first day of the year all Denmark*3, 4	5.806.081	5.822.763	5.840.045	5.857.858	5.881.129	5.904.400	5.927.671	5.950.942	5.974.213
Population growth					1,0039726	1,0039569	1,0039413	1,0039258	1,0039105
DM313 Granulomatosis with polyangiitis (GPA)									
Incidens		168	136	152	153	153	153	153	154
Dead	30	38	44	47	51	55	58	62	65
Prevalens	992	1.130	1.228	1.320	1.425	1.527	1.625	1.720	1.811
% døde af prævalens	3,02	3,36	3,58	3,58	3,58	3,58	3,58	3,58	3,58
DM317 Mikroskopisk polyangiitis (MPA)									
Incidens		28	26	27	27	27	27	27	27
Dead*1	<5	<5	<5	3	3	4	4	4	5
Prevalens	116	140	162	186	210	234	257	280	303
% døde af prævalens*1	2,16	1,79	1,54	1,54	1,54	1,54	1,54	1,54	1,54
DM313 and/or DM317 *5									
Incidens		200	167	184	184	185	185	185	186
Dead		41	41	50	54	58	62	66	70
Prevalens	1.109	1.275	1.400	1.527	1.660	1.791	1.917	2.039	2.158
% døde af prævalens		3,18	2,89	3,29	3,27	3,26	3,24	3,23	3,22
*1 LPR3 data extract: number of observations<5 is discretionated. To the calculation of proportion of deaths during the year, the number 2,5 is used									
*2 Data-extract LPR3 2019-2021. The method to extract the data is described in more details in Appendix K.									
*3 Statistic Danmark, www.statistikbanken.dk/FOLK1A									
*4 Statistic Denmark, www.statistikbanken.dk Befolkningsfremskrivning for hele landet (FRDK 121) in average 23.297/year									
*5 due to discretion, all rows do not add up correctly									

5.1.4.1 Patient population relevant for this application

Tavneos, in combination with a rituximab or cyclophosphamide regimen, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) [154].

Tavneos is documented to treat newly diagnosed or relapsed patients with GPA or MPA. The patient population consist of [154]:

- Patients newly diagnosed with GPA (incidence patients)
- Patients newly diagnosed with MPA (incidence patients)
- 50 % of the prevalent patients are expected to have one or more relaps during the first 5 years [188]. This is applied to both diagnoses with 20 % per year:
  - Patients diagnosed with GPA (prevalence patients)
  - Patients diagnosed with MPA (prevalence patients)

Assumptions:

1. Based on the clinical program and the approved SPC, approximately 30 % of the incident patients with GPA and MPA are assumed not eligible for treatment with Tavneos (pediatric patients, mild disease, refractory, very severe disease) and therefore excluded from the relevant patient population.
2. The first year expected to be 2023 and the market uptake the first year 2023 is expected to be successive over the full year, this is applied to year with a factor 0,5416.

3. 50 % of the prevalent patients are expected to have one or more relapse during the first 5 years after the first diagnoses. DRS Guidelines 2014 [188]. It is assumed that the number of relaps is evenly distributed over time ~20%/year among the 50 % of the prevalent patients or approximately 10 % of the patients are expected to have at least one relaps during a year [188].
4. The medical treatment (Intervention ava and comparator GC as well as RTX and CYC) of the two indications GPA and MPA are similar, applied to the calculations of the patientpopulation suitable for treatment with Tavneos/avacopan are based on total number of prevalent or incident cases with GPA and/or MPA.

The estimated number of incidence patients eligible for treatment with Tavneos are shown in Table 7. Number of incidence patients from Table 5 is reduced with 30 % due to assumption 1 and the first year 2023 is adjusted in accordance with assumption 2.

Likewise, the estimated number of prevalent patients with relaps eligible for treatment with Tavneos are shown in Table 7. Number of prevalent patients from Table 6 is reduced with 30 % due to assumption 1 and with 90 % due to assumption 3. The first year 2023 is adjusted in accordance with assumption 2.

Table 7 Estimated number of patients eligble for teatment with Tavneos

	2022	2023	2024	2025	2026	2027
Number of incident patients MPA*1	27	27	27	27	27	27
Number of incident patients GPA*1	152	153	153	153	153	153
Total number of incident patients MPA and or GPA*2	179	180	180	180	180	180
Calculated number of patients eligblible for Avacopan*3	0	68	126	126	126	127
Calculated number of patients eligblible for GC*4	179	112	54	54	54	53
Number of prevalent patients MPA*1	186	210	234	257	280	303
Number of prevalent patients GPA*1	1.320	1.425	1.527	1.625	1.720	1.811
Total number of prevalent patients MPA and or GPA*2	1.506	1.635	1.761	1.882	2.000	2.114
Calculated number of prevalent patients with relaps		164	176	188	200	211
Calculated number of patients eligblible for Avacopan*3	0	62	123	132	140	148
Calculated number of patients eligblible for GC*4		102	53	56	60	63
*1 From table 6						
*2 Calculated						
*3 Calculated based on the assumptions mention above the table						
*4 assuption patients not eligblible for AVA will be treated with GC						

GPA diagnosis and PR3-ANCA positive are risk factors for relaps [188].

In the Danish cohort-study including 1.631 patients with incident AAV were about 52 % male, mean (SD) age at the time of diagnosis was 60,2 (16,7) years [185]. The predictors of death were higher age, cardiovascular disease (CVD) and renal involvement [185].

5.2 Current treatment options and choice of comparator

Summery

- While the majority of patients achieve remission with current SOC, they remain at high risk of relapse and require long-term GC treatment
- Up to 64% of patients with ANCA-AV achieve remission (BVAS = 0, with 4 weeks GC withdrawal) at 6 months with contemporary regimens [69]
- Up to 48% achieve sustained remission at 12 months with contemporary regimens [69]
- Nearly 50% of patients require long-term GC use and receive GCs for nearly 5 years after initiation of RTX to sustain remission [110]
- Relapses lead to more complications including long-term organ and tissue damage in ANCA-AV [5]
- Renal relapse is defined as a >30% increase in serum creatinine since the previous measurement and/or new haematuria or proteinuria, as indicated on the BVAS [63]
- More than one renal relapse is an independent risk factor for end-stage renal disease (ESRD), with a sub hazard ratio of 9, 95% 4–9, p<0.001) [63]
- ANCA-AV patients have a 2.6 times higher death rate vs. general population over 5.2 years (p<0.0001) [3]
- Main causes of death include infection, active vasculitis, cardiovascular events and malignancy [3]
- ESRD (eGFR < 15 ml/min/1.73m^2) increases the risk of mortality by >2-fold in ANCA-AV patients [125]

5.2.1 Overview of the European treatment guidelines

ANCA-AV is a long-term health condition that relapses and remits [1]. Controlling ANCA-AV 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 [41].

Guidelines, or recommendations/considerations, for the treatment of ANCA-AV have been produced by several bodies both at a European level and at a Danish level.

The EULAR/ERA-EDTA recommendations setting bodies include collaborations between the European League Against Rheumatism (EULAR) and European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) [1].

The Danish treatment guideline for Antineutrofil cytoplasmisk antistof-associeret vaskulitis (AAV) is developed by DanskReumatology, Dansk Reumatologisk Selskab (DRS) and Danske Reumatologers og Fysiurgers Organisation (DRFO) [188].

The treatment of ANCA-associated glomerulonephritis is described in the Danish Society of Nefrology (DNS)'s Guideline for treatment of Glomerulonephritis (Retningslinjer for behandling af glomerulonephritis) [189].

All the guidelines broadly include four different disease stages: 1) Remission induction, 2) Remission maintenance, 3) Disease relapse, 4) Refractory disease.

Table 8 Guidelines for the treatment of ANCA-AV

Guideline citation and year	Body producing guideline	Remission induction	Remission maintenance	Relapse	Refractory patients
2016 [1]	EULAR/ ERA_EDTA	Organ-threatening: - GCs plus CYC or RTX - PLEX should be considered for patients with ANCA-AV and a serum creatine level of >500 mmol/L (5,7 mg/dL) Non-organ threatening: - GCs plus MTX or MMF	- Low-dose GCs and either AZA, RTX, MTX or MMF. - Continued for at least 24 months following induction of sustained remission	Organ-threatening: - GCs plus CYC or RTX (as per new disease) -PLEX should be considered for patients with ANCA-AV and a serum creatine level of >500 mmol/L (5,7 mg/dL) Non-severe: -Temporary increase in GC dose	- Switch from CYC to RTX or from RTX to CYC - Patients should be managed in close conjunction with, or referred to, an expert centers for further evaluation and potential enrolment in clinical trials
2015 [188]	Dansk Reumatology/ DRS/DRFO	Organ-threatening: - Prednisolon plus CYC or RTX - PLEX should be considered for patients with ANCA-AV and severe renal involvement and/or life-threatening lung manifestations Non-organ threatening: - Prednisolon p.o. plus MTX p.o.	- Induction therapy MTX p.o. and prednisolon p.o. - Relaps preventing treatment Azathioprin p.o. or MTX p.o. - consider RTX - GC tapering should be considered after 2 years without recidiv	- RTX is more effective than CYC (RAVE-study) [109}	
2020 [106]	KDIGO	GCs plus CYC or RTX Organ-threatening: - GCs plus CYC or CYC plus RTX considered in patients with reduced or rapidly declining GFR (SCr>354 µmol/l) - PLEX considered for patients with a GFR ≥ 500 µmol/l and for those receiving dialysis Non-organ-threatening: - MMF considered an alternative to CYC	Low-dose GCs plus AZA or RTX. Following CYC induction: -AZA plus low dose GCs or RTX - AZA treatment for 18 months-4 years Following RTX induction: -Maintenance immune-suppressive therapy	Reintroduced to RTX therapy	- Increase in GCs (IV or oral) - Switch from CYC to RTX or from RTX to CYC - PLEX should be considered
2020 [189]	Dansk Nefrologisk Selskab (DNS)	Remission induction treatment for patients with active renal vasculitis - Prednisolon plus CYC or RTX - CYC is preferable or rapidly declining GFR - PLEX should be considered for patients with ANCA-AV and reduced or rapidly declining GFR and/or life-threatening lung manifestations	- AZA p.o. begin immediately after CYC - Maintenance treatment should continue at least 18 months after remis sion and possible up to 4 years. - GC tapering should be considered after 6-12 months without disease activity	- Follow the principle for induction treatment - RTX was non-inferior to CYC or more effective than CYC (RAVE-study) [109}	- If resistant to CYC switch to RTX and the opposite way

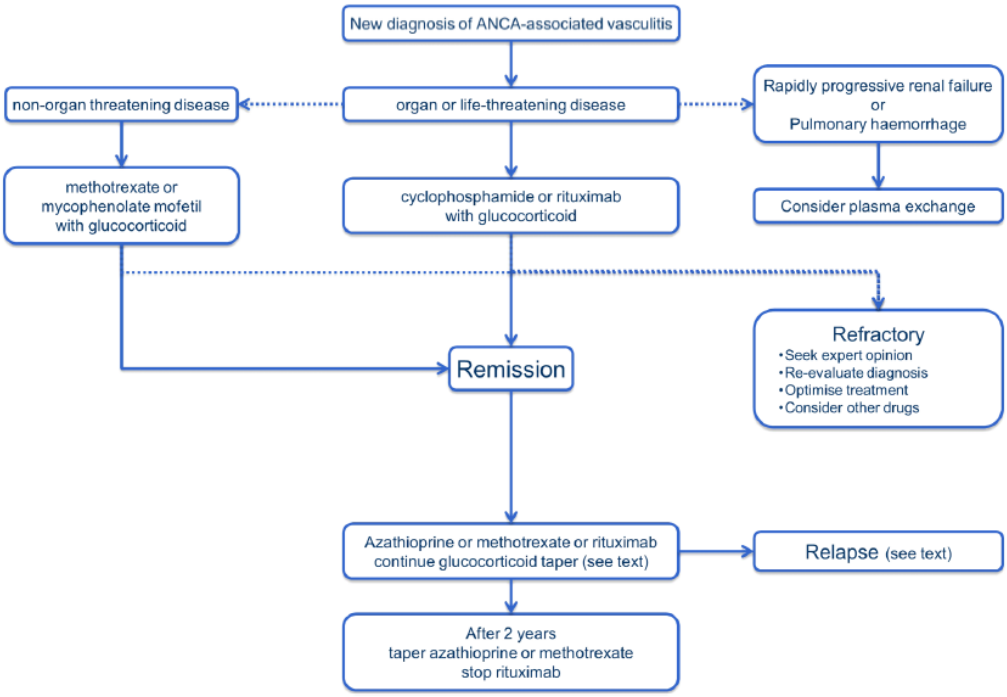
Abbreviations: ANCA-AV, antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis; AZA, azathioprine; BVAS, Birmingham vasculitis activity score; eGFR, estimated glomerular filtration rate; EGPA, eosinophilic granulomatosis with polyangiitis; GCs, glucocorticoids; GPA, granulomatosis with polyangiitis; IV, intravascular; MMF, Mycophenolate mofetil; MPA, microscopic polyangiitis; MPO, myeloperoxidase; MTX, methotrexate; NR, not reported; PR3, leukocyte proteinase 3; PLEX, Plasma Exchange; UACR, urine albumin-to-creatinine ratio; VDI, vasculitis damage index.

5.2.1.1 Current treatment options in Denmark

According to the Danish guidelines, patients with suspected AAV must be referred for assessment in a highly specialized setting. Assessment and treatment of AAV usually presupposes a multidisciplinary collaboration between different highly specialized medical and surgical departments, the diagnosis should be supported by a biopsy from affected organ [188,189].

The Danish standard treatment is in line with the EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis based on the EULAR and European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) recommendations is presented in **Fejl! Henvisningskilde ikke fundet.** [1].

Figure 11 Algorithm to describe the management of new antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis [1].



Dashed lines indicate alternative or supplementary action to consider.

Remission is the primary goal in ANCA-AV management. EULAR/ERA-EDTA guidelines define full remission in ANCA-AV as the absence of disease activity attributable to active disease, which has been validated using a recognized scoring tool, such as the Birmingham Vasculitis Activity Score (BVAS) [11]. BVAS is validated tool for assessment of disease activity in patients with many different forms of vasculitis used predominantly in clinical trials but the complexity of the tool may make it difficult to use in practice [108]. Remission means in practice absence of clinically recognizable active disease on the current treatment, but there is no unambiguous definition [189].

5.2.1.1.1 Induction of remission

Overview of the Literature for efficacy of Standard of Care for Remission Induction

Current standard induction therapies such as CYC-AZA or MTX/RTX, result in remission in many patients, but remission rates are still variable, and less than a third of ANCA-AV patients remain in relapse-free remission for more than a decade [69, 70].

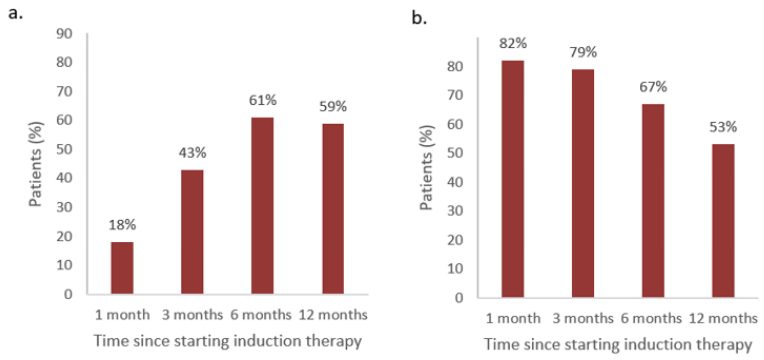
The RAVE trial evaluated the achievement of full remission (defined as BVAS/WG of 0 and no GCs at 6 months) using RTX or CYC in patients with organ/life-threatening GPA or MPA. Data at 6 months showed that in patients on RTX and CYC, 64% and 53% respectively achieved full remission induction [69, 70, 109]. The remission maintenance phase of ANCA-AV is critical for good long-term outcomes

including renal preservation, as well as preventing ANCA-AV relapse [109]. Longer term follow-up in the RAVE trial showed that only 39% and 33% of patients on CYC, and 48% and 39% of patients on RTX, were still in complete GC-free remission at 12 and 18 months respectively [69]. However, other studies have shown that nearly 50% of patients require long-term GC use and receive GCs for nearly 5 years after initiation of RTX to sustain remission [110].

A retrospective review of real-world data, involving 929 incident ANCA-AV patients treated with CYC or RTX plus GCs, found that almost 40% of patients did not achieve full remission by 6 months, and that by 12 months of treatment only 59% had shown a full-response. In addition, patients remained dependent upon adjunct GC treatment for a significant period, with more than 50% of patients still using GCs 12 months after starting induction therapy.

Despite this significant treatment burden, 6% of patients relapsed during the first 12 months of therapy and required additional treatment to regain disease remission **Fejl! Henvisningskilde ikke fundet.** [111].

Figure 12 a Patients showing full response to introduction therapy (no ANCA-AV activity and GC taper on track)
B Continued GC use following initiation of induction therapy [111]



EUVAS data, from 4 clinical trials conducted between 1995 and 2002 (CYCAZAREM, NORAM, MEPEX, CYCLOPS) and involving a total of 354 ANCA-AV patients, showed that 84.8% and 89.8% achieved remission at 3 and 6 months, respectively, with remission defined as BVAS of 0, but no restriction on GC use. At 6 months, 79.9% were in sustained remission, 10% experienced late remission, 5.1% had relapsing disease, and 5.1% had refractory disease. Disease status at 3 and 6 months following the diagnosis of ANCA-AV were predictors of the composite end point of death or renal survival (i.e. the development of ESRD). For death, late remission (HR 2.94, 95% CI 1.10-7.85; p=0.031) and relapsing disease (HR 8.21, 95% CI 2.73-24.65; p<0.001) were predictors when compared to sustained remission, with relapsing disease (HR 34.22, 95% CI 4.72–247.8; p<0.001) and refractory disease (HR 9.64, 95% CI 2.25–41.29; p=0.002) at 6 months significant predictors of ESRD [112].

Overview of the Literature for burden of SoC for Remission induction

Physicians managing ANCA-AV need to determine their treatment approach based on an assessment of disease severity, and balance achieving remission quickly but also avoiding the adverse effects from therapy [1, 44, 113, 114]. Real-world data confirm that initial remission induction therapy varies according to disease severity, although GCs are used frequently (in ≥80% patients) across all severities [114].

In a retrospective clinical audit of healthcare records from 929 incident ANCA-AV patients (GPA: 54%; MPA: 46%) in France, Germany, Italy and the UK, adverse events were highest during the first 3 months of remission induction therapy [115]. The number of patients experiencing ≥1 AEs and complications reaction or AE is highest in the first 3 months, from 45% at 1 month, to 30% at 12 months, with 53% patients still receiving GC therapy after 12 months [47, 116].

In terms of QoL, based on an HTA review conducted by NICE assessing ANCA-AV patients treated with rituximab (RTX) in combination with GCs, average utility scores of 0.71 for patients with uncontrolled disease, 0.84 for those in remission falling to 0.79 on the 2nd consultation were reported [117]. A lower utility score of 0.671 was reported for uncontrolled disease in a similar review by the Scottish medicines consortium, with scores of 0.837 and 0.754 for remission and non-remission, respectively [118].

The Danish treatment guidelines for standard treatment of remission induction are referenced below and are in line with the European guidelines (EULAR/ERA_EDTA and KDIGO), [188,189].

Remissionsinducerende standardbehandlingen i Danmark af GPA/MPA

Remmissionsinducerende standardbehandling i Danmark af GPA/MPA med organ- eller livstruende sygdomsmanifestationer er kombinationsbehandling med cyklofosfamid og prednisolon eller rituximab og prednisolon [188,189].

Patienter med høj sygdomsaktivitet behandles typisk efter cyclophosphamid/prednisolon-baserede regimer [188,189].

- *Cyclophosphamid gives peroralt eller intravenøst (puls behandling) [194,195]. Intravenøs behandling resulterer sædvanligvis i lavere kumulerede cyclophosphamid-doser end peroral behandling uden at dette medfører lavere remissions-rater, men relaps-risikoen er højere [195,196].*
  Den kumulerede (livstids) cyklofosfamid-dosis bør tilstræbes at være under 36 g [207], da større dosis er forbundet med øget risiko for malignitet [189].
  Cyklofosfamid gives til klinisk remission og som hovedregel i mindst tre måneder og i højst 6 måneder [189].
- *Induktionsbehandling med rituximab i kombination med kortikosteroider synes at udgøre et ligeværdigt alternativ til cyclophosphamid-baseret førstelinje-behandling. Denne vurdering baserer sig indtil videre på relativt få randomiserede studier [69,109,199.200].*
  Retuximab doseres 4 gange af 375 mg/m² med 1 uges mellemrum eller 1 g x 2 med 14 dages mellemrum. Effekten er ens for de to doseringsregimer. Det anbefales, at der samtidig gives prednisolon, som doseres som ved behandling med cyklofosfamid [189].
- *Prednisolon administreres initialt i dosering 1 mg/kg/dag (maks. 75 mg/dag) i den første uge og herefter reduceret til 0,5 mg/kg/dag Der stiles mod aftrapning til ≤5 mg prednisolon/dag efter 6 måneder [188,189].*
  Ved svær vaskulitis kan det erfaringsmæssigt være nødvendigt med højdosis prednisolon i op til 14 dage inden nedtrapning og evt. langsommere udtrapning.
- *Ved svær nyrepåvirkning og/eller livstruende lungemanifestationer kan supplerende plasmaferese-behandling overvejes, idet der dog ikke foreligger entydig dokumentation for effekten af denne behandlingsmodalitet [147,197,198].*

Efter opnåelse af remission indledes recidivforebyggende behandling. Dette kan typisk finde sted efter 3-6 måneders induktionsterapi [194,201]. Senest efter 6 måneder bør man ved utilstrækkeligt behandlingsrespons overveje induktions-behandling med rituximab.

Remissionsinducerende behandling ved limiterede former for GPA/MPA uden organ- eller livstruende sygdomsmanifestationer [188,189].
Hos patienter med limiteret/tidlig systemisk sygdom kan overvejes induktionsterapi med:

- *t. methotrexat og t. prednisolon (V). Methotrexat-baseret induktionsbehandling er dog associeret til mindre stabil sygdomskontrol end cyclophosphamid-baseret førstelinje-terapi [203]."*

Patienter følges klinisk mindst hver 1.-2. uge til remission, ved aggressivt sygdomsbillede foregår behandlingen i den indledende fase under indlæggelse og derefter hver 1-3 måned alt efter relapsrisiko/frekvens og sygdomsaktivitet [188,189]. Patienter med inaktiv sygdom vurderes klinisk og paraklinisk hver 3-6 måned [188,189].

5.2.1.1.2 Maintenance of Remission

Overview of the literature for efficacy of Standard of Care for Remission Maintenance

Once remission is obtained, there follows maintenance therapy. Recommended minimum treatment times differ between guidelines, with 18 months for KDIGO and 24 months for EULAR/ERA-EDTA and BSR/BHPR.

Maintenance of remission is important as demonstrated by Gopaluni et al. who showed in a study of 354 ANCA-AV patients across four EUVAS studies that predictors of the composite end point of death or ESRD included late remission (HR 2.94, 95% CI 1.10-7.85; p=0.031) and relapsing disease (HR 8.21, 95% CI 2.73-24.65; p<0.001) [112].

All guidelines recommend administration of low-dose GCs, as well as AZA if CYC was used for remission induction, or a continuation of RTX if used for remission induction. MTX is indicated (in place of AZA) as a replacement option for CYC in all guidelines except KDIGO, which recommends AZA or RTX only. BSR/BHPR state that AZA/MTX can be replaced by MMF and leflunomide (LEF) due to intolerance or lack of efficiency. Whilst EULAR/ERA-EDTA also recommend MMF, with RTX included as an option for remission maintenance [1, 105, 106].

There are two major concerns associated with the treatment of ANCA-AV: controlling vasculitis activity and minimizing the acute adverse effects from therapy, which apply both at the time of diagnosis, and following disease relapse. Once remission has been achieved, cumulative organ damage (often related to long-term low-dose GCs) and patient experience, are considered more important [1, 44, 113].

Overview of the Literature for burden of Standard of Care for Remission Maintenance

Current therapies, rather than the underlying disease itself, potentially contribute to more than half of the elevated 12-month mortality risk in ANCA-AV patients, the odds of high level of organ damage increases by 1.26 for every 12 months of GC use (p=0.022) [5]. The medications commonly used to treat vasculitis, including corticosteroids and immunosuppressive drugs, carry substantial risk for treatment related adverse events and complications, including malignancy, infections, and other related side effects [119].

In a cohort of 524 GPA and MPA patients who were enrolled in four EUVAS trials to assess the burden of vasculitis and its treatment, of the 10.7% (n=56) who died within one year of diagnosis, 59% died of treatment-related AEs (50% from infection, 9% from other treatment-related AEs), 14% of active vasculitis, and 27% of other causes [64]. Cox regression analysis showed that infection score ($p<0.001$), AE score ($p<0.001$), leucopenia score ($p<0.001$), and GFR ($p=0.002$) were independently associated with mortality, and the risk of 1 year mortality increased with the number and severity of AEs (leucopenia, infection, and other AEs) experienced [64].

High doses of GCs and often prolonged GC use remain a mainstay of therapy for most types of vasculitis but are commonly associated with a wide range of potentially debilitating side effects [120, 121], with acute treatment-associated AEs and complications thought to cause approximately 60% of deaths [122]. Because there is a need to better balance vasculitis control with the risk of treatment-related adverse events, minimizing glucocorticoid use is a high priority in vasculitis management, and algorithms to reduce the duration and total amount of glucocorticoid are currently being investigated within ongoing clinical trials [123, 124].

With approximately 50% of patients requiring long-term GC use for up to 5 years [110], treatment-related AEs and side effects are a huge burden for patients with ANCA-AV.

Maintenance treatment includes immunosuppressive drugs such as azathioprine (AZA), mycophenolate mofetil (MMF), or methotrexate (MTX). Glucocorticoid [GCs] treatment is also often used during maintenance.

The Danish treatment guidelines [188,189] are referenced below:

"Recidivforebyggende standardbehandling i Danmark ved GPA/MPA påbegyndes ved komplet remission [189]. Hos patienter med renal-limited sygdom og i kronisk dialyse i over 3 måneder er der næppe behov for vedligeholdelsesbehandling [189].

Cirka halvdelen af patienter med GPA/MPA oplever et eller flere tilbagefald af vaskulitis-aktivitet indenfor de første 5 år efter sygdomsdebut [204;10], og man tilstræber derfor at opretholde et recidiv-forebyggende immunosuppressivt regime i flere år efter opnåelse af primær remission. Den optimale varighed af den relaps-forebyggende immunosuppressiv terapi ved GPA/MPA er uafklaret. Øre/næse/hals-involvering, GPA-diagnose og PR3-ANCA-positivitet er risikofaktorer for tilbagevendende sygdom [10,196,204].

For patienter, der er bragt i remission med rituximab, anbefales rituximab som vedligeholdelsesbehandling. For patienter, der er bragt i remission med rituximab, anbefales rituximab som vedligeholdelsesbehandling. For patienter, der er bragt i remission med cyklofosfamid vælges primært azathioprin som vedligeholdelsesbehandling, men rituximab kan dog også anvendes.

- *T. azathioprin eller t. methotrexate kan anvendes som relaps-forebyggende behandling ved GPA/MPA, og medikamenterne er lige effektive [205]. Behandling med AZA påbegyndes umiddelbart efter ophør med peroral cyklofosfamid, og en uge efter sidste puls i.v. cyklofosfamid. Dosis er typisk 2 mg/kg, som kan reduceres til 1-1,5 mg/kg hos ældre patienter og/eller patienter i risiko for svære bivirkninger [188,189].*
- *T. mycophenolat mofetil (dosis 1-2 g/dag) kan også anvendes, men relaps-raten under mycophenolat mofetil-behandling synes dog at være højere end relaps-raten under behandling med t. azathioprin [206].*

Et randomiseret klinisk studie har vist, at vedligeholdelses-terapi med gentagne rituximab-infusioner repræsenterer en effektiv relaps-forebyggende behandling ved GPA/MPA (71). Der anbefales som udgangspunkt 500-1000 mg rituximab hver 4-6 mdr. [188,189].

Hvis der ikke er tegn på klinisk sygdomsaktivitet, kan prednisolon søges udtrappet efter 6-12 måneder [189].

5.4.1.1.3 Relapsing ANCA-AV

Relapsing disease is defined as previously well-controlled disease, with or without therapy, that has become active. EULAR state that "a major relapse should be defined as the re-occurrence or new onset of potentially organ- or life-threatening disease activity that cannot be treated with an increase of GC alone and requires further escalation of treatment (i.e., the administration of CYC); all other relapses should be classified as minor" [126]. The BSR/BHPR guidelines define a minor relapse as "an increase in at least one new or worse minor item and no major Birmingham Vasculitis Activity Score (BVAS) items", and a major relapse as "an increase in at least one major BVAS item" [105].

Treatment decisions can be challenging for those treating relapsing patients, as this group present with acute vasculitis in addition to chronic organ damage from vasculitis and long-term GC treatment [1]. Physicians must manage patients with different underlying type (GPA and MPA), severity, and frequency of renal involvement, and as such, experience different clinical challenges.

RTX is preferred to CYC within the KDIGO guidelines. In the RAVE trial, RTX was found to be superior to CYC for the treatment of relapsing disease [69]. For relapses that are considered 'minor' or non-organ threatening, EULAR/EDTA and BSR/BHPR recommend increasing the GC dosage and re-evaluating maintenance therapy for optimization. Recommendations for patients experiencing a major relapse in all guidelines are broadly like those described for remission induction and include reintroduction of GCs plus CYC or RTX [1,105,106].

Overview of the literature of the Efficacy of SoC for Relapsing ANCA-AV

Non-severe relapses are more common than severe relapses in ANCA-AV but are an under-recognised clinical problem. Accumulating organ and tissue damage in ANCA-AV increases the number of relapses, which in turn causes further long-term damage [5, 127, 128]. Recurrent relapses within a relatively short interval occur frequently and given that the treatment of relapse usually involves an increase in prednisone dose, alternative treatment approaches are needed for this subset of patients [129]. Nearly 50% of patients require long-term GC use and receive GCs for nearly 5 years after initiation of RTX to sustain remission [110]. Despite the current SOC, 2.6 times more ANCA-AV patients die over 5.2 years vs. general population ($p<0.0001$) [3] with the main causes of death including infection, active vasculitis, cardiovascular events and malignancy [3, 58]. This is particularly prominent in ANCA-AV patients with ESRD, where there is a >2-fold increased risk of mortality [125].

In a study of relapsing ANCA-AV patients (n=268) from four European countries, 76.5% received GC therapy [130]. Glucocorticoid exposure based on relapse has been estimated in patients in the WEGENT trial. Over a 12-month period, cumulative dose of 3.9 g was recorded for patients who had no relapse (n=78), rising to 6.0 g in those with a single relapse (n=42), and 7.9 g in patients with multiple relapses (n=37) [131].

Outcomes of non-severe relapses in patients from the RAVE trial were analyzed. Following non-severe relapse, an increase in prednisone dose led to remission in 80% of patients (n=35); the median prednisone dose to treat the first non-severe relapse was 17.5mg/day. However, only 30% of patients maintained this second remission over the 12.5-month follow-up period; 70% (n=31) had a second disease relapse (mean time to second release was 9.5 months), 14 with severe disease. Compared to patients who maintained relapse-free remission over 18 months, patients who experienced non-severe release were more likely to have a higher mean accumulative prednisone dose (6.7 vs 3.8g; p<0.01), as well as PR3- vs. MPO-ANCA positive disease (p<0.02) and a GPA, rather than MPA, diagnosis (p<0.01) [129].

Analysis of EUVAS data (7 RCTS, 535 patients) to determine rate of death and relapse, showed relapse rate was 44.6%, with 18.6% experiencing relapse during a trial, and 40.2% during long-term follow-up. Mean time to relapse was 10.7 months. Of those who experienced a relapse at any point, 51.5% scored ≥5 items of damage on the VDI. Over 70% of patients with ≥4 relapses reported >5 items on the VDI [5]

The MAINRITSAN 1 and 2 trials compared AZA to RTX for remission maintenance. In both trials, RTX was superior to AZA for maintaining remission, but data showed that relapses still occur in the maintenance phase (Table 9). At month 28, there was a significant improvement in the rate of major relapse in the RTX group (p =0.002), which was not seen with minor relapses (p=0.43) [71]. In addition, long-term GC use remained common, with patients in both the AZA and RTX group still requiring prednisone at 28 months (58.5% and 45.5%, respectively) [71]. Between months 28-60, the benefit of RTX was not sustained with 23% experiencing a major relapse (after being previously major relapse free) [72]. Mean GC dose at month 60 was 3.3 mg /day in both groups [72]. For the AZA and RTX groups, respectively, the major relapse-free survival rates were 49.4% and 71.9% (p=0.003); minor and major relapse-free survival rates were 37.2% and 57.9%, p=0.012; overall survival rates were 93.0% and 100% (p=0.045) [72].

Table 9 Rates of death and relapse in maintenance phase from the MAIRITSAN 1 and 2 trails

	Treatment group	% major relapse		% minor relapse	p value	Reference
Month 28	AZA	29	p=0.002	16	0.43	[71, 72]
	RTX	5		11		
Month 28-60	AZA	19		5		[72]
	RTX	23		12		
Major relapse survival rate	AZA	49.4	p=0.003			[72]
	RTX	71.9				

Overview of the Literature for Burden of SoC for Relapsing ANCA-AV

While most ANCA-AV patients achieve remission with current therapies, many do not achieve or maintain a GC-free remission. Disease relapse is common, with over one third relapsing within 18 months of remission, and less than one third remaining relapse free which is a major concern as relapses can be fatal [132].

The chronic relapsing and remitting nature of ANCA-AV, and requirement for prolonged treatment, significantly impacts patients' physical and emotional well-being and reduces quality of life, with high levels of fatigue, depression, sleep disturbances, and high BMI associated with significant work disability among working-age ANCA-AV patients [97]. Patients report that ANCA-AV can impact the

quality and quantity of work they are able to do and leads to increased absenteeism alongside hindering career progression and limiting pay increases [92].

The Danish Guidelines for standard treatment of relapsing GPA/MPA are referenced below.

Behandling af sygdomsrelaps ved GPA/MPA

I RAVE studiet var rituximab mere effektiv end cyclophosphamid til behandling af patienter med relaps [109]. Behandlingsstrategien ved sygdomstilbagefald afhænger dog af sygehistorien i det enkelte tilfælde, herunder typen og varigheden af tidligere behandling, samt af sværhedsgraden af det diagnosticerede relaps [188].

Dansk Nefrologisk Selskabs deler relaps i "major relaps" og "minor relaps" [189]:

Ved major relaps forstås ny eller forværring, organtruende sygdomsaktivitet efter induktion af remission. Denne kan omfatte nyrefunktionspåvirkning, lungeblødning, neurologiske symptomer, gastrointestinal vasculitis, hjertevaskulitis, påvirket øjenfunktion eller andet som anses for umiddelbart truende.

Behandlingen følger principperne for induktionsbehandling beskrevet ovenfor. Hvis major relaps følger kort efter remission kan alternativ (Rituximab) eller supplerende behandling (genoptagelse af cyklofosfamid (obs for maksimal dosis), supplement med rituximab, plasma exchange og/eller intravenøs immunglobulin) overvejes. Øgning eller skift i remissionsbevarende behandling bør overvejes ved gentagende relaps.

Ved minor relaps forstås tegn på sygdomsaktivitet, der ikke er omfattet af ovenstående.

Behandlingen vil ofte være at øge dosis af prednisolon (eks. 30 mg/dag), der aftrappes som initialt. Øgning eller skift i vedligeholdelsesbehandling bør, som ovenfor, overvejes ved gentagende relaps.

5.2.1.1.4 Refractory patients in ANCA-AV

EULAR defined Refractory disease as [126]:

- Unchanged or increased disease activity in acute ANCA-AV after 4 weeks of treatment with standard therapy in acute ANCA-AV, or
- Lack of response, defined as <50% reduction in the disease activity score (e.g., BVAS) after 6 weeks of treatment, or
- Chronic, persistent disease defined as presence of at least one major or three minor items on the disease activity score after >12 weeks of treatment

CYC administration is considered for patients that are RTX experienced by all guidelines. In refractory disease, the EULAR/ ERA-EDTA recommendation is that patients that are CYC experienced should be switched to RTX. KDIGO guidelines also state that plasma exchange (PLEX) should be considered in refractory patients. Except for KDIGO, the guideline consensus in refractory patients is that they should be referred to specialist centres where drivers of refractory disease can be sought, and patients can be referred to clinical trials (Table 8) [1,105,106].

5.2.2 Choice of comparator

Tavneos®/avacopan, in combination with rituximab or cyclophosphamide regimen, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) [154].

Tavneos®/avacopan are compared with prednison in the clinical trial program pivotal phase 3 study ADVOCATE [155] and in the two phase 2 studies CLEAR [149] and CLASSIC [152].

Tavneos®/avacopan is expected to replace or partly replace prednisolon for the treatment of adult patients with severe active GPA/MPA in Denmark.

Prednisolon is the preferred glucocorticoid for treatment of inflammatory og immunologic diseases in Denmark and Europe [1,188,189,211]. It is broadly accepted prednisone and prednisolone can substitute each other and the ekvi-effective doses are equal mg per mg [188,189,211].

Against this background, Vifor Pharma has chosen the prednison-arm in the head-to-head study ADVOCATE as the comparator and a proxy for the Danish standard treatment with prednisolone.

Table 10 Danish basis information of prednisolon

Generic name, ATC-kode	Prednisolon, H02AB06
Mode of action	Prednisolon er et kortikosteroid med glykokortikoid og mineralkortikoid aktivitet. Sammenlignet med hydrokortison, det vigtigste humane antiinflammatoriske kortikoid, har det 4 gange højere glukokortikoid styrke, men lavere mineralkortikosteroid styrke. Prednisolon er generelt foretrukket af glykokortikoider til antiinflammatorisk og immunosuppresiv behandling [188.189.211]
Pharmaceutical form	Tabletter
Posology	Ifølge produktresumeet [210}: Individuel. Generelt afhænger dosering af sygdommens karakter og sværhedsgrad. Der begyndes med en dosis, som giver den ønskede kontrol af sygdomsaktiviteten. Herefter reduceres til laveste dosis, der giver den ønskede kontrol af sygdomme. Seponering må altid overvejes afhængig af indikation og sygdomsaktivitet. Efter længerevarende behandling (for voksne typisk over 3 ugers varighed) bør seponering ske gradvist over uger eller måneder afhængigt af dosis og behandlingsvarighed. Gradvis seponering bør også overvejes efter korterevarende behandling med højere doser eller hos patienter med risikofaktorer for binyrebarkinsufficiens. Den gradvise seponering bør tilpasses individuelt, men hovedparten af voksne patienter vil tolerere dosisreduktioner på 2,5 mg hver tredje til syvende dag til en dosis på 5 til 10 mg/dag [210]. Inflammatoriske og immunologiske tilstande Den daglige dosis er typisk mellem 0,1-2 mg/kg kropsvægt fordelt på 1-4 doser. [210] De Danske kliniske retningslinjer [188,189]: Remissionsinducerende behandling: 1 mg prednisolon/kg/dag. Der stiles mod aftrapning til ≤ 5 mg prednisolon/dag efter 6 måneder [188]. I den nefrologiske guideline foreslås 1 mg prednisolon/kg/dag (max. 75 mg/dag) i den første uge, og herefter reduceres til 0,5 mg/kg/dag med aftrapning til 5 mg over 3-6 mdr. Forslag til aftrapning over 6 måneder efter PEXIVAS-protokollen [207]. Ved svær vasculitis kan det erfaringsmæssigt være nødvendigt med højdosis prednisolon i op til 14 dage inden nedtrapning og evt. langsommere udtrapning [189]
Method of administration	Peroral behandling
Dosing	Ifølge produktresumeet: Individuel.

	Generelt afhænger dosering af sygdommens karakter og sværhedsgrad. Der begyndes med en dosis, som giver den ønskede kontrol af sygdomsaktiviteten. Herefter reduceres til laveste dosis, der giver den ønskede kontrol af sygdomme. Seponering må altid overvejes afhængig af indikation og sygdomsaktivitet. Efter længerevarende behandling (for voksne typisk over 3 ugers varighed) bør seponering ske gradvist over uger eller måneder afhængigt af dosis og behandlingsvarighed. Gradvis seponering bør også overvejes efter korterevarende behandling med højere doser eller hos patienter med risikofaktorer for binyrebarkinsufficiens. Den gradvise seponering bør tilpasses individuelt, men hovedparten af voksne patienter vil tolerere dosisreduktioner på 2,5 mg hver tredje til syvende dag til en dosis på 5 til 10 mg/dag [210]. Inflammatoriske og immunologiske tilstande Den daglige dosis er typisk mellem 0,1-2 mg/kg kropsvægt fordelt på 1-4 doser. [210] De Danske kliniske retningslinjer: Remissionsinducerende behandling: 1 mg prednisolon/kg/dag. Der stiles mod aftrapning til ≤ 5 mg prednisolon/ dag efter 6 måneder [188]. I den nefrologiske guideline foreslås 1 mg prednisolon/kg/dag (max. 75 mg/dag) i den første uge, og herefter reduceres til 0,5 mg/kg/dag med aftrapning til 5 mg over 3-6 mdr Forslag til aftrapning over 6 måneder efter PEXIVAS-protokollen [207]. Ved svær vasculitis kan det erfaringsmæssigt være nødvendigt med højdosis prednisolon i op til 14 dage inden nedtrapning og evt. langsommere udtrapning [189]
Should the pharmaceutical be administrated with other medicines?	No, but for the indication GPA/MPA the treatment will also consist of high dose immunosupressiva cyclophosphamid or rituximab
Treatment duration/criteria for end of treatment	Remissionsinducerende behandling: 1 mg prednisolon/kg/dag. Der stiles mod aftrapning til ≤ 5 mg prednisolon/dag efter 6 måneder [188]. I den nefrologiske guideline foreslås 1 mg prednisolon/kg/dag (max. 75 mg/dag) i den første uge, og herefter reduceres til 0,5 mg/kg/dag med aftrapning til 5 mg over 3-6 måneder Forslag til aftrapning over 6 måneder efter PEXIVAS-protokollen [207]. Ved svær vasculitis kan det erfaringsmæssigt være nødvendigt med højdosis prednisolon i op til 14 dage inden nedtrapning og evt. langsommere udtrapning [189]. Maintenance or relaps treatment up to several years.
Necessary monitoring, both during administration and during the treatment period	No
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Packaging	Varenr. 154615 Prednisolon “EQL Pharma” 2,5 mg, 100 tabletter Varenr. 398747 Prednisolon ”DAK” 5 mg, tabletter Varenr. 416469 prednisolon ”EQL Pharma” 25 mg, 10 tabletter Varenr. 163096 prednisolon ”EQL Pharma” 25 mg, 100 tabletter

The prespecified Prednisolon Dose Trapping schedule in The Advocate Study is similar to the Pexivas trapping schedule and the Danish treatment guidelines [155,188,189,207].

1 mg/kg/day in week 1 trapping down to 5 mg/day in week 15-21, Optionally to trapping out after week 21 in the Advocate protocol and in the Danish treatment guidelines it is suggested to stay on 5mg prednisolon/day until week 52 and then optionally to trapping out [155,188,189].

5.2.3 Description of the comparator

Current European guidelines recommend the use of high-dose immunosuppressants to achieve and sustain remission in organ or life-threatening ANCA-AV. A high-dose GC regimen usually consists of prednisone/prednisolone at 1mg/kg/day (to a maximum daily dose of 80 mg), gradually decreased

to a target dose of 7.5–10 mg prednisolone (or equivalent) where the disease is controlled, after 3 months of treatment (this is called titration) [1]. However, in practice it may be 5 months before patients are at a GC dose level where the disease is controlled [1].

Fully in line with the European Guidelines and the ADVOCATE study, the Danish guidelines recommend an initial dose of 1 mg prednisolone/kg/day, gradually decreased to a target dose $\leq$5 mg prednisolon/day [188] and for patients with ANCA-AV glomerulonephritis is the max daily dose 75 mg [189].

There is no clear guidance available regarding balancing dose, benefits, and risks, of GC therapy, as this depends on the goals of treatment, initial response to treatment, development of AEs, and individual patient characteristics [135]. There is no consensus on optimal dose, titration regimen, and duration of GC use [2]. The joint EULAR/EDTA guidelines are also not able to give guidance on when to cease GC treatment, as this varies according to patient treatment response. There is variation in the investigated dose and duration of GC therapy; trials report courses ranging from 5.5 months to >24 months [136]. In the absence of a structured, predictable, treatment regimen, patients have reported concerns over the uncertainty of the dose-reduction process [113].

Treatment with GCs is associated with complex dosing regimens, treatment-related adverse events and complications, which add to morbidity and patient burden [137]. The prolonged harmful effects of steroid use are well known, however even with short-term use, such as during induction, ANCA-AV patients have reduced survival compared to matched controls [125] and acute treatment-associated AEs and complications may cause approximately 60% of deaths in ANCA-AV [122].

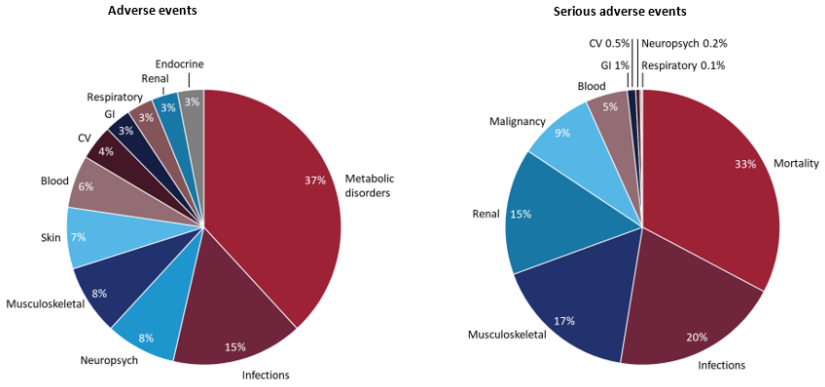
ANCA-AV patients have reported several significant, negative impacts attributed to GC therapy and these drugs are associated with a high risk of significant metabolic, psychiatric, and cardiovascular disease [120, 121].

5.2.3.1. Evidence of GC adverse effects

Whilst even short-term GC use is linked to potentially life-threatening GC-induced diseases, GC treatment is often needed long-term, with 39% of ANCA-AV patients found to be receiving GCs 58 months (4 years 10 months) after initiation when RTX was used to sustain remission [110]. However, long-term and repeated high-dose GC use is associated with increased risk of infection, new onset diabetes, hypertension, avascular bone necrosis, osteoporosis, progressive organ damage, and other complications [5]. In the EUVAS cohort, nearly half (47.8%) of patients were still receiving GC therapy at their last trial visit, with the mean length of GC use reported as 40.4 months and patients with a longer duration of GC use were more likely to have total VDI score ≥5 (p=0.022) [5, 127, 128, 139].

A systematic literature review reported that 31% of patients (n=1102/3543) experience GC-related serious AEs, and 19% of patients (n=4284/22278) experience GC-related AEs [140]. The frequency of the most commonly reported GC-related AEs is presented in **Fejl! Henvisningskilde ikke fundet.**, where the most common adverse events and serious adverse event are metabolic disorders and mortality, respectively, with infections the second most common event in both categories [140].

Figure 13 Most commonly reported glucocorticoid adverse events and serious adverse events in 33 ANCA-AV studies (% of total number of events) [140]



Another systematic review including 1684 ANCA-AV patients treated with GCs across 15 RCTs demonstrated that the most commonly reported serious adverse events (SAEs) were blood disorders (reported by 34% of patients; neutropenia (21.5%), blood disorder affecting platelets (6.3%), and thrombotic disorder 6.1%), with 10% of patients reporting infections (including pulmonary infection, sepsis, and bone infection) and organ damage (hepatic, skin, or renal). Among the 1837 ANCA-AV patients treated with GC in 23 prospective non-randomised studies, 385 patients reported SAEs and proportions of musculoskeletal disorders (bone fracture, osteonecrosis, bone marrow failure) and infection were 46% and 18.7%, respectively. Similarly, of the 938 SAEs reported in 5135 patients in 43 retrospective studies, the proportion of infections and blood disorders was 24% and 11%, respectively [122].

Fifty ANCA-AV patients recruited from rheumatology centers in the UK, Canada and US were interviewed about their experience with GCs, and reported a wide range of physical, social, and emotional adverse events [113]. Patients described fatigue, diabetes mellitus, increased appetite, and muscle weakness, with weight gain, and changes in appearance including facial “puffiness”, making their condition more obvious to others and having significant detrimental impact on self-esteem, which also linked to higher anxiety and feelings of depression. Patients also voiced concern about the risk of GC-induced diseases linked to long-term GC use: they reported wanting to reduce their maintenance GC use to avoid these impacts, however, this was balanced by anxiety about the risk of disease flare ups following dose reduction [113].

Real-world UK data show that 3 years post-diagnosis, GPA is associated with increased risk of hypertension (hazard ratio (HR)=2.45, 95% CI: 1.84, 3.26), Type 2 diabetes (HR=2.13, 95% CI: 1.36, 3.32), dyslipidaemia (HR 1.98, 95% CI: 1.29, 3.04) and depression (HR=1.77, 95% CI: 1.10, 2.86), compared to match controls [141]. Whilst the link to GC use was not explicitly examined, it is unlikely that active ANCA-AV would have a role in the development of metabolic (particularly diabetes mellitus), neuropsychological, cardiovascular, or musculoskeletal, disorders [130].

In 2019, Vifor conducted a study to gather high quality, real-world data on patient outcomes and resource utilisation associated with ANCA-AV in the UK, more specifically, the use of GCs in this patient group, and the potential implications of reducing GC doses [142]. The study utilised a large English source of real-world data, the Clinical Practice Research Datalink (CPRD) Hospital Episode Statistics (HES) linked database. All patients with a diagnostic code indicative of an ANCA-AV

diagnosis recorded during follow-up, and between 01/01/1997 and 01/01/2018, were identified. A total of 567 eligible ANCA-AV cases, were identified, and analyses were completed on 450 patients whom had at least one GC prescription [142]. In this population the mean number of low dose GC prescriptions per patient was higher than high dose GC prescriptions Table 11 [142].

Table 11 GC use following diagnosis in the overall and incident ANCA-AV population

Prednisolone dose category	Number of prescriptions per patient (median (IQR))	Daily dose (mg) (median (IQR))	Number of days per prescription (median (IQR))
Low dose (<30mg/day)	25 (8-52)	5.6 (5.0-10.0)	28 (28-55)
High dose (> =30mg/day)	2 (0-4)	40.0 (33.3-62.5)	14 (7-28)

In the year following ANCA-AV diagnosis, the median GC dose in the overall population tapered such that at 6 months it was 9.3mg/ day and at 1 year it was 5.1mg/day: this trend, suggests that the GC taper may not be too dissimilar to that observed in clinical trials [142].

Notably, it was observed that at 5 and 12 months, ~50% and ~25% of the population, respectively, were on a daily dose >10mg/day, indicating a patient subgroup that fail to reach target doses within a year. The primary adverse patient outcome was infections, the rate of which was 515 events per 1000 person years i.e., one infection every 2 person years. This rate was lower in the incident population. In those taking high dose GCs, compared to low dose: the rate of infections was ~2 times higher (CI95 1.77, 2.63), and lowest in those not currently using GCs (IRR 0.47 (CI95 0.40, 0.54). The incidence of new onset cardiovascular and renal disease was ~3 times higher and the incidence of new onset renal disease was almost 3 times higher than the general population. Despite lower GC use side effects were still a problem for this patient group [142].

5.2.3.1.1 Increased Cardiovascular Risk with GC

Glucocorticoids may play an important role in increasing cardiovascular risk through their metabolic side effects [140]. In patients with vasculitis there is an association between time-variant oral GC prednisone-equivalent dose (PED) and incident all-cause CVDs, for example at daily doses of 1-14.9 mg GC the adjusted HR for CVD is 1.92 [137]. A population-based cohort analysis of data from CPRD was conducted to quantify GC dose-dependent CV risk in immune mediated inflammatory diseases, including vasculitis (5199 patients) [137]. Across all diseases, an increased risk of CVD associated with GC dose was observed, even at lower GC doses of <5mg (HR=1.74; 95% CI 1.64-1.84). One-and five-year cumulative risk of all-cause CVD increased from 1.4% and 7.1% respectively in periods where no GCs were used, to 8.9% and 28.0% respectively, for a daily prednisone-equivalent dose of ≥ 25mg [137]. A meta-analysis conducted by Walsh et al. showed that studies with longer courses of GCs were associated with fewer relapses, however, extended GC use is associated with significant adverse effects [143].

5.2.3.1.2 Increased Infection Risk with GC

Infection, thought largely to be the consequence of high-dose GCs, is the cause of death in the first year in approximately half of patients [3], with patients experiencing major infections having increased mortality from any cause [144]. The high number of deaths attributed to infections reflects the burden of GC treatment [145]. Estimates of all-cause infection per level of time-variant current daily GC dose indicate that for daily doses up to 14.9 mg there is a 5-year cumulative probability of 69.8% [134].

In a recent retrospective study of 130 ANCA-AV patients from two German centres where patients had received GC induction and maintenance, chronic higher doses of GC (>7.5 mg) correlated with significantly higher infection rates (p=<0.001). In addition, dose of GC maintenance therapy had no effect on time to relapse or patient survival in any ANCA-AV subtype [146].

Data from the PEXIVAS trial comparing PLEX plus a standard-dose GC regimen or a lower-dose GC regimen in a cohort of patients with severe ANCA-AV showed no difference in a combined outcome of ESRD or death between the two treatment regimens, but that the reduced-dose regimen was associated with a significant reduction in serious infections in the first year of treatment (27.2% vs 33.0% for the standard-dose regimen) [147].

Real-world data from a different vasculitis (GCA/PMR), which employs similar steroid regimens as in ANCA-AV, shows that long-term prednisone even at low-dose (<5 mg/day) increases the risk of infection compared with non-use of oral GCs (HR: 1.13 (95% CI: 1.12–1.14) [143]. In addition, the population-based cohort analysis of data from CPRD in UK showed a 2.15-fold higher rate of infection, and a 2.75-fold higher rate of new-onset renal disease in individuals on high-dose GCs than in those on low-dose GCs [142].

5.2.3.1.3 Vasculitis Damage Index Questionnaire

Questionnaire data, provided by study investigators for 535 newly diagnosed GPA and MPA patients enrolled into four EUVAS trials approximately 7 years prior, was analysed to determine cumulative GC use at trial completion, and Vasculitis Damage Index (VDI) score at long-term follow-up [5]. The VDI is a validated checklist of items to measure damage in ANCA-AV, with 10 of 11 categories relating to specific organ systems and defines damage as an item that occurs after vasculitis onset and is present for longer than 3 months [5,138]. The data showed that frequency of damage, including damage potentially caused by treatment, accumulates over time, odds ratio increases 1.26 for every 12 months of GC use (p<0.01) [127], and that high levels of long-term vasculitis damage are independently associated with increased cumulative GC use (p=0.022). Five or more items of damage were reported in 46.8% of patients who were on GCs at the last trial visit (vs. 23.0% not on GCs at this time, p<0.001), and in 47.0% of those using GCs for 60 months compared with 32.6% of those with 1-18 months of use (p=0.022) [5].

5.3 The intervention Tavneos®/avacopan

Dosing:

30 mg Tavneos®/avacopan (3 hard capsule of 10 mg each) taken orally twice daily, morning and evening, with food [154].

Method of administration:

oral.

Treatment duration/criteria for treatment discontinuation:

Clinical study data are limited to 52 weeks of exposure followed by 8 weeks of observation [155].

The expected treatment would be up to 12 months due to that the phase III study (ADVOCATE) evaluated outcomes measure up to week 52 [154,155].

- In the ADVOCATE study, participants received avacopan for 52 weeks and the case for continuing treatment for 52 weeks is reinforced by the significant benefit observed on the 1 year sustained remission primary endpoint. Therefore, we anticipate that patients will continue avacopan for 1 year, except for a minority who may need to cease for any safety or tolerability issues.
- Background standard of care therapy during maintenance is anticipated to take into account the induction therapy used, current national and international guidelines and the existing label. Therefore, once remission has been established we would anticipate that avacopan would be administered in combination with azathioprine or mycophenolate in patients receiving cyclophosphamide based induction therapy [238] and ongoing rituximab maintenance therapy in patients receiving rituximab induction [212]. An update of the Eular recommandations will be published shortly and it is expected that the Danish Guidelines will be reviewed in continuation of this [188,189].
- It is anticipated that the use of avacopan may permit physicians to reduce or cease glucocorticoids during remission in some instances. This is based on data from the ADVOCATE study that showed that avacopan was able to successfully maintain remission in a number of participants without the requirement for non-protocol GCs, and the strong desire of clinicians to minimise GC exposure in their AAV patients.

Treatment must be re-assessed clinically and temporarily stopped if:
• alanine aminotransferase (ALT) or aspartate aminotransferase (AST) is more than 3 times the upper limit of normal (ULN).

Treatment must be temporarily stopped if:
• ALT or AST > 5 × ULN,
• a patient develops leukopenia (white blood cell count < 2 × 10^9/L) or neutropenia (neutrophils < 1 × 109/L), or lymphopenia (lymphocytes < 0.2 × 10^9/L),
• a patient has an active, serious infection (i.e. requiring hospitalisation or prolonged hospitalisation).

Treatment may be resumed:
• upon normalisation of values and based on an individual benefit/risk assessment.

If treatment is resumed, hepatic transaminases and total bilirubin are to be monitored closely.

Permanent discontinuation of treatment must be considered if:
• ALT or AST > 8 × ULN,

• ALT or AST > 5 × ULN for more than 2 weeks,
• ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or international normalised ratio (INR) > 1.5,
• ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%),
• an association between avacopan and hepatic dysfunction has been established [154]

Should the pharmaceutical be administered with other medication? Tavneos, in combination with a rituximab or cyclophosphamide regimen, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA).

Necessary monitoring, during administration, during the treatment period, and after the end of treatment:
Patients must be monitored for hepatic transaminases and total bilirubin as clinically indicated and as part of the routine follow-up of patient's underlying condition.

Need for diagnostics or other tests (i.e. companion diagnostics):
No

In the pivotal phase III study ADVOCATE avacopan is compared with prednisone [155] and demonstrates its glucocorticoid-sparing effect and disease control in treatment of patients with GPA and MPA.

Against this background, avacopan in combination with rituximab or cyclophosphamide is expected to replace or partly replace prednisolon in the current treatment algorithm for the treatment of patients with severe, active GPA and MPA.

6. LITERATURE SEARCH AND IDENTIFICATION OF EFFICACY AND SAFETY STUDIES

6.1 Identification and selection of relevant studies

The systematic literature review (SLR) of the published literature reporting the clinical efficacy and safety data of avacopan in combination with cyclophosphamide or rituximab with or without steroids, compared with relevant comparator therapies for adult patients with granulomatosis with polyangiitis GPA formerly called Wegener's granulomatosis or microscopic polyangiitis MPA.

The phase 3 ADVOCATE study demonstrated the superiority of avacopan over prednisone in clinical remission, toxicity, and sustained remission.

Vifor Pharma Group conducted a SLR to identify all studies reporting on the clinical efficacy, safety, and tolerability of therapies for the treatment of GPA or MPA to support future health technology assessment submissions for avacopan.

The research question:

> "What is the clinical efficacy and safety of avacopan, in combination with cyclophosphamide or RTX with or without steroids, compared with relevant comparator therapies for adult patients with GPA or MPA?"

To assemble all available relevant evidence using explicit, valid, and replicable methods to minimise the risk of bias in the selection of studies (CRD 2009; Higgins 2011; NICE 2013; Charlier C. 2009).

A full SLR was undertaken on 4 June 2018, updated on 16 June 2020, and again on 16 June 2021, 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 steroids, compared with relevant comparator therapies for adult patients with GPA or MPA.

The review was conducted in 3 stages

- A comprehensive and systematic database search (including: Embase, MEDLINE, and Cochrane Central Register of Controlled Trials) to identify all relevant published literature related to the review question
- A systematic screening process conducted by 2 analysts to capture relevant studies based on explicit inclusion and exclusion criteria
- Extraction of relevant data from eligible studies to assess comparative clinical evidence

Detailed information of the literature search is provided in appendix A. It is including focused questions, PICO, search strategy and strings, in- and exclusions criteria, list of databases, description of process of selected studies, PRISMA-diagram, tables of study included for analysis, studies excluded at full-text screening.

6.2 List of relevant studies

Studies identified

32 randomised controlled trials (RCTs) were identified from 54 citations, including 2 phase 2 avacopan trials (CLEAR and CLASSIC) and a pivotal phase 3 study (ADVOCATE).

Direct comparisons of remission induction were challenging because of the differences in definition of remission found between studies. However, RTX was associated with a greater likelihood of disease remission at 6 months than was CYC.

Comparisons of relapse rates were difficult because of differences in definitions of relapse between studies.

Assessments of disease activity showed that patients treated with avacopan had significantly less disease activity as measured by Birmingham Vasculitis Scale (BVAS) than those treated with prednisone ($P \leq 0.001$) and a smaller increase in disease-related damage.

The data show that avacopan or plasma exchange better protect kidney function than glucocorticoids, with avacopan-treated patients showing significantly greater estimated glomerular filtration rate (eGFR) than prednisone-treated patients.

Table 12 Relevant studies included in the assessment for the comparison of the Tavneos and the comparator prednison

Reference		Trial name	NCT number	Dates of study
Avacopan for the Treatment of ANCA-Associated Vasculitis, Jayne DRW et al, N Engl J of Med 2021; 384: 599-609. DOI:10.1056/NEJMoa2023386 [155]	ADVOCATE	A phase 3 Clinical Trial of CCX168 (Avacopan) in Patients with ANCA-associated Vasculitis	NCT02994927	Study completed. Inclusion: 15/03/2017-01/11/2019
Adjunctive Treatment With Avacopan, an oral C5a Receptor Inhibitor, in patients With Antineutrophil Cytoplasmic Antibody-Assocoated Vasculitis. Merkel PA et al. ACR Open Rheumatology 2 (11): p 662-671. DOI: 10.1002/arc2.11185 [152]	CLASSIC	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	NCT02222155	Study completed. Inclusion: 04/02/2015-19/07/2016
Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis. Jayne DRW et al. J Am Soc Nephrol 28. 2756-2767, 2017, DOI: 10.1681/2016111179 [149]	CLEAR	A Randomized, Double-Blind, Placebo-controlled, Phase 2 Study to Evaluate the safety and Efficacy of CCX 168 in Subjects with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis on Background of Cyclophasphamide or Rituximab Treatment	NCT01363388	Study completed. Inclusion: 12/10/2011 – 18/01/2016

The SLR of the published literature didn't contribute any further relevant data and the application is based on the direct comparative study ADVOCATE between intervention (Tavneos®/avacopan) and comparator prednison/prednisolon [155].

For detailed information about the SLR refers to appendix A.

7. EFFICACY AND SAFETY

The clinical efficacy and safety of an Avacopan-based regimen has been investigated in two Phase 2 trials CLEAR and CLASSIC, and the pivotal phase 3 trial, ADVOCATE.

The Marketing Authorisation is based on these three studies.

7.1 Efficacy and safety of avacopan compared to prednison for patients with ANCA-AV

The 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. See the description of the Systematic Literature Review report for details section 6 and appendix A. In total, three studies investigating the efficacy and safety of avacopan in MPA and GPA were identified: Two Phase 2 randomised controlled trials, CLEAR (NCT01363388; study number CL002_168) [149] and CLASSIC (NCT02222155; study number CL003_168) [152], and a pivotal Phase 3 randomised controlled trial, ADVOCATE (NCT02994927; study number CL010_168) [153,155].

The efficacy data from the two Phase 2 and the head-to head phase 3 study have not been integrated in this application, given the substantial differences in the primary efficacy endpoints, treatments regimens, and the treatment duration among 3 studies [184].

As the ADVOCATE study is a head-to-head comparison (avacopan versus prednison, both in combination with a RTX/CYC regime), and the treatment in the comparator arm corresponds to Danish clinical practice (initial dose, trapping regime, the combination treatment etc.) as well as the ADVOCATE-patient population are similar to the Danish patient population, cf. appendix C, no further studies are included in this application for efficacy and safety. The results from ADVOCATE study are presented in appendix D and E for the ITT-population.

7.1.1 The pivotal phase 3 study ADVOCATE

ADVOCATE was a global, randomised, blinded, active- controlled clinical trial designed to evaluate the efficacy and safety of an Avacopan based regimen in the treatment of newly diagnosed or relapsing patients with GPA and MPA. Specifically, the trial aimed to compare the ability of an Avacopan based regimen to induce and sustain remission in GPA and MPA patients against GC SOC, while assessing its GC-sparing benefits. The trial was conducted in 18 countries in North America, Europe, Australia, New Zealand, and Japan enrolling 331 patients [153, 155].

From Denmark participated six centers representing the five Danish regions.

7.1.1.1 Summery of key efficacy and safety findings

High-dose prednisone is considered the clinical comparator for Avacopan in the ADVOCATE study. The ADVOCATE study therefore included the following two treatment groups [153, 155]:

1. Control/SOC group: patients received Avacopan-matching placebo BID plus CYC or RTX, plus a full starting dose of prednisone (60 mg/day, tapered to discontinuation by 21 weeks).
2. Avacopan group: patients received Avacopan 30 mg BID plus CYC or RTX plus prednisone-matching placebo.

The trial assessed clinically relevant endpoints regarding disease remission, GC-related AEs and complications, QoL, renal function and relapse [153,155,156].

Sustained Disease remission:

- Significantly more patients achieved sustained remission with an Avacopan-based regimen over SOC at 52 weeks
- With an Avacopan-based regimen 72.3% patients achieved remission (BVAS = 0 and stopped all GCs) at 26 weeks compared with 70.1% for SOC (p<0.001 for non-inferiority)

Lower risk of relapse:

- A greater proportion of patients remained relapse-free and in remission over 52 weeks with an Avacopan-based regimen compared with SOC (65.7% vs. 54.9% respectively, p <0.001)
- Time to relapse (BVAS > 0) in patients who achieved BVAS = 0 (regardless of GC use in prior 4 weeks) at any point during the trial was greater for the Avacopan-based regimen group (HR 0.46 [95% CI 0.25,0.84])
- More than 2-fold less relapses occurred in the Avacopan based regimen group versus SOC (p <0.01)

Improved renal function:

- An Avacopan-based regimen significantly improved renal function vs a GC-based Regimen with patients transitioning from CKD stage 4 to CKD stage 3b.
- An Avacopan-based regimen may reduce the risk of ESRD in patients with progressive renal disease.
- Rise in eGFR at Week 26 and 52 was 5.8 and 7.3 mL/min/1.73 m2 in the Avacopan-based regimen group, compared with 2.9 and 4.1 mL/min/1.73 m2 in the SOC group (p=0.046 and 0.029 respectively)

Reduced need for glucocorticoids (GC) treatment:

- Patients on the Avacopan-based regimen had a significant reduction in GC cumulative exposure: the mean cumulative GC dose during the treatment period was 2.002,9 mg for an Avacopan-based regimen versus 4.382,3 mg for SOC.
- Treatment-related AEs and complications remained consistently lower in the Avacopan-based regimen group versus the SOC (p=0.008 at 26 weeks).
- Infection rates and serious infection rates were lower in the Avacopan-based regimen groups compared with the SOC group (15.2% vs 13.3% respectively).
- The greatest benefits from GC reduction were a decrease in BMI, glucose tolerance, skin complications, and rate of infections.

See Section 7.1.2 and Appendix D for details.

7.1.1.2 Study design

ADVOCATE was a randomised, blinded, active- controlled clinical trial designed to evaluate the efficacy and safety of an Avacopan based regimen in the treatment of newly diagnosed or relapsing patients with GPA and MPA. Specifically, the trial aimed to compare the ability of an Avacopan based regimen to induce and sustain remission in GPA and MPA patients against GC SOC, while assessing its GC-sparing benefits. [153, 155].

High-dose prednisone is considered the clinical comparator for Avacopan. The ADVOCATE study therefore included the following two treatment groups [153, 155]:
Control/SOC group: patients received Avacopan-matching placebo BID plus CYC or RTX, plus a full starting dose of prednisone (60 mg/day, tapered to discontinuation by 21 weeks).
Avacopan group: patients received Avacopan 30 mg BID plus CYC or RTX plus prednisone-matching placebo.

The treatment period of the study was 52 weeks, with a follow-up period of eight weeks off-treatment. Patients were eligible to take part in the ADVOCATE study if they, [153, 155]:

- Had a clinical diagnosis of GPA or MPA;
- Were aged at least 18 years (12-17 years where approved) with newly diagnosed or relapsed ANCA-AV where treatment with CYC or RTX was needed;
- Were using adequate contraception;
- Tested positive for anti-PR3 or anti-MPO (current or historic) antibodies;
- Had at least one major item, or at least three minor items, or at least the two renal items of proteinuria and haematuria in the BVAS;
- eGFR ≥15 mL/min/1.73 m^2 at screening;
- Were judged by the Investigator to be fit for the study, based on medical history, physical examination (including ECG), and clinical laboratory assessments.

Eligible patients were stratified based on [153, 155]:

- SOC regimen selected at the discretion of the investigator: IV RTX or IV/oral CYC followed by oral AZA (mycophenolate if AZA was contraindicated)
- Positive test for PR3- or MPO-ANCA at diagnosis
- Newly diagnosed or relapsing ANCA-AV

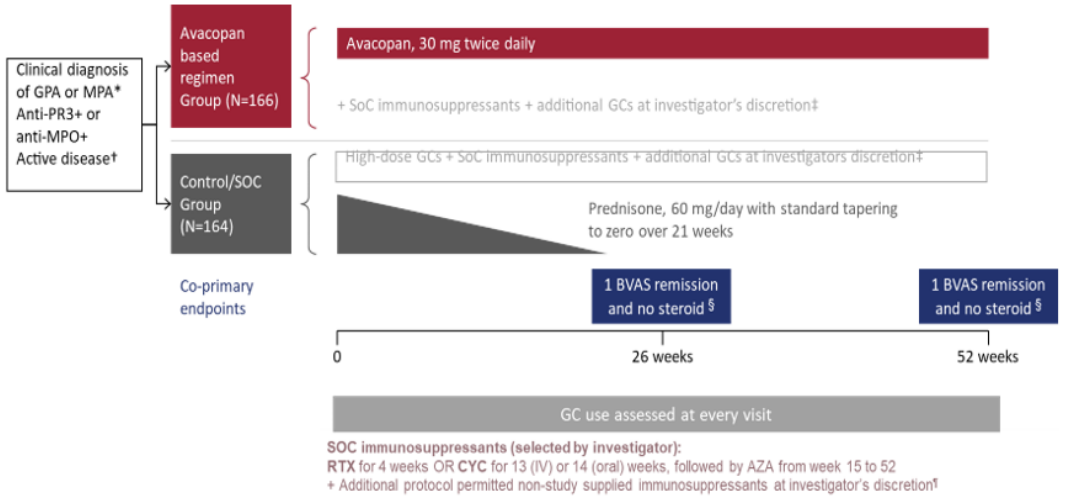
Efficacy data from the CLEAR and CLASSIC trials confirmed the 30 mg dose BID regimen as the preferred dose in treatment of patients with ANCA-AV [149, 152].

The dose regimens selected for oral prednisone, IV CYC, oral CYC, IV RTX, oral AZA, and oral MYC were in line with current standard clinical practice. RTX was at the time of the trial not approved post 4 weeks and therefore not part of study protocol past the 4 week timepoint [156].

Use of any drug other than protocol-specified avacopan or avacopan-matching placebo, oral prednisone or prednisone-matching placebo supplied as part of the study medication, IV or oral cyclophosphamide or rituximab, azathioprine, glucocorticoid pre-medication for rituximab infusions, medication to treat relapses, worsening of disease, or non-responders, or prophylactic medicine was prohibited over the course of the study [153, 155].

An overview of the ADVOCATE study design is given in **Fejl! Henvisningskilde ikke fundet.** and Table 13.

Figure 14 Advocate study design [153,155]



* Newly-diagnosed or relapsed, where treatment with CYC or RTX is needed;
† Patients must have ≥ 1 major item or ≥ 3 non-major items, or ≥ 2 renal items of proteinuria and haematuria on BVAS; ‡ after checking with medical monitor; § BVAS = 0 and no GCs in prior 4 weeks Protocol-permitted,
¶ Non-study supplied additional GCs given as accompanying RTX infusion as per RTX SmPC, tapering to 0 mg by week 4 of pre-randomisation GCs, resistant disease (within first 4 weeks), worsening of ANCA-AV (i.e. relapse), adrenal insufficiency.
ANCA-AV, ANCA-associated vasculitis; **AZA**, azathioprine; **BVAS**, Birmingham Vasculitis Activity Score, **CYC**, cyclophosphamide; **RTX**, rituximab, **SOC**, standard of care.

Table 13 Overview ADVOCATE study design [153,155]

Study	Phase 3-study ADVOCATE, Jayne, D.R.W., et al., *Avacopan for the Treatment of ANCAAssociated Vasculitis.* https://doi.org/10.1056/NEJMoa2023386, 2021.
Sample size (N)	330
Study design	Randomised, blinded, active- controlled clinical trial designed to evaluate the efficacy and safety of an Avacopan based regimen in the treatment of newly diagnosed or relapsing patients with GPA and MPA. The trial aimed to compare the ability of an Avacopan based regimen to induce and sustain remission in GPA and MPA patients against GC SOC, while assessing its GC-sparing benefits. Treatment period of the study was 52 weeks, with follow-up period of eight weeks off-treatment.
Patient population	Patients were eligible to take part in the ADVOCATE study if they [153,155]: • Had a clinical diagnosis of GPA or MPA; • Were aged at least 18 years (12-17 years where approved) with newly diagnosed or relapsed ANCA-AV where treatment with CYC or RTX was needed; • Were using adequate contraception; • Tested positive for anti-PR3 or anti-MPO (current or historic) antibodies; • Had at least one major item, or at least three minor items, or at least the two renal items of proteinuria and haematuria in the BVAS; • eGFR ≥15 mL/min/1.73 m^2 at screening; • Were judged by the Investigator to be fit for the study, based on medical history, physical examination (including ECG), and clinical laboratory assessments. Eligible patients were stratified based on [153,155]:

	• SOC regimen selected at the discretion of the investigator: IV RTX or IV/oral CYC followed by oral AZA (mycophenolate if AZA was contraindicated) • Positive test for PR3- or MPO-ANCA at diagnosis • Newly diagnosed or relapsing ANCA-AV
Intervention(s)	High-dose prednisone is considered the clinical comparator for Avacopan. The ADVOCATE study therefore included the following two treatment groups [153, 155]: **Avacopan group**: patients received Avacopan 30 mg BID plus CYC or RTX plus prednisone-matching placebo.
Comparator(s)	High-dose prednisone is considered the clinical comparator for Avacopan **Control/SOC group**: patients received avacopan-matching placebo BID plus CYC or RTX, plus a full starting dose of prednisone (60 mg/day, tapered to discontinuation by 21 weeks).
Follow-up period	Treatment period of the study was 52 weeks, with follow up period of 8 weeks off treatment
Is the study used in the health economic model?	Yes

7.1.1.3 Study objectives and endpoints

The primary objective of the study was to evaluate the efficacy of an Avacopan -based regimen to achieve and sustain remission in subjects with active ANCA-AV when used in combination with CYC followed by AZA, or in combination with RTX [153]. Primary endpoints, secondary endpoints and study definitions of remission and sustained remission are detailed in Table 14.

Study definitions of:
Remission is defined as: Proportion of patients in remission at week 26; defined as Birmingham Vasculitis Activity Score (BVAS) = 0 and not taking glucocorticoid for antineutrophil at week 26.

Sustained, steroid free remission is defined as: Proportion of patients achieving sustained remission at week 52; defined as remission at week 26 and week 52, without relapse through week 52, and not taking glucocorticoids for ANCA-associated vasculitis within 4 weeks before week 52.

Relapse is defined as > 1 major item in BVAS, > 3 minor items in BVAS, or 1 or 2 minor items in BVAS at 2 consecutive visits.

The overall efficacy hypotheses for the trial were [153]:

- Avacopan, in combination with RTX or with CYC followed by AZA (or MMF), is at least as effective as GCs for induction of remission in severe, active ANCA-AV;
- Control of disease activity will be achieved with less GCs, resulting in less GC-related AEs, complications and subsequent organ damage.

Table 14 ADVOCATE efficacy endpoint [153,155]

Endpoints in ADVOCATE	Definition/description
Primary	
Steroid-free remission	The proportion of patients in remission at Week 26; defined as Birmingham Vasculitis Activity Score (BVAS) = 0, and not taking glucocorticoids (GCs) for antineutrophil cytoplasmic antibody (ANCA)- associated vasculitis within 4 weeks before week 26.
Sustained steroid-free remission	Proportion of patients achieving sustained remission at week 52; defined as remission at week 26 and week 52, without relapse through week 52, and not taking glucocorticoids for ANCA-associated vasculitis within 4 weeks before week 52. Relapse is defined as ≥ 1 major item in BVAS, ≥3 minor items in BVAS, or 1 or 2 minor items in BVAS at 2 consecutive visits. and no GCs in prior 4 weeks protocol-permitted
Secondary	
Glucocorticoid-induced AEs and complications	Change from baseline, over the first 26 weeks, in the GTI
Early remission	BVAS of 0[a] at Week 4
Change in HRQoL	Change from baseline, over 52 weeks, as measured by the SF-36 v2 and EQ-5D VAS and index
Relapse	**Exploratory endpoint** Proportion of patients, and time to, experiencing a relapse after achieving remission. A relapse was defined as worsening of disease, after having previously achieved remission (BVAS = 0), that involved: • One or more major item in the BVAS, or • Three or more minor items in the BVAS, or • One or two minor items in the BVAS recorded at two consecutive study visits
Change in renal disease	**Exploratory endpoint** Change from baseline, over 52 weeks, of eGFR, UACR (if albuminuria diagnosed at baseline), and urinary monocyte chemoattractant protein-1 (MCP-1): creatinine ratio, measured in subset of patients with active renal disease at baseline
Change in cumulative organ damage	**Exploratory endpoint** Change from baseline of VDI scores
Safety	• Patient incidence of treatment-emergent SAEs (TESAEs), AEs, and withdrawals due to AEs • Change/shift from baseline from baseline in all safety laboratory parameters • Change from baseline in vital signs • Incidence of clinically significant ECG changes from baseline • The relationship of Avacopan/placebo as well as the relationship of GC use[b], CYC, RTX, and AZA or MYC use, to an AE • Safety endpoints of special interest: infections, hepatic system abnormalities, WBC count decreases, and hypersensitivity
Pharmacokinetic (PK) and pharmacodynamic (PD) endpoints	• Assessment of changes in PK markers in plasma and urine • Evaluation of the PD profile of Avacopan in subjects with ANCA-AV

AEs; Adverse Events; **AZA**, azathioprine; **BVAS**, Birmingham Vasculitis Activity Score; **CYC**, cyclophosphamide; **eGFR**, estimated glomerular filtration rate; **ECG**, Electrocardiogram; **EQ-5D VAS,** EQ-5D Visual Analogue Scale; **GC**, Glucocorticoids; **GTI**, Glucocorticoid induced AEs and complications; **HRQoL,** Health related quality of life; **MYC**, mycophenolate; **PD**; Pharmacodynamic; **PK**, Pharmacokinetic; **RTX**, rituximab; **SAEs**, Serious Adverse Events; **SF-36,** 36 item Short Form Survey; **TESAEs**, Treatment Emergent Serious Adverse Events; **UACR**, Urine Albumin to creatinine ratio; **VDI,** vasculitis damage index;
[a] as determined by the Adjudication Committee (AC) to ensure the consistency of data;
[b] based on EULAR-recommended event terms.

7.1.1.4 Study measures

The efficacy, safety, tolerability and pharmacokinetic (PK) measurements used in the ADVOCATE trial are widely used and generally recognised to be reliable, accurate, and relevant for the study design.

The Birmingham Vasculitis Activity Score (BVAS) is firmly established within the vasculitis community as the standard tool for measuring disease activity in ANCA-associated vasculitis studies, being used for eligibility and as an endpoint in all major vasculitis studies since its initial development in 1994 and current version in 2008 [234]**.**

BVAS form is divided into 9 organ-based systems, with each section including symptoms/signs that are typical of that particular organ involvement in systemic vasculitis. The clinician only scores features belived to be due to active vasculitis. Completion of the form provides a numerical score. Over the past years, there have been a number of changes to further improve the assessment form. Consequently, a newer version has been developed called BVAS V3.0 [108,239].

Table 15 The Birmingham Vasculitis Activity Score (BVAS) version 3 [240]

Manifestation	Definition	Persistent	New / Worse
1. General	**Maximum scores**	**2**	**3**
Myalgia	Pain in the muscles	1	1
Arthralgia or arthritis	Pain in the joints or joint inflammation	1	1
Fever ≥38° C	Documented oral / axillary temperature. If rectal temperature is measured, raise threshold to 38.5° C	2	2
Weight Loss ≥2 kg	Loss of dry body weight without dieting	2	2
2. Cutaneous	**Maximum scores**	**3**	**6**
Infarct	Area of tissue necrosis or splinter haemorrhages	1	2
Purpura	Subcutaneous or submucosal haemorrhage in the absence of trauma	1	2
Ulcer	A disruption in the continuity of the skin	1	4
Gangrene	Extensive tissue necrosis	2	6
Other skin vasculitis	Livedo reticularis, subcutaneous nodules, erythema nodosum, etc	1	2
3. Mucous Membranes / eyes	**Maximum scores**	**3**	**6**
Mouth ulcers / granulomata	Aphthous stomatitis, deep ulcers, strawberry gingival hyperplasia	1	2
Genital ulcers	Ulcers on the genitalia or perineum	1	1
Adnexal inflammation	Salivary or lacrimal gland inflammation.	2	4
Significant proptosis	>2 mm protrusion of the eyeball	2	4
Scleritis / Episcleritis	Inflammation of the sclera	1	2
Conjunctivitis / Blepharitis / Keratitis	Inflammation of the conjunctiva, eyelids or cornea - but not due to sicca syndrome	1	1
Blurred vision	Deterioration of visual acuity from previous or baseline	2	3
Sudden visual loss*	Acute loss of vision	*	6
Uveitis	Inflammation of the uvea (iris, ciliary body, choroid)	2	6
Retinal changes (vasculitis, thrombosis / exudate / haemorrhage)	Sheathing of retinal vessels or evidence of retinal vasculitis on fluorescein angiography; thrombotic retinal arterial or venous occlusion; soft retinal exudate (exclude hard exudates) / retinal haemorrhage	2	6

4. ENT	Maximum scores	3	6
Bloody nasal discharge / crusts / ulcers / granulomata	Bloody, mucopurulent, nasal secretion, light or dark brown crusts frequently obstructing the nose, nasal ulcers or granulomatous lesions observed on rhinoscopy	2	4
Paranasal sinus involvement	Tenderness or pain over paranasal sinuses (usually confirmed by imaging)	1	2
Subglottic stenosis	Stridor or hoarseness due to inflammation and narrowing of the subglottic area observed by laryngoscopy	3	6
Conductive hearing loss	Hearing loss due to middle ear involvement (usually confirmed by audiometry)	1	3
Sensorineural hearing loss	Hearing loss due to auditory nerve or cochlear damage (usually confirmed by audiometry)	2	6

5. Chest	Maximum scores	3	6
Wheeze	Wheeze on clinical examination	1	2
Nodules or cavities*	New lesions detected on imaging	*	3
Pleural effusion / pleurisy	Pleural pain and/or friction rub on clinical assessment; radiologically confirmed pleural effusion.	2	4
Infiltrate	Detected on chest X-ray or CT scan	2	4
Endobronchial involvement	Endobronchial pseudotumor or ulcerative lesions. NB: smooth stenotic lesions to be included in VDI; subglottic lesions to be recorded in the ENT section.	2	4
Massive haemoptysis / alveolar haemorrhage	Major pulmonary bleeding, with shifting pulmonary infiltrates	4	6
Respiratory failure	The need for artificial ventilation	4	6

6. Cardiovascular	Maximum scores	3	6
Loss of pulses	Clinical absence of peripheral arterial pulsation in any limb	1	4
Valvular heart disease	Clinical or echo detection of aortic / mitral / pulmonary valve involvement	2	4
Pericarditis	Pericardial pain / friction rub on clinical assessment	1	3
Ischaemic cardiac pain	Typical clinical history of cardiac pain leading to myocardial infarction or angina.	2	4
Cardiomyopathy	Significant impairment of cardiac function due to poor ventricular wall motion confirmed on echocardiography	3	6
Congestive cardiac failure	Heart failure by history or clinical examination	3	6

7. Abdominal	Maximum scores	4	9
Peritonitis	Typical abdominal pain suggestive of peritoneal involvement	3	9
Bloody diarrhoea	Of recent onset	3	9
Ischaemic abdominal pain	Typical abdominal pain suggestive of bowel ischaemia, confirmed by imaging or surgery	2	6

8. Renal	Maximum scores	6	12
Hypertension	Diastolic >95 mm Hg	1	4
Proteinuria	>1+ on urinalysis or >0.2g/24 hours	2	4
Haematuria	'Moderate' on urinalysis or ≥10 RBC per high power field, usually accompanied by red cell casts	3	6
Serum creatinine 125-249 µmol/L	At first assessment only	2	4
Serum creatinine 250-499 µmol/L		3	6
Serum creatinine ≥500 µmol/L		4	8
>30% rise in creatinine or >25% fall in creatinine clearance *	Progressive worsening of renal function. Can be used at each assessment if the renal function has deteriorated from prior value	*	6

9. Nervous system	Maximum scores	6	9
Headache	Unaccustomed & persistent headache	1	1
Meningitis	Clinical evidence of meningism	1	3
Organic confusion	Impaired orientation, memory or other intellectual function in the absence of metabolic, psychiatric, pharmacological or toxic causes.	1	3
Seizures (not hypertensive)	Clinical or EEG evidence of aberrant electrical activity in the brain	3	9
Stroke	Focal neurological signs lasting >24 hours due to a CNS vascular event	3	9
Spinal cord lesion	Clinical or imaging evidence of spinal cord involvement	3	9
Cranial nerve palsy	Clinical evidence of cranial nerve palsy – score VIII nerve palsy as sensorineural hearing loss, do not score ocular palsies if they secondary to pressure effects	3	6
Sensory peripheral neuropathy	Objective sensory deficit in a non-dermatomal distribution	3	6
Mononeuritis multiplex	Single or multiple specific motor nerve palsies	3	9

Rules for scoring BVAS:

1. Disease manifestations are scored only when they are attributable to active vasculitis. The manifestation should not be scored if there is reasonable evidence of another aetiology for the symptoms e.g. infection, drug reaction, other co-morbidity.
2. Tick "Persistent Disease" box if all the abnormalities are due to active (but not new or worse) vasculitis. 3. Specialist opinion, or the results of laboratory or imaging investigations will be required for some items. Excepting those circumstances, the whole form should be completed at the time of the consultation.
4. The bands of serum creatinine should be scored only on the first visit.
5. Items marked with an asterisk (*) are not compatible with 'persistent' disease. These manifestations always suggest new or worse disease when due to active vasculitis.

The BVAS used in ADVOCATE was BVAS 3 (cf. Table 15) with minor changes as outlined in the protocol. For the week 4 BVAS assessment, disease activity within 7 days prior to the week 4 visit was assessed. The BVAS looked at active disease, so the persistent label was removed. In addition, since hematuria is such an important sign in AAV but is often overlooked, it was pulled specifically into the 'Other' category so it could not be missed [153]. These changes improve the utility of BVAS in looking at active disease [153]. Another reference is Merkel et al *J Rheumatol* 2011 Jul; 38(7):1480-1486 which describes the validation of BVAS 3 compared to the older versions [233].

It should be noted, though, that while the BVAS can be scored on an ordinal scale with points assigned to individual disease activity items (see references) its implementation in the ADVOCATE study did not directly reference this. Participants were enrolled based on "At least one major item, or at least 3 minor items, or at least the 2 renal items of proteinuria and hematuria in the BVAS" and the primary endpoints of remission and sustained remission were defined using BVAS on a binary scale (i.e. BVAS = 0 versus BVAS > 0).

The Glucocorticoid Toxicity Index (GTI) was developed to score glucocorticoid toxicity [136]. The two scores, elaborated in version 2 of the instruments [136, 241] contains the Cumulative Worsening Score (CWS) that captures cumulative improvement and worsening of toxicity over time, and the Aggregate Improvement Score (AIS) that captures both improvement and worsening of toxicity over time.

The two different scores (CWS and AIS) differ in ways that affects their interpretation. Therefore, it is only possible to build a complete picture by considering both scores together:

- CWS will be always positive and as toxicity is experienced by the patient it will be added to the score. Therefore, it will be less important as to whether the patient starts with a high baseline or a low baseline but doesn't capture whether toxicity is temporary.
- AIS will be positive or negative because if GC toxicity resolves over time it is subtracted from the score. However, if a patient has a low baseline, there is less room for them to improve over time and an effective steroid sparing agent might actually result in no change whereas it could have resulted in a negative score (e.g. improvement) if the patient had started from a high score.

That does means is that any differences observed with the AIS could be a lower bound, depending on the baseline GTI domain measurements, because the AIS alone can't distinguish a low baseline (no room to improve) from no improvement (despite a high baseline and room to improve). The way to resolve this should be to compare AIS and CWS domain by domain.

Stone et al 2022 have in a review of GTI, its development and properties also looked in details at the GTI in the ADVOCATE study, including presenting a domain-specific analysis for AIS and CWS [242].

The pharmacodynamic (PK) measures were exploratory. Brief description of the measures used in the study can be found in Appendix D.

7.1.1.5 Statistical considerations

The analysis of the efficacy endpoints was conducted when all randomised subjects completed at least the Week 52 study visit. Data were summarised descriptively by treatment group. For continuous variables, numbers, means, medians, ranges, standard deviations (SDs), and standard error of means (SEMs) 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 presented for categorical variables [149].

The two primary efficacy end points were the proportion of patients who (1) achieved remission at week 26 and (2) sustained remission at week 52. For each primary efficacy end point, noninferiority of the avacopan group to the prednisone group was tested using a one-sided testing procedure (or equivalently, using a one-sided confidence interval [CI]) and a non-inferiority limit of –0.20. Subject to the procedures for controlling the overall Type I error, a test for avacopan superiority could also be performed for each primary efficacy end point. To preserve the overall Type I error at the 0.05 level for testing two primary efficacy end points and two tests of noninferiority and superiority for each primary efficacy end point, the hierarchical procedure was implemented: (1) non-inferiority at week 26, (2) non-inferiority at week 52, (3) superiority at week 52, and (4) superiority at week 26. The Summary score test [223] was used for both noninferiority and superiority tests of the stratified analyses of the two primary efficacy end points. The stratification factors were the same factors used in the randomization stratification: either newly diagnosed or relapsing vasculitis, PR3 or MPO-ANCA, and cyclophosphamide or rituximab treatment. Summary score estimates [223] of the common difference in remission rates between the avacopan and prednisone groups were provided using inverse-variance stratum weights and Miettinen-Nurminen (score) confidence limits for the common difference in remission rates. Primary end point analyses were conducted after all patients have completed the 52-week treatment period. No interim analyses were performed.

The primary efficacy analyses were conducted on the modified intention-to-treat population defined as all randomized patients who received at least one dose of study medication (avacopan/placebo). Per-protocol analyses were also conducted where patients with major

eligibility criteria deviations and missing week 26 data were excluded, and non-remission was imputed for patients who were <75% compliant with taking study medication based on returned capsule count, or used non-allowed immunosuppressants during the treatment period. For the primary end points, if the lower bound of the 2-sided 95% confidence interval for the difference (avacopan group minus prednisone group) in remission rate was greater than –0.20, the avacopan group would be considered not inferior to the prednisone group. If the lower bound was greater than 0.0, the avacopan group would be considered superior to the prednisone group. For the primary end points, missing data at week 26 and week 52 were imputed as not being in remission. For the week 26 remission end point, 10 patients in each group had missing data. For the week 52 sustained remission end point, 15 patients in the avacopan group and 12 patients in the prednisone group had missing data.

Other binary end points were analysed similarly to the primary end points. Continuous variables were analysed using mixed effects models for repeated measures (MMRM). The least squares means (LSMs), standard errors, and CIs are from models incorporating treatment group, visit, treatment-by-visit interaction and stratification factors as covariates. Longitudinal measurements from the same patients were considered as repeated measure units in the model. In the MMRM model, missing data were not imputed. This analysis is unbiased under the missing at random assumption. A compound symmetry covariance matrix was used to model the within-subject variance-covariance structure for the model errors. For the secondary end points, point estimates and 95% CIs are presented as no multiple comparison adjustments were made and no definitive conclusions can be drawn.

Analysis population

For the purposes of data analysis, four populations were defined as follows [153, 155]:

- Randomised Population: all subjects who provided written informed consent and were randomised in the study
- Intent-to-Treat (ITT) Population: all subjects who were randomised in the study and who received at least one dose of blinded study drug
- Safety Population: all subjects who were randomised and had received at least one dose of study drug
- Per Protocol (PP) Population: all subjects in the ITT population who were compliant with taking Avacopan/placebo and who did not have major protocol deviations that could have significantly affected the interpretation of the results.

Unless specified, efficacy data presented in subsequent sections are for the ITT population follows [153, 155, 184].

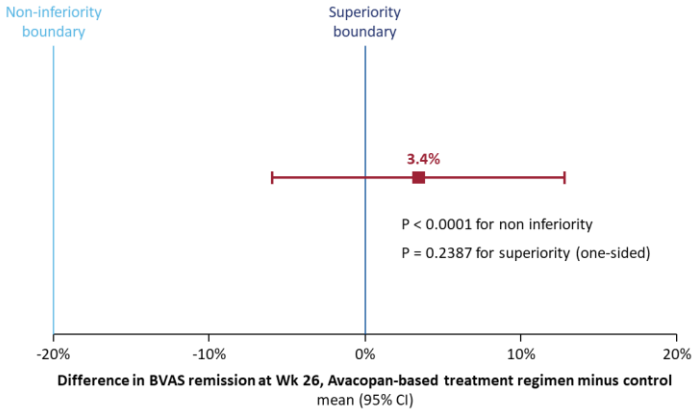
7.1.2 Efficacy and safety – ADVOCATE

7.1.2.1 Efficacy of Avacopan

A total of 120 of 166 patients (72.3%) in the Avacopan-based regimen group achieved remission (BVAS=0, without the use of GCs in the prior 4 weeks), at Week 26. 115 of 164 subjects (70.1%) in the Soc control group achieved remission at the same time-point. See **Fejl! Henvisningskilde ikke f undet.**, and **Fejl! Henvisningskilde ikke fundet.** in the next subsection [184].

Whilst no statistical difference in rate of remission at Week 26 was detected between the groups, these data suggest that an Avacopan-based regimen can control ANCA-AV as rapidly as SOC and substantially reduce the use of GCs by a cumulative 2.7-fold [155].

Figure 15 Difference in BVAS remission at week 26. Avacopan-based regimen minus control mean (95% CI) [156]



BVAS Remission BVAS of zero and no GCs for ≥ 4 weeks. BVAS, Birmingham Vasculitis Activity Score

Sustained, steroid-free remission

In the ADVOCATE trial, superior efficacy was observed in the Avacopan-based regimen group compared with the SOC group based on sustained remission at Week 52. In addition, improvement in HRQoL measurements and renal function, and a lower relapse rate, together with lower treatment-related AEs and complications associated with less GC use were observed [155].

Remission is defined as: Proportion of patients in remission at week 26; defined as Birmingham Vasculitis Activity Score (BVAS) = 0 and not taking glucocortioid for antineutrophil at week 26.

Sustained, steroid free remission is defined as: Proportion of patients achieving sustained remission at week 52; defined as remmision at week 26 and week 52, without relapse through week 52, and not taking glucocorticoids for ANCA-assocoated vasculitis within 4 weeks before week 52.

Relapse is defined as > 1 major item in BVAS, > 3 minor items in BVAS, or 1 or 2 minor items in BVAS at 2 consecutive visits.

A total of 109 of 166 patients (65.7%) achieved sustained disease remission at Week 52 in the Avacopan-based regimen group compared with 90 of 164 subjects (54.9%) in the SOC group (Table 16, **Fejl! Henvisningskilde ikke fundet.**). The rate of sustained remission at Week 52 was significantly higher in the Avacopan-based regimen group compared with the prednisolone group (65.7 vs. 54.9%; p=0.0066). Treatment with an Avacopan-based regimen was demonstrated to be more successful at keeping patients relapse-free and in remission over the 52 week period than is possible with current SOC [155].

Table 16 Proportion of patients with remission and sustained remission (ITT Population) [155,184]

Treatment	N	n	%	95% CI[a]	Diff. in %	Est. of Common Diff. in %[b]	Two-sided 95% CI for Diff. in %[c]	Non-inferior P-value	Superior P-value
Remission (Week 26)									
SOC	164	115	70.1	62.5, 77.0	2.2	3.4	-6.0,12.8	<0.0001	0.2387
Avacopan	166	120	72.3	64.8,78.9					

based regimen									
Sustained remission (Week 52)									
SOC	164	90	54.9	46.9, 62.6	10.8	12.5	2.6, 22.3	<0.0001	0.0066
Avacopan based regimen	166	109	65.7	57.9, 72.8					

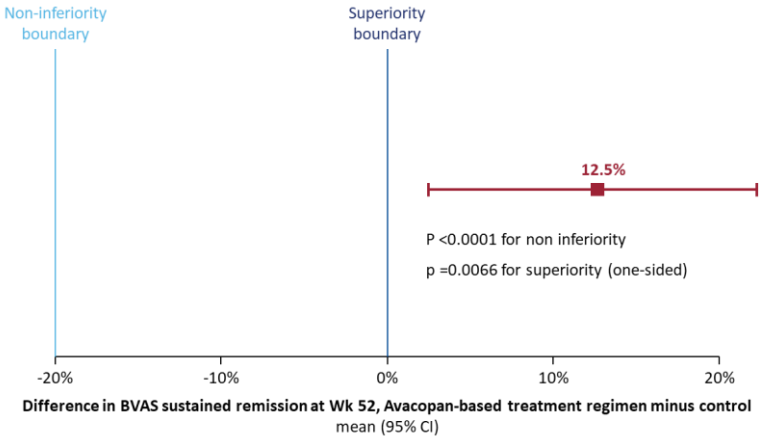
CI=confidence interval; **Diff**.=difference; **ITT**=intent to treat; **N**=number of subjects in the analysis population for the specified treatment group; **n**=number of subjects with disease remission; **%**=100*n/N

[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

Figure 16 Difference in BVAS sustained remission at week 52, Avacopan-based regimen minus control mean (95% CI) [156]



BVAS sustained remission: BVAS of zero at week 26 without relapse to week 52, and no GCs for ≥4 weeks at week 52. BVAS Birmingham Vasculitis Activity Score

Subgroup analysis

The ADVOCATE study was not designed nor powered to provide definitive results regarding pre-specified subgroups.

Treatment with an Avacopan-based regimen rather than SOC resulted in a greater proportion of patients in sustained disease remission in all subgroups of interest, with the greatest differences seen in patients with relapsed ANCA-AV, patients receiving RTX, patients with MPA, and patients with MPO+ ANCA-AV [164], Outcomes for these subgroups at weeks 26 and 52 are summarised in Table 17 and Table 18 [155.a, 184].

We refer to tables S8 covering subgroups week 26 and S9 covering subgroups week 52 in the supplementary appendix to Jayne et al [155.a]. For more results from the subgroup of patients with GPA and MPA we refer to the attached Appendix M where further details are described. It should be noted, however, that consideration of efficacy by GPA and MPA classification was not statistically powered and is confounded by differences in baseline factors known to correlate with clinical outcomes (for example, differences in baseline renal function).

Table 17 Proportion of Subjects with Disease Remission at week 26 by Stratification Factor and Subgroup in ADVOCATE Study (ITT Population) [184]

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

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

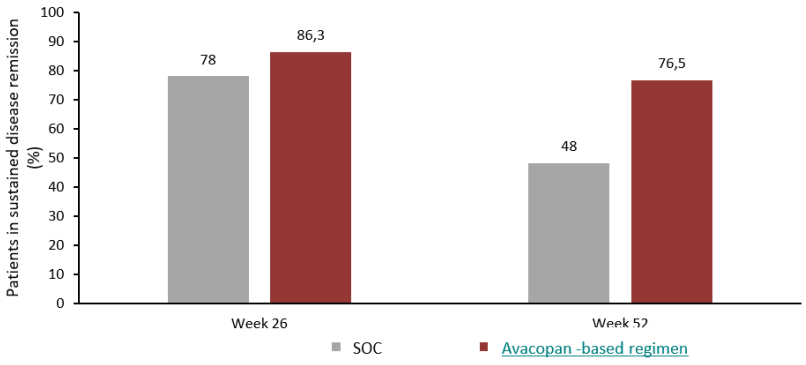
Table 18 Proportion of Subjects with Sustained Disease Remission at Week 52 by Stratification Factor and Subgroup in ADVOCATE Study (ITT Population) [184].

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

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

In the relapsing disease subgroup 78.0% and 86.3% of SOC and Avacopan-based regimen patients were in remission at week 26. However, by week 52, 48.0% of SOC patients were in sustained remission versus 76.5% of Avacopan-based regimen patients (see Table 18) indicating that treatment with an Avacopan-based regimen results in fewer disease relapses than SOC [155, 184].

Figure 17 Patients with relapsing disease in sustained disease remission in the ADVOCATE trial at week 26 and 52 (ITT population) [155]



Greater efficacy was also seen in the RTX treatment subgroup, in which sustained remission was achieved at week 52 by 56.1% and 71.0% of the SOC control group and Avacopan-based regimen groups respectively (p<0.0001). At the same timepoint 70.2% of Anti-MPO+ patients treated with an Avacopan-based regimen were in sustained remission versus 53.2% of that subgroup treated with SOC control group [155].

In the GPA subgroup 72.2% of SOC patients, and 71.4% of Avacopan-based regimen patients had achieved remission by week 26, and at week 52 rates of sustained remission had decreased to 57.8% and 61.5% respectively. Rates of remission at week 26 were comparable in the MPA cohort, with 67.6% and 73.3% of SOC and Avacopan-based regimen patients in remission at this timepoint, however, at week 52 the proportion of patients in sustained remission had fallen to 51.4% amongst patients treated with SOC versus 70.7% of those treated with an Avacopan-based regimen Table 17 and Table 18 [155,184].

Lower risk of relapse

The number of patients experiencing relapse after achieving remission (BVAS=0) at Week 26 was lower in the Avacopan-based regimen group compared with the control SOC group (7.5% vs. 12.2%), (Table 19) [155, 184].

Relapse is defined as > 1 major item in BVAS, > 3 minor items in BVAS, or 1 or 2 minor items in BVAS at 2 consecutive visits.

Table 19 Proportion of patients experiencing a relapse after previously achieving remission at Week 26 (ITT population) [184]

Treatment	N	N	%	95% CI[a]	Diff. in %	Est. of Common Diff. in %[b]	Two-sided 95% CI for Diff. in %[c]	Superior P-value
Relapse after previous remission (BVAS=0) at Week 26								
SOC	115	14	12.2	6.8, 19.6	-4.7	-6.0	-14.4, 2.4	0.0810
Avacopan based regimen	120	9	7.5	3.5, 13.8				

CI=confidence interval; **Diff**.=difference; **ITT**=intent to treat; **N**=number of subjects in the analysis population for the specified treatment group; **n**=number of subjects with disease remission; **%** = 100*n/N

[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 after achieving remission (BVAS=0) at any point during the study showed a lower rate of relapse (10.1% vs. 21.0%) and a 54% significantly lower relative risk of relapse (HR: 0.46, 95% CI (0.25, 0.84), p=0.0091) in the Avacopan-based regimen group compared with control SOC group [156]

Table 20 Exploratory analysis of rate of relapse after any time point when remission (BVAS=0) was achived (ITT population) [156]

Statistic	SOC (N=164)	Avacopan-based regimen (N=166)
Number of patients who achieved BVAS=0	157	158

Number of patients experiencing relapse after BVAS=0 was achieved, n (%)*	33 (21.0)	16 (10.1)
Number of patients censored, n (%)	124 (79.0)	142 (89.9)
Treatment Comparison (vs. SOC)		
Hazard Ratio (HR)	NA	0.461
95% CI for HR	NA	0.254, 0.838
P-value	NA	0.0091

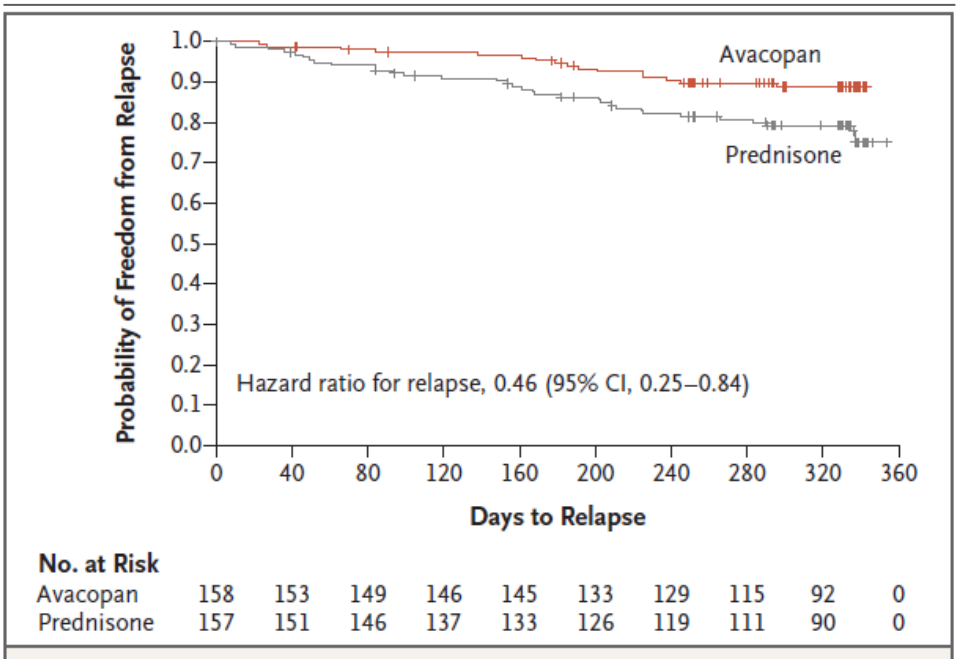
BVAS, Birmingham Vasculitis Activity Score; **CI,** confidence interval; **ITT,** intent to treat; **N,** Number of subjects in the ITT Population. N' = number of subjects who achieved BVAS=0 during the 52-week treatment period and is used as the denominator for percentage calculations; n (%) = number of subjects in the specified category.
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.

*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 one or more major items in the BVAS, three or more minor items in the BVAS, or one or two minor items in the BVAS recorded at two consecutive trial visits. A total of 16 of 158 patients (10.1%) in the Avacopan-based regimen group and 33 of 157 patients (21.0%) in the SOC group had relapses

Fejl! Henvisningskilde ikke fundet. shows the probability of remaining relapse-free* after induction of remission for patients in the Avacopan-based regimen arm and those in the comparator SOC arm [155, 184].

*Absence of worsening of disease, as measured by BVAS, with no involvement of major items in the BVAS, less than three minor items in the BVAS, and no minor items in the BVAS recorded at two consecutive trial visits.

Figure 18 kaplan-Meier Plot of time to relaps (ITT population). [155, 184]



A relapse was defined as worsening of disease, after previous achievement of a Birmingham Vasculitis Activity Score (BVAS) of 0 (on a scale from 0 to 63, with higher scores indicating greater disease activity), that involved one or more major items in the BVAS, three or more minor items in the BVAS, or one or two minor items in the BVAS recorded at two consecutive trial visits.

A total of 16 of 158 patients (10.1%) in the avacopan group and 33 of 157 patients (21.0%) in the prednisone group had relapses. A test of proportionality was performed by incorporating a time-varying covariate in the Cox regression model by creating an interaction of the treatment groups and log of the time to relapse. The Wald chi-square test for the interaction term was 0.48. The corresponding P value was 0.49, which indicates no significant evidence of nonproportionality of the hazard. Tick marks indicate censored data [155].

For number of subjects censored at each time point for time to relapse are attached in the two confidentielle Appendix AA Table MHRA9 and Appendix AH Figure FDK.1.

Improved renal function

Change from baseline in kidney function, as measured by eGFR, was assessed in patients with renal disease (based on the BVAS renal component at baseline). At baseline, mean kidney function was 45.6 and 44.6 mL/min/1.73 m^2 in the SOC control and Avacopan-based regimen groups respectively. Treatment with an Avacopan-based regimen had a significant beneficial effect on kidney function at both Week 26 and Week 52, with increases in eGFR of 5.8 and 7.3 mL/min/1.73 m^2 seen in the Avacopan-based regimen group compared with 2.9 and 4.1 mL/min/1.73 m^2 in the SOC control group (p=0.046 and 0.029 respectively) [155, 156] (Table 21, **Fejl! Henvisningskilde ikke fundet.**).

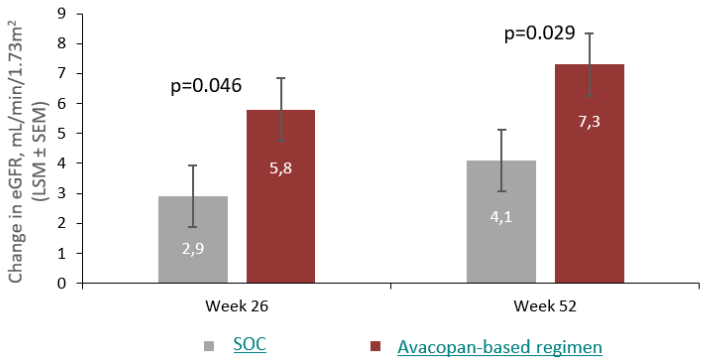
In patients with ANCA-AV patients with renal disease and baseline eGFR <30ml/min/1.73m^2, 5 year risk of ESRD was lower in the Avacopan-based regimen group than SOC (7.9% versus 10.9%) [155]. Patients with CKD stage 4 at baseline (eGFR <30 mL/min/1.73m2) improved to CKD stage 3b after 52 weeks of treatment with the Avacopan-based regimen [155, 156].

Table 21 Change in eGFR in patients with renal disease at baseline (ITT population) [155, 156]

Treatment	N	n[a]	Baseline kidney function (eGFR) mL/min/1.73 m^2	LSM increase in eGFR at Week 26 mL/min/1.73 m^2	p-value	LSM increase in eGFR at Week 52 mL/min/1.73 m^2	p-value
Kidney function in all patients with renal disease at baseline							
SOC	134	134	45.6	2.9	0.046	4.1	0.029
Avacopan based regimen	134	131	44.6	5.8		7.3	
Kidney function stratified by renal disease severity at baseline							
SOC	48	48	<30 mL/min/1.73 m^2	-	-	13.7	0.0050
Avacopan	52	52		-	-	8.2	
SOC	51	51	30 to 59 mL/min/1.73 m^2	-	-	10.5	0.2115
Avacopan-based regimen	46	46		-	-	7.8	
SOC	35	35	>59 mL/min/1.73 m^2	-	-	5.9	0.6721
Avacopan-based regimen	33	33		-	-	7.5	

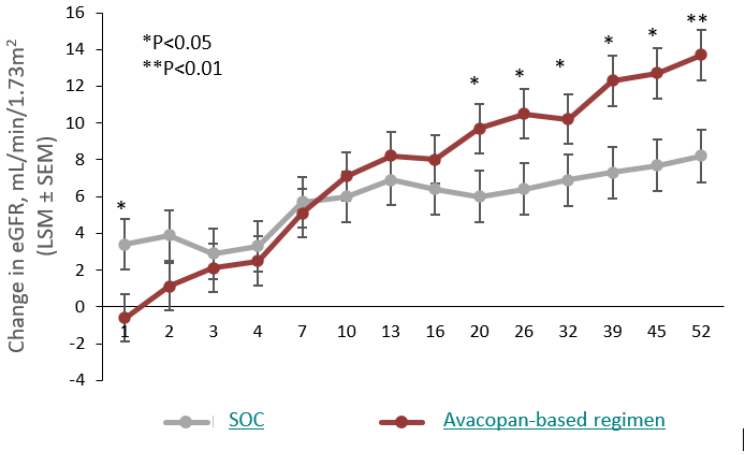
[P]Patients with renal disease at baseline (based on the BVAS renal component), **LSM** = Least Squares Mean

Figure 19 Change from baseline in eGFR in patients with renal disease at baseline (based on BVAS) (ITT Population) [156]



Improvement in kidney function was most prominent in patients with the most severe renal disease (eGFR <30 mL/min/1.73 m2 at baseline). For this subgroup, the increase in eGFR in the Avacopan-based regimen group was 13.7 mL/min/1.73 m2 at Week 52 compared with 8.2 mL/min/1.73 m2 in the SOC group (p=0.0050) (**Fejl! Henvisningskilde ikke fundet.**) [156].

Figure 20 Change from baseline in eGFR in patients with renal disease and eGFR < 30 at baseline [156]



These data confirmed the renal benefit seen in the CLEAR study, where haematuria and eGFR improved similarly across all three treatment groups, and the urinary MCP-1:creatinine ratio improved (decreased) 50% (p=0.02 vs. the SOC control group) in both Avacopan based regimen groups combined, compared with 43% in the SOC control group at Week 12 [149].

In the ADVOCATE trial, although improvement in UACR at Week 52 was similar between the treatment groups (-74% in the Avacopan-based regimen group compared with -77% in the SOC group), this measure on average decreased 40% in the Avacopan-based regimen group earlier, at week 4, compared with no change in the SOC group (p<0.0001) [156].

These findings were consistent with the CLEAR trial, where there was a faster improvement from baseline in UACR in the Avacopan-based regimen group compared with the SOC group. At week 4, there was a mean decrease of 41% (p<0.0001 vs SOC) in both Avacopan-based regimen groups

compared with a 2% increase in UACR in the SOC group. Similarly, mean decrease from baseline in urinary MCP-1 excretion was significantly higher in the Avacopan-based regimen group compared with the SOC group at Week 13 (-59% vs. -52%, p=0.03), but there was no significant difference between groups for this measure at Week 52, where mean decrease from baseline was -71% in the SOC group and -73% in the Avacopan-based regimen group [149,156].

Reduced glucocorticoid AEs and complications

An Avacopan-based regimen reduces the need for GC treatment in ANCA-AV patients. Over 52 weeks, GC exposure in the Avacopan-based regimen group was 64% less with the mean cumulative GC dose during the treatment period being 2.002,9 mg for an Avacopan-based regimen versus 4.382,3 mg for SOC (Figure 21**Fejl! Henvisningskilde ikke fundet.**). Sources of additional, non-study supplied GCs in both groups were tapering in first 4 weeks from pre-randomisation GC dosing, GC from co-administration with RTX (65% of all subjects) over 1st four weeks, and off-protocol GC use (for ANCA-AV relapse or no improvement in major BVAS item in the first 4 weeks) as prescribed by clinician. [155]. 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. [155, 156].

The fact that similar results were obtained using multiple distinct analytic strategies reinforce the validity and relevance of the observations related to reduced glucocorticoid use. In addition, the terms used to determine the GC-relevance of given adverse event were drawn from an independent source and defined prior to unblinding.

• For the analysis of sponsor-defined GC associated TEAEs, a list of preferred terms was developed from the list of the adverse consequences of GCs described in the EULAR recommendations on the management of medium to high-dose GCs in rheumatic diseases [135]. This list was documented in the ADVOCATE statistical analysis plan prior to unblinding (Appendix 15.5) Table 22 below. It is acknowledged that each individual term may represent other aetiologies than GCs, but even then it would be argued that GCs are an important contributing factor. For example, osteoporosis may be related to age or long-term calcium/vitamin D deficiency but it is inarguable that GC use exacerbates bone loss. This analysis was performed independently of investigator or patient attribution of adverse events to glucocorticoids, minimising the attribution risk described above.

Table 22 Preferred Terms of Adverse Events Potentially Associated with Glucocorticoid-Related Toxicity

Preferred Terms may be clustered according to EULAR terms (defined below).

Sponsor-defined GC-associated TEAE EULAR Terms and Cluster Designations		
Terms included in EULAR recommendations		For analysis
EULAR category/SOC	EULAR event term	Cluster designation
Cardiovascular	Dyslipidemia	Dyslipidemia
	Edema	Edema
	Ischemic CVD/atherosclerosis	CVD
Infectious	Infections	Infections
Gastro-intestinal	Peptic ulcer disease	Peptic ulcer disease
	Pancreatitis	Pancreatitis
Psychological	Mood disturbances	Mood disturbance
	Psychosis	Mood disturbance
Endocrine, metabolic	Diabetes/glucose intolerance	Hyperglycemia
	Body weight and fat redistribution	Body weight and fat redistribution
	Interference with hormone secretion	Interference with hormone secretion
Dermatological	Skin atrophy	Skin
	Acne, hirsutism, alopecia, bruisability	Skin
Musculoskeletal	Osteoporosis	Bone
	Osteonecrosis	Bone
	Myopathy	Myopathy
Ophthalmological	Cataract	Ophthalmological
	Glaucoma (intra-ocular pressure)	Ophthalmological

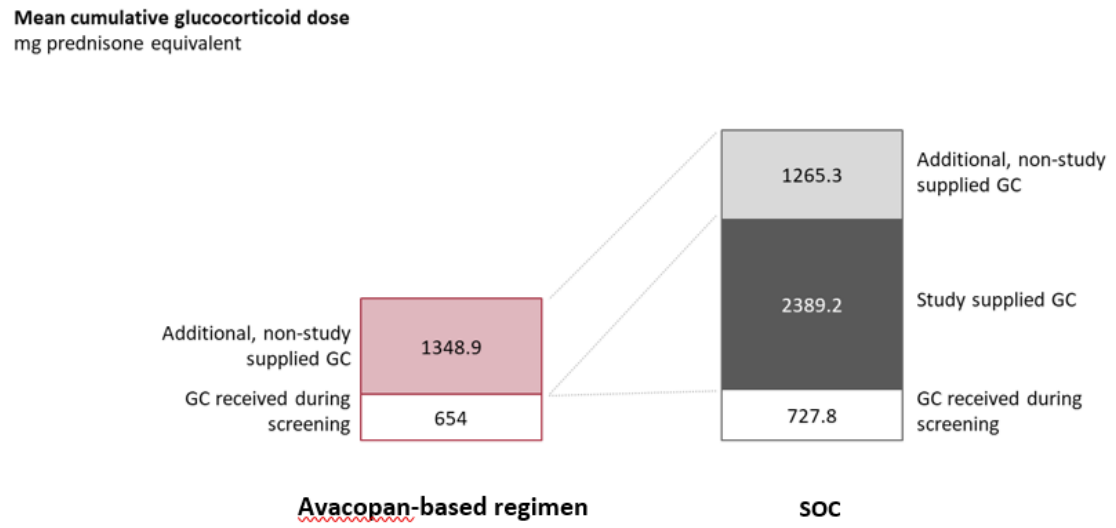
• Nonetheless, when Investigator attribution of AEs to GCs was examined in a separate analysis, reduced GC-related adverse events were still observed both when AEs and SAEs were considered. The majority of these were in infections and infestations and skin MedRA SOCs, which it would be anticipated should be identified consistently regardless of any beliefs an individual Investigator may have formed around treatment allocation.

•Recognising that no one method of assessing the impact of GC use is perfect, the Glucocorticoid Toxicity Index was also implemented in the study as another means of assessing the impact of GC exposure, this time using a validated index to represent GC-induced toxic effects on two numeric scales. The results of this analysis was consistent with the other analyses again suggesting that reduced GC use in the avacopan arm resulted in less GC-related toxicity.

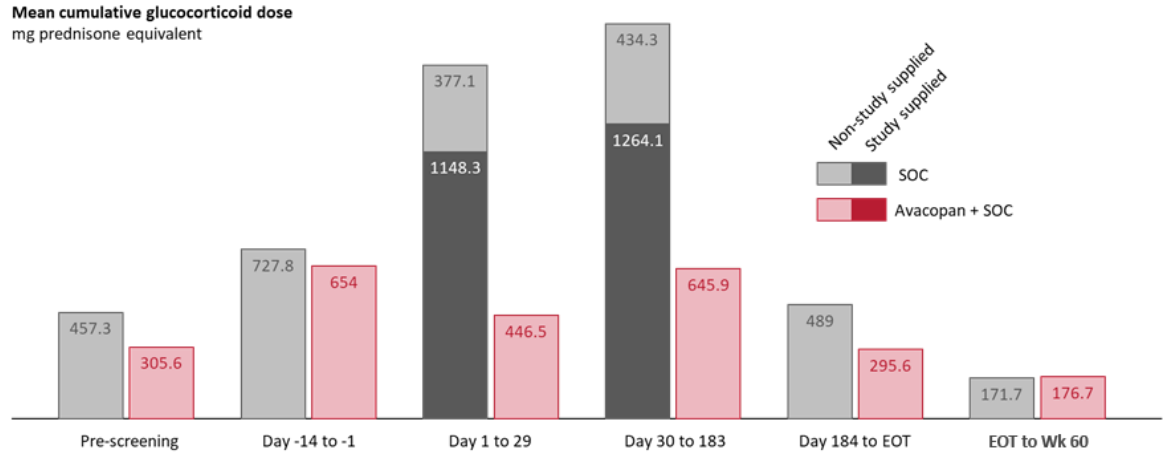
• Finally, a question was raised as to the practicality of blinding patients and investigators to GCs, given their well-known adverse effects at high doses. Both the study protocol and Investigator training emphasises the importance of an unbiased approach to adverse event reporting and the use of a double-blind design also crucially ensures ambiguity. Each individual site recruited comparatively few participants, which also helps maintain blinding and it should be noted that many participants in the avacopan group were receiving GCs on Day 1 (as permitted by the protocol), which were then rapidly tapered to zero. The limited GC exposure in the avacopan group was clinically necessary (glucocorticoids should generally be tapered not abruptly ceased) but had an additional benefit of further reducing the likelihood that Investigators could correctly 'guess' treatment allocation.

Figure 21 Mean cumulative glucocorticoid dose over time in the ADVOCATE trial (ITT population) A overall and B by time period [155]

A



B



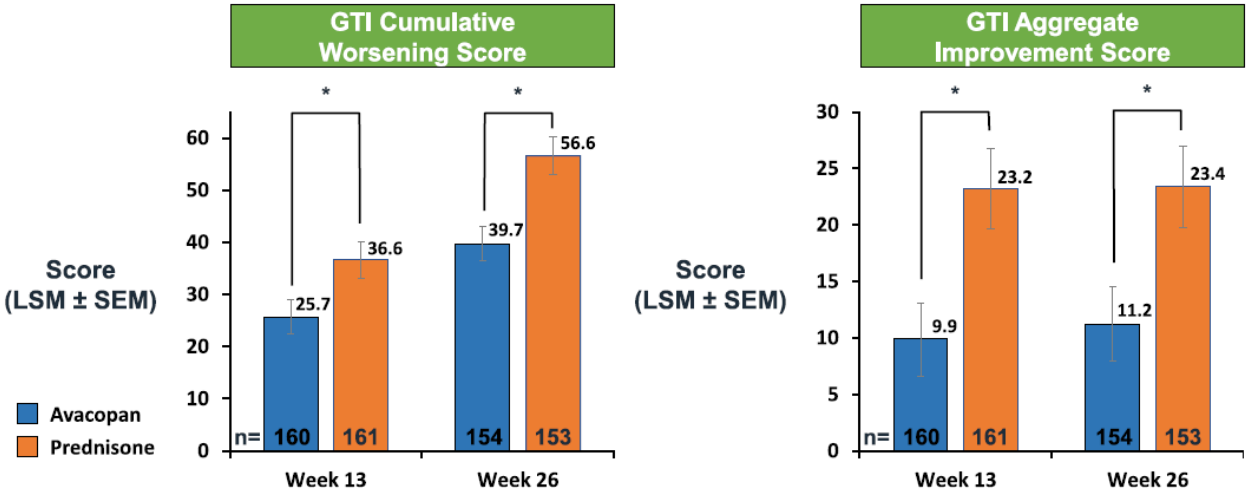
In addition to recording the cumulative use of glucocorticoid over the course of the ADVOCATE trial, different measures of glucocorticoid AEs and complications were also taken. The Glucocorticoid AEs and complications Index (GTI) is a measure of side effects related to the use of GCs comprising the Cumulative Worsening Score (CWS) and the Aggregate Improvement Score (AIS). Increases in both the CWS and AIS indicate increased GC AEs and complications.

Per protocol GTI was performed on day 1 (as baseline), Week 13 and Week 26. The choice of these 13- and 26-week time point assessments of GTI links primarily to the treatment duration of prednisone in ADVOCATE. This covered a period of 20 weeks with subsequent carry-over of side effects. In addition, non-study supplied GCs were given during the following six weeks (from Week 21 until Week 26) in both treatment groups so needed to be accounted for in the assessment of the GTI [153]. The final measure' analysis referred to in Table 21 uses the last available GTI value. It includes all GTIs at week 26 and where this is missing the GTI at week 13 is used. This is a valid

approach given that missing data at Week 26 were balanced between treatment arms, and in conservative given that the adverse impact of glucocorticoids accrues over time.

Treatment with Avacopan-based regimen in the ADVOCATE trial was seen to lead to a significantly lower level of glucocorticoid AEs and complications compared with SOC, as seen by lower GTI-CWS and GTI-AIS at weeks 13 and 26 (**Fejl! Henvisningskilde ikke fundet.** a and b). At Week 13, the least squares mean (LSM) of the GTI-CWS was 36.6 in the SOC group compared with 25.7 in the Avacopan-based regimen group (p=0.0140). At Week 26, the GTI-CWS were 56.6 and 39.7, respectively (p=0.0002). At the same timepoint, the LSM of the GTI-AIS was 23.2 in the SOC group compared with 9.9 in the Avacopan-based regimen group (p=0.003), and at Week 26, the GTI-AIS were 23.4 and 11.2, respectively (p=0.008) [155, 156]. The p-values for GTI-CWS and AIS are for superiority.

Figure 22 GTI scores in the ADVOCATE trial at weeks 13 and 26. Left: the Cummulative Worsening Score (CWS). Right Aggregate Improvement Score (AIS) [155,156,242]



Abbreviations: LSM, Least Squares mean; SEM standard error of mean.
Glucocorticoid (GC) toxicity in the avacopan group was lower at both 13 and 26 weeks for both GTI scores (CWS: P=0,01 at 13 weeks; 0,0002 at 26 weeks. AIS: P=0,003 at 13 weeks; P=0,008 at 26 weeks).
The data shown are least square means (LSM) and the standard error of measurement (SEM), estimated based on mixed-model repeated measures of the longitudinal GTI data from day 1 to Week 26.

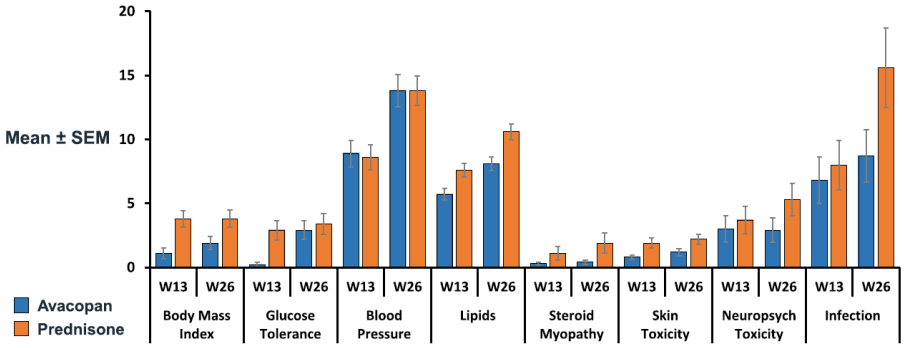
Table 23 GTI scores in the ADVOCATE trial at Weeks 13 and 26. The Cumulative Worsening Score (CWS) and the Aggregate Improvement Score (AIS) [155a].

Secondary End Point Results Glycocorticoid Toxicity Index Cummulative Worsening Score (GTI-CWS) [155a]			
	Prednisone (N=164)	Avacopan (N=166)	Difference Avacopan minus Prednisone (95% Confidence Interval)
Week 13 (LSM ± SEM)	36,6 ± 3,41 (n=161)	25,7 ± 3,40 (n=160)	-11,0 (-19,7 to -2,2)
Week 26 (LSM ± SEM)	56,6 ± 3,45 (n=153)	39,7 ± 3,43 (n=154)	-16,8 (-25,6 to -8,0)
Secondary End Point Results Glycocorticoid Toxicity Index Aggregate Improvement Score (GTI-AIS) [155a]			
	Prednisone (N=164)	Avacopan (N=166)	Difference Avacopan minus Prednisone (95% Confidence Interval)

Week 13 (LSM ± SEM)	23,2 ± 3,46 (n=161)	9,9 ± 3,45 (n=160)	-13,3 (-22,2 to -4,4)
Week 26 (LSM ± SEM)	23,4 ± 3,50 (n=153)	11,2 ± 3,48 (n=154)	-12,1 (-21,1 to -3,2)

Summary of GTI Specific List Items by visit (baseline, week 13, week 26 and Last Measured GTI) is shown in Appendix W.

Figure 23 Cumulative Worsening Score (CWS) by GTI domain in the ADVOCATE trial [242].

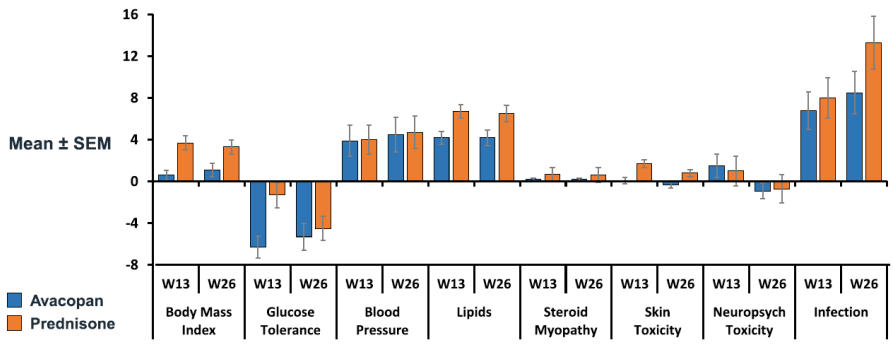


Seven of 8 GTI domains of GC toxicity differentiated the two treatments, with all favoring the avacopan group in a statistically significant manner. Only the hypertension domain showed no significant difference between the treatment groups.

Please find the summary table of individual components for CWS in the Appendix U.

Examination of the individual GTI domain scores from the ADVOCATE trial is also instructive. The GTI scores demonstrated a consistent reduction in GC toxicity across domains in the avacopan group. As shown in Figure 23 above, 7 of the 8 domains differentiated the two treatment groups well with regard to the development of new GC toxicities after baseline. The only domain that did not differentiate the two treatment groups was the blood pressure domain. This finding was not surprising because 81% of the patients in the trial overall had glomerulonephritis, a disease feature often associated with hypertension and the need for anti-hypertensive therapies [242].

Figure 24 Aggregate Improvement Scores (AIS) by GTI domain in the ADVOCATE-trial [242].



Four of 8 domains strongly favored the avacopan group. A fifth domain (glucocorticoid myopathy) also suggested a larger impact in the avacopan group but was not statistically significant.

Similar findings were observed with regard to the AIS figure 24 above. Three of the domains (glucose tolerance, skin toxicity, and neuropsychiatric toxicity) actually improved over time in the avacopan group, with bigger improvements occurring at the 26-week timepoint compared to the 13-week timepoint. This observation corresponded to the pattern of GC use in the avacopan group. Glucose tolerance and neuropsychiatric toxicity also approved in the standard care group, consistent with the lower mean daily GC doses over time. Comparisons within the body mass index, lipid, skin toxicity, and infection domains all strongly favored the avacopan group. The tendency across domains with regard to GC toxicity [242].

The tendency across domains with regard to GC toxicity – likely more pronounced within individual patients as opposed to treatment cohorts as a whole - underscores the importance of a composite measure that accounts for the occurrence of GC toxicities in multiple domains [242].

Findings with regard to GC toxicity as measured by the GTI were highly consistent with the incidence of individual GC toxicities as outlined in the EULAR guidelines [1]. They were also consistent with adverse events in the trial overall [155], suggesting that GC-related adverse events accounted for a substantial proportion of the treatment- related morbidity in the trial. Finally, the GTI scores were consistent with data observed in patient-reported outcomes such as the SF-36 and the EuroQoL 5D-5L [155,242].

Please find the Summary of Glucocorticoid Toxicity Index Cumulative Worsening Score (GTI-CWS) Individual Components Through week 26 (Intention to Treat Population) in Appendix U confidential.

Please find three ad-hoc analysis summary of baseline composite GTI in appendix AB (confidential) and the summery of GTI-AIS Individual Components Categories Through Week 26 in appendix AC (confidential) as well as the summery of GTI-CWS Individual Components Categories Through Week 26 in appendix AD (confidential).

The fact that the phase 3 ADVOCATE-study was an RCT, which should mean baseline GTI/steroid burden is balanced between groups – therefore the comparison robust regardless of baseline.

Less GC use was associated with lower increases in a number of factors, with the greatest benefits seen in the 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 (22,23,24). 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 [156].

Table 24 GTI aggregate improvement score individual components in ITT population at week 13, 26 and last measure in the SOC and Avacopan-based regimen groups [156].

	SOC group (N=164)		Avacopan-based regimen group (N=166)	
Body Mass Index (BMI)				
Week 13	n=161	3.7 (±8.32)	n=160	0.6 (±6.19)
Week 26	n=153	3.3 (±8.72)	n=154	1.1 (±7.70)
Final GTI measure	n=162	3.2 (±8.62)	n=163	1.0 (±7.48)

Glucose tolerance				
Week 13	n=161	-1.3 (±15.47)	n=160	-6.3 (±13.37)
Week 26	n=153	-4.5 (±14.38)	n=154	-5.3 (16.30)
Final GTI measure	n=162	-3.6 (±15.04)	n=163	-5.2 (±16.02)
Blood Pressure				
Week 13	n=161	4.0 (±17.85)	n=160	3.9 (±19.14)
Week 26	n=153	4.7 (±19.24)	n=154	4.5 (±20.45)
Final GTI measure	n=162	4.8 (±19.26)	n=163	4.1 (±20.50)
Lipids				
Week 13	n=161	6.7 (±8.20)	n=160	4.2 (±7.89)
Week 26	n=153	6.5 (±9.62)	n=154	4.2 (±9.41)
Final GTI measure	n=162	6.4 (±9.51)	n=163	3.9 (±9.39)
Steroid Myopathy				
Week 13	n=161	0.7 (±7.99)	n=160	0.2 (±1.73)
Week 26	n=153	0.6 (±8.64)	n=154	0.2 (±1.44)
Final GTI measure	n=162	0.6 (±8.40)	n=163	0.3 (±1.56)
Skin AEs and complications				
Week 13	n=161	1.7 (±5.01)	n=160	0.1 (±3.94)
Week 26	n=153	0.8 (±4.22)	n=154	-0.3 (±4.29)
Final GTI measure	n=162	1.1 (±4.99)	n=163	-0.3 (±4.22)
Neuropsychiatric AEs and complications				
Week 13	n=161	1.0 (±17.72)	n=160	1.5 (±14.55)
Week 26	n=153	-0.7 (±16.72)	n=154	-0.9 (± 9.34)
Final GTI measure	n=162	-1.0 (±16.99)	n=163	-0.5 (±10.84)
Infection				
Week 13	n=161	8.0 (±24.59)	n=160	6.8 (±22.72)
Week 26	n=153	13.3 (±31.34)	n=154	8.5 (±25.09)
Final GTI measure	n=162	13.1 (±31.23)	n=163	9.2 (±26.18)

GTI, Glucocorticoid AEs and complications Index; **N,** Number of subjects in the ITT Population; **n**, number of subjects with GTI data at this time point.

7.1.2 Safety and tolerability of Avacopan

7.1.2.1 Safety populations

A total of 166 patients received an Avacopan-based regimen for a dosing period of 52 weeks in the ADVOCATE trial [156]. As both the CLEAR and CLASSIC trials had a 12-week treatment duration, safety data from these trials were integrated. A total of 73 subjects received an Avacopan-based regimen in the Phase 2 trials for a dosing period of 12 weeks [149, 152]. The total exposure to Avacopan in the Phase 2 and 3 studies has been 212,31 subject-years.

7.1.2.2 Overview of Avacopan-based regimen - safety profile in ANCA-AV patients

Overall, the patient incidence of treatment emergent adverse events (TEAEs), was comparable between the Avacopan-based regimen and SOC groups (98.8% vs. 98.2%, respectively). However, the number of TEAEs reported was 20% lower in the Avacopan-based regimen group compared with the SOC group (1.779 vs. 2.139 respectively, (Table 26) [156,184].

The EPAR for Tavneos/avacopan [184] have been consulted and the safety data and full tables from the EPAR are included in Appendix E. The data discussed below is extracted from the EPAR [184].

All TEAEs reported by ≥5% of patients occurred at a higher patient incidence in the SOC group compared with the Avacopan-based regimen group, or at a similar incidence in both treatment groups. In both treatment groups, the majority of TEAEs were moderate in severity (41.5% and 49.4%, in the SOC and Avacopan-based regimen groups, respectively), and approximately a quarter of patients in both treatment groups experienced severe TEAEs [155,156,184].

Severe and serious TEAEs and infection in the ADVOCATE-phase III study was defined as follows:

- Serious TEAEs: Adverse events newly occurring after treatment was started and fulfilling standard regulatory criteria for seriousness (i.e. death; life-threatening; required or prolonged hospitalization; persistent or significant disability or incapacity; congenital anomaly or birth defect; important and significant medical event).
- Severe TEAEs: Adverse events newly occurring after treatment was started and graded by the investigator as severe or worse (i.e. inability to carry out usual activities or worse).
- Serious infections: Adverse events mapping to the MedDRA Infections and Infestations SOC and fulfilling standard regulatory criteria for seriousness.
- Severe infections: Adverse events mapping to the MedDRA Infections and Infestations SOC and graded by the investigator as severe or worse (i.e. inability to carry out usual activities or worse).

The side effects in these various calculations are based on cumulated events up to week 52 including the 8 weeks follow-up period. An adverse event (AE) is considered treatment-emergent if the start date/time of the event is on or after the date/time of first dose of study drug through 56 days following the last dose administered during the randomized treatment period, cf. table 22-26.

Table 25 Overview of patient incidence of treatment-emergent advance events in the ADVOCATE study (Safety Population)[156,184]

	SOC (N=164)	Avacopan-based regimen (N=166)
All TEAEs		
TEAEs, n	2.139	1.779
Patient incidence of TEAEs, n (%)	161 (98.2)	164 (98.8)
Maximum severity of TEAE, n (%)		
Mild	34 (20.7)	33 (19.9)
Moderate	68 (41.5)	82 (49.4)
Severe	41 (25.0)	39 (23.5)
Life-threatening	14 (8.5)	8 (4.8)
Death	4 (2.4)	2 (1.2)
Patient incidence of discontinuation due to AEs, n (%)	28 (17.1)	27 (16.3)
Serious TEAEs		
Number of serious TEAEs	166	116
Patient incident of serious TEAEs, n (%)	74 (45.1)	70 (42.2)
Patients with any serious infection, n (%)	25 (15.2)	22 (13.3)
Deaths due to infection, n (%)	2 (1.2)	1 (0.6)
Patients with any serious hepatic system AE, n (%)	6 (3.7)	6 (3.6)
GC-related AEs		
Patients with any AE potentially related to GCs*, n (%)	132 (80.5)	110 (66.3)

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)
*investigators blinded assessment
The side effects in these various calculations are based on cumulated events up to week 52 including the 8 weeks follow-up period. An adverse event (AE) is considered treatment-emergent if the start date/time of the event is on or after the date/time of first dose of study drug through 56 days following the last dose administered during the randomized treatment period.

Overall, there were more SAEs in the SOC group compared with 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 the Avacopan-based regimen and SOC groups (16.3%. vs. 17.1% respectively). A lower number of patients experienced life-threatening TEAEs in the Avacopan-based regimen group compared with the SOC group (4.8% vs. 8.5% respectively). Four (2.4%) patients in the SOC group died compared with two (1.2%) patients in the Avacopan-based regimen group [156,184].

The incidence of SAEs in the majority of system organ classes was higher in the SOC group compared with the Avacopan-based regimen group. The most common SAE system organ class in both treatment groups was infections and infestations (15.2% and 13.3% in the SOC and Avacopan-based regimen groups respectively), with patient incidence of infections and infestations lower in the Avacopan-based regimen group as compared with the SOC 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 regimen group compared with the SOC group. Data on infections are presented in Table 27 [156].

In support of the efficacy results, there was a numerically lower number of events in the Avacopan-based regimen group (30 events in 26 subjects, 15.7%) compared with the SOC group (46 events in 34 subjects, 20.7%), indicating a worsening of vasculitis (anti-neutrophil cytoplasmic antibody positive vasculitis) [156,184].

Table 26 Overview of patient incidence of treatment-emergent advance events in the ADVOCATE study (Safety Population)[156,184]

Category	SOC (N=164) n (%)	Avacopan-based regimen (N=166) n (%)
Any Treatment-Emergent Infection	124 (75.6)	113 (68.1)
Any Serious Treatment-Emergent Infection	25 (15.2)	22 (13.3)
Any Severe Treatment-Emergent Infection	10 (6.1)	9 (5.5)
Any Treatment-Emergent Infection Leading to Study Withdrawal	5 (3.0)	4 (2.4)
Any Treatment-Emergent Life-threatening Infection	2 (1.2)	1 (0.6)
Any Treatment-Emergent Infection Leading to Death	2 (1.2)	1 (0.6)
Most common TEAEs of infection (≥3% in any treatment group)		
Nasopharyngitis	30 (18.3)	25 (15.1)
Upper respiratory tract infection	24 (14.6)	24 (14.5)
Urinary tract infection	23 (14.0)	12 (7.2)
Pneumonia	11 (6.7)	11 (6.6)
Sinusitis	12 (7.3)	10 (6.0)
Bronchitis	10 (6.1)	5 (3.0)
Gastroenteritis	1 (0.6)	5 (3.0)
Lower respiratory tract infection	8 (4.9)	5 (3.0)
Rhinitis	2 (1.2)	5 (3.0)
Herpes zoster	6 (3.7)	4 (2.4)
Influenza	8 (4.9)	4 (2.4)
Oral candidiasis	7 (4.3)	4 (2.4)

Category	SOC (N=164) n (%)	Avacopan-based regimen (N=166) n (%)
Oral herpes	6 (3.7)	4 (2.4)
Viral upper respiratory tract infection	5 (3.0)	4 (2.4)
Viral infection	5 (3.0)	2 (1.2)
Most common serious TEAEs of infection (≥1% [2 subjects] in any treatment group)		
Pneumonia	6 (3.7)	8 (4.8)
Urinary tract infection	2 (1.2)	3 (1.8)
Device related infection	0 (0)	2 (1.2)
Influenza	1 (0.6)	2 (1.2)
Herpes zoster	2 (1.2)	0 (0)
Infectious pleural effusion	2 (1.2)	0 (0)
Pneumonia bacterial	2 (1.2)	0 (0)
Respiratory syncytial virus infection	2 (1.2)	0 (0)

TEAEs, treatment-emergent adverse events
The side effects in these various calculations are based on cumulated events up to week 52 including the 8 weeks follow-up period. An adverse event (AE) is considered treatment-emergent if the start date/time of the event is on or after the date/time of first dose of study drug through 56 days following the last dose administered during the randomized treatment period.

In the Phase 3 study, SAEs occurred with higher frequency in the prednisone group compared to avacopan (prednisone: 166 events reported by 74 subjects [45.1%] vs avacopan: 116 events in 70 subjects [42.2%]) Appendix N. The most common SAE system organ class (SOC) was Infections and infestations: 15.2% in the prednisone group and 13.3% in the avacopan group Appendix N. The incidence of SAEs in the majority of SOCs was higher in the prednisone group compared with the avacopan group. The only SOC with an SAE incidence ≥2% in the avacopan group compared with the prednisone group was Hepatobiliary disorders (3.6% in the avacopan group compared with 0.6% in the prednisone group). When all SAEs of liver function test elevations were considered, the SAE incidence was 5.4% in the avacopan group and 3.7% in the prednisone group (CSR CL010_168 Section 12.3.1.3.2.2)*1. Causality assessment was confounded by other concomitant medications with hepatotoxicity such as co-trimoxazole, azathioprine, and alcohol abuse, and viral etiologies.

The most common SAE was worsening ANCA positive vasculitis, with 12.2% in the prednisone group and 7.2% in the avacopan group.

The SAE profile in the Phase 2 studies was generally consistent with the Phase 3 study profile.

The exposure-adjusted SAE rate across Phase 2 and 3 studies was statistically lower in the avacopan compared to prednisone group (Section 2.7.4.2.5.1)*1.

A total of 7 subjects died in the Phase 3 study, including 2 subjects who had received avacopan. Of the five other deaths, one died during the screening period and 4 were in the prednisone group (CSR CL010_168 Section 12.3.1.1)*1. The 2 subjects in the avacopan group were off avacopan treatment at the time of death (79 days and 110 days, respectively) (CSR CL010_168 Table 14.1.2.2)*2. No deaths were reported in the phase 2 studies. Thus, no deaths were attributed to the use of avacopan [156,184].

References: eCTD (electronic Common Technical Document), CSR CL010_168, Summary of Clinical Safety

*1 The sections are not included in this application.
*2 The table is not included in this application

A table with Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population) are attached in appendix R.

7.1.2.3 Incidence of GC-related adverse events

Incidence of glucocorticoid-related adverse events are reduced with an Avacopan-based regimen compared with SOC. In the ADVOCATE study, treatment with Avacopan-based regimen led to a significantly lower number of potentially GC-related adverse events (based on EULAR criteria) overall, when compared with the SOC arm (66% vs 81% of patients respectively) (Table 27). A statistically significant difference was found in the endocrine/metabolic (14% vs 29%) and dermatological (8% vs 17%) systems ($p < 0.05$). Metabolic effects included diabetes, Cushingoid signs (facial swelling and weight gain) and adrenal insufficiency. 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 [156].

Table 27 Adverse events potentially related to glucocorticoid use in the ADVOCATE study [156]

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

CI, confidence interval; **SOC**, standard of care. *p<0.05
The side effects in these various calculations are based on cumulated events up to week 52 including the 8 weeks follow-up period. An adverse event (AE) is considered treatment-emergent if the start date/time of the event is on or after the date/time of first dose of study drug through 56 days following the last dose administered during the randomized treatment period.

7.1.2.4 Serious adverse events/deaths/other significant events

Serious Adverse Events reported by ≥ 1 % of subjects both treatment groups are presented in the **Fejl! Henvisningskilde ikke fundet.** below, [184].

Table 28 Serious Treatment-Emergent Adverse Events by Preferred Term Occurring in > 1 % of subjects in Either Treatment Group in Study CL010-168 (Safety population).

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

The side effects in these various calculations are based on cumulated events up to week 52 including the 8 weeks follow-up period. An adverse event (AE) is considered treatment-emergent if the start date/time of the event is on or after the date/time of first dose of study drug through 56 days following the last dose administered during the randomized treatment period.

7.1.2.4 Incidence of adverse events related to background treatment

Incidence of AEs were generally higher in patients with background treatment with CYC compared with those treated with RTX in both the SOC and Avacopan-based regimen groups. In the SOC group, there was no difference in overall non-serious TEAEs between patients treated with CYC compared with RTX (98.2% vs. 98.1% respectively). SOC + CYC was generally associated with higher incidence of AEs compared with SOC + 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) [156].

During the discussion of clinical safety, the CHMP notes that it is important to be aware that all subjects in the phase 2 and 3 studies received either a background treatment with cyclophosphamide/azathioprine or rituximab [184]. These medicinal products are also known to potentially affect the liver, cause cytopenia and an increased risk of infections [184,212,213].

While overall treatment emergent adverse event rates in participants who received cyclophosphamide compared to those who received rituximab were similar in both avacopan and prednisone treatment arms (Table 14.3.1.2.1.1 Appendix 0 in the CSR) [156], the proportion of participants experiencing a serious adverse event was greater in those receiving cyclophosphamide compared to those receiving rituximab. This was observed in both the avacopan and prednisone treatment arms (Table 14.3.1.3.3 Appendix N in the CSR) [156] and would be consistent with the known toxicities of cyclophosphamide compared to rituximab as used in this population.

7.1.2.5 Comparative analyses of efficacy and safety of the two phase 2 studies

Results from the CLEAR trial showed that an Avacopan-based regimen appeared to be effective in improving ANCA-AV activity based on the BVAS, UACR, and improving HRQoL, while also allowing for the elimination of the prednisone regimen to achieve a treatment response. These results were supported by data from the CLASSIC study that showed a rapid onset of action of Avacopan, and selection of a dose regimen of 30 mg Avacopan BID as the preferred dose in treatment of patients with ANCA-AV [149, 152].

Results from the Phase 2 studies were consistent with those from the pivotal Phase 3 ADVOCATE trial. The CLASSIC study was not powered statistically to evaluate efficacy. The efficacy results presented for this trial are therefore descriptive summary statistics. As 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 following summary Table 29 [149, 152].

Table 29 Summary of TEARs during CLEAR and CLASSIC trials (combined) Pooled Phase 2 Safety Population [184]

Demographic Variable Statistic/Category	Prednisone (N=36)	Avacopan based regimen (N=73)
Participants reporting ≥TEAE	34 (94.4)	69 (94.5)
Maximum severity of TEAE		
Mild	15 (41.7)	21 (28.8)
Moderate	15 (41.7)	34 (46.6)

Demographic Variable Statistic/Category	Prednisone (N=36)	Avacopan based regimen (N=73)
Severe	4 (11.1)	12 (16.4)
Life-threatening	0 (0)	2 (2.7)
Death	0 (0)	0 (0)
SAE	8 (22.2)	24 (32.9)
TEAEs leading to discontinuation of study medications	4 (11.1)	8 (11.0)

The side effects in these various calculations are based on cumulated events up to week 52 including the 8 weeks follow-up period. An adverse event (AE) is considered treatment-emergent if the start date/time of the event is on or after the date/time of first dose of study drug through 56 days following the last dose administered during the randomized treatment period.

7.2 Improved Quality of Life with Tavneos (avacopan)

7.2.1 Quality of life measures

7.2.1.1 SF-36-v2 and EQ-5D

The SF-36 and EQ-5D quality of life measures were utilised in the Advocate study, as both are universally used to produce utility scores for cost utility models and have historically been used to assess HRQoL in ANCA-AV patients. Analyses of SF-36 data shows that this tool can discriminate between ANCA-AV disease states of significance and provide information on disease burden [95].

The SF-36 is a generic measure and the most used tool to assess health-related quality of life (HRQoL) in ANCA-AV patients. The SF-36 contains 36 items that measure 8 multi-item dimensions of health: physical functioning, bodily pain, vitality, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health. Each scale is transformed into a 0–100 scale in which higher scores indicate better QoL, except for the domain Reported Health Transition where a decrease corresponds to an improvement in health compared with 1 year previously. Two standardised summary scores can also be calculated from the SF-36: the physical component summary (PCS) and the mental health component summary (MCS) [95].

The EQ-5D was introduced by the EuroQoL group in 2009 [158]. It is divided into a descriptive system and a visual analogue scale (VAS). The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients select a statement that matches their health state for each of the five dimensions and this is converted to a one-digit number. The digits for each of the five dimensions can be presented as a five-digit number that describes the patient's health state [158].

The EQ-5D is usually reported as a utility value of 0–100, where 1 is the best possible health. Occasionally, patients may have a negative EQ-5D score [158].

7.2.1.3 Disease-Specific Quality of Life Measures

A disease-specific patient reported outcome (PRO) measure for the assessment of outcomes of importance to ANCA-AV patients has been developed, the AAV-PRO. However, this measure was not available at the time of patient inclusion in the ADVOCATE phase 3 trial and so could not be used in that study.

AAV-PRO is a 35-item candidate questionnaire, with six domains, 'organ symptoms severity (OSS)', 'systemic symptoms severity (SSS)', 'treatment side effects (TSE)', 'social and emotional impact

(SEI)', 'concerns about the future (CAF)' and 'physical function (PF)', validated using qualitative interviews in the UK, USA and Canada [159, 160]. Baseline data showed that mean domain scores were higher (indicating worse QoL) for patients with active disease (>25% of cohort) than those in remission (p<0.001). Domain scores correlated with EQ-5D scores indicating that the PRO is valid in this patient population (p<0.0001) [160].

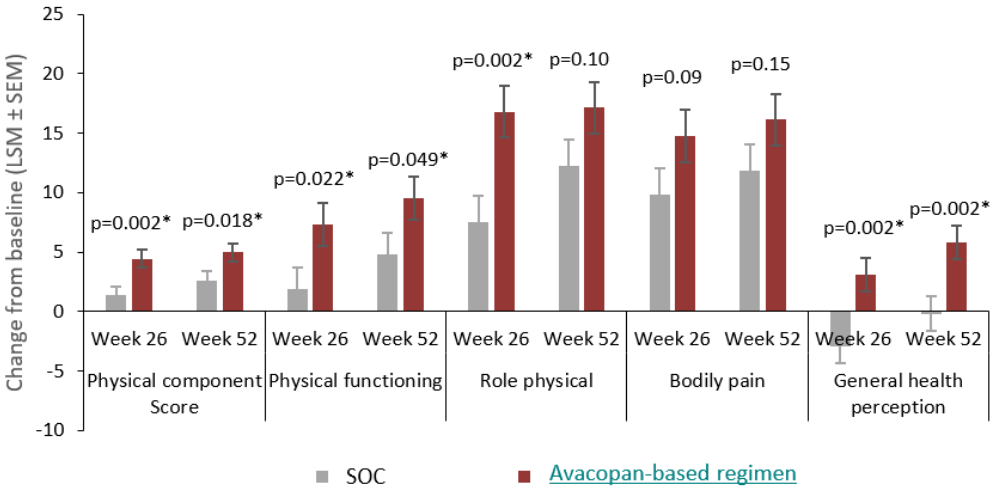
7.2.3 QoL results

7.2.3.1 Superior SF-36 outcomes

Treatment with an Avacopan-based regimen significantly improved patients' QoL compared with SOC, with an improvement in the Physical Component Score at Weeks 26 and 52 compared with SOC: 4.445 vs. 1.344 (p=0.002) and 4.980 vs. 2.626 (p=0.018) respectively (Figure 25**Fejl! Henvisningskilde ikke fundet.**). Specifically, scores for the domains Physical Functioning (at 26 and 52 weeks) and Role Physical (at 26 weeks) showed a significant improvement in the Avacopan-based regimen group compared with SOC [155].

Additionally, whilst an improvement in General Health Perception, which is highly relevant to patients with ANCA-AV, was seen in the Avacopan-based regimen group, scores for this domain deteriorated in the SOC group at both 26 and 52 weeks: 3.12 vs. -2.89 (p=0.002) and 5.84 vs. -0.17 (p=0.002) respectively [155, 156].

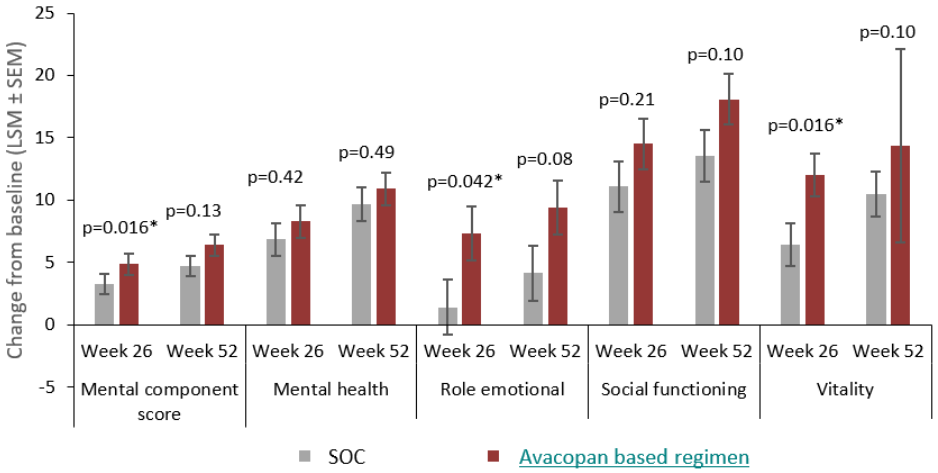
Figure 25 SF-36 v2.0 Change from Baseline for Physical Component Score and Other Physical Aspects during the Study Period (ITT Population) [156]



ITT=intent to treat; LSM=least square mean; SEM=standard error of mean; *statistically significant

Patients on Avacopan-based regimen also scored higher than patients on SOC in the Mental Component Score 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 26**Fejl! Henvisningskilde ikke fundet.**) [156].

Figure 26 SF-36 v2 Change from Baseline for Mental Component Score and Other Mental Domains during the Study Period (ITT Population) [156].



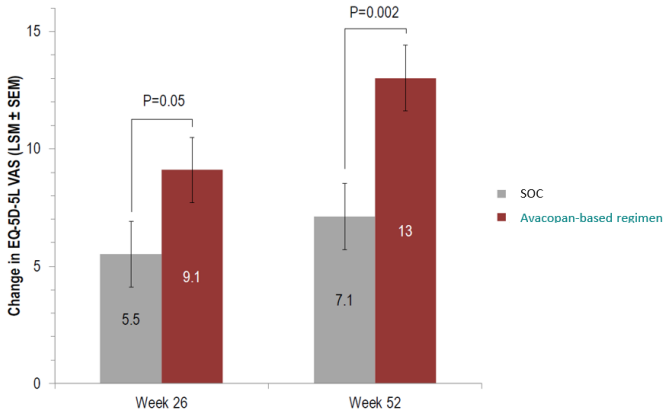
The table 3 from CSR (Appendix P) are enclosed for the physical and mental component scores and individual components baseline, week 4, 10, 16, 39, 52, early termination and follow-up.

We also refer to Supplementary appendix table S-10 from the Jayne D, et al. N Engl J Med 2021;384(7):599–609. [Suppl Appendix] [155.a] where the physical and mental component scores baseline, week 26 and week 52 are listed.

7.3.2.2 Superior EQ-5D outcomes

Treatment with an Avacopan-based regimen resulted in a significantly higher EQ-5D VAS score at Week 52, when compared with the SOC group: LSM change from baseline in the Avacopan-based regimen group was 9.1 vs. 5.5 (p=0.05) and 13.0 vs. 7.1 (p=0.002) respectively (Figure 27**Fejl! Henvisningskilde ikke fundet.**) [156].

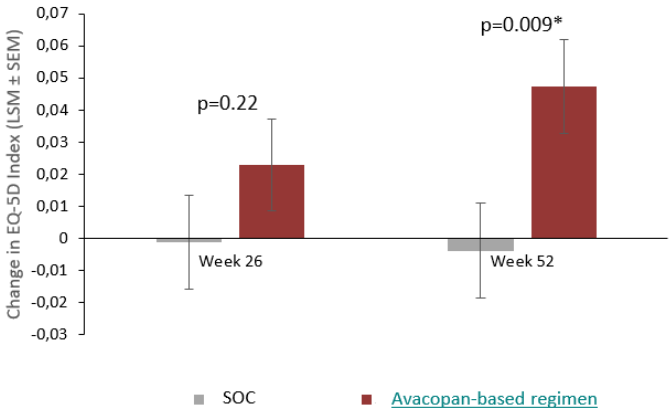
Figure 27 EQ-5D Health Scale VAS Score Change from Baseline during the Study Period (ITT Population) [156]



ITT=intent to treat; **LSM**=least square mean; **SEM**=standard error of mean; **VAS**=visual analog scale; *statistically significant

Patients in the Avacopan-based regimen group also had a numerically higher EQ-5D Index Score at Week 26 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 28**Fejl! Henvisningskilde ikke fundet.**) [156].

Figure 28 EQ-5D Health Scale Index Score Change from Baseline during the Study Period (ITT Population) [156]



ITT=intent to treat; LSM=least square mean; SEM=standard error of mean; *statistically significant

8. HEALTH ECONOMIC ANALYSIS

The objective of this analysis was to evaluate the cost-effectiveness of Tavneos® (avacopan) compared to standard of care (SoC) for the treatment of patients with anti-neutrophil cytoplasmic antibody-associated vasculitis (ANCA-associated vasculitis) over a lifetime horizon from a Danish payer perspective.
A previously developed cost-effectiveness model (CEM) for the UK was adapted to the Danish setting and used to perform the cost-effectiveness analysis. The model comprises nine health states describing the treatment and disease progression of ANCA-associated vasculitis. Current standard of care (SoC) in Denmark was assumed to be a mix of the glucocorticoid (GC) prednisolone and either cyclophosphamide (CYC; 80%), or rituximab (RTX; 20%). The analysis was performed from the payer perspective, only including direct healthcare costs with a lifetime time horizon. Effect of treatments were sourced from the pivotal trial for Tavneos®, ADVOCATE, supplemented by studies identified in targeted searches of relevant literature. Costs were sourced from:

- the Danish price lists medicinpriser.dk 06/04/2022
- InteractiveDRG DRG2022 (LPR3)
- Overenskomst om almen praksis 01/04/2022-01/10/2022
- DMC Værdisætning af enhedsomkostninger, version 1.6.

The outcomes of the analysis were costs, life-years, and quality-adjusted life years. Both costs and benefits were discounted with 3,5% (year 0-35) and 2,5 % (year 36-70).

8.1 Model

There are no previously published cost-effectiveness analyses for the use of Tavneos® in treating patients with ANCA-associated vasculitis. A *de novo* global economic model (UK setting) was adapted to the Danish setting.

A state transition or Markov model was previously developed in Microsoft Excel. The structure was based on a previous model used for the cost-effectiveness analysis of rituximab (RTX) in the NICE evaluation of RTX (TA308) in combination with glucocorticoids (GCs) for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [117].

The original CEM was developed for the UK setting and adapted to Denmark. Adaptations were made according to guidelines set by the Danish Medicines Council and Danish-specific inputs were incorporated.

8.1.1. Objective

The objective of model is to investigate if Tavneos®/avacopan is a cost-effective alternative to SoC for the treatment of patients with ANCA-associated vasculitis in Denmark.

8.1.2 Model structure

Tavneos® is indicated for the treatment of adult patients with granulomatosis with polyangiitis (Wegener's) (GPA) or microscopic polyangiitis (MPA).

The population in the base case analysis reflects the indication and was based on the intention to treat (ITT) population in ADVOCATE, being either newly diagnosed GPA and/or MPA patients or GPA/MPA patients that have relapsed on previous treatment.

Four subgroups of patients according to inclusion criteria in ADVOCATE have been explored in the base case: GPA, MPA, Relapsed and Treatment naïve. Same patients might be included in more than one subgroup since the ADVOCATE study was not designed nor powered to provide definitive results pre specified subgroups.

The model was designed to reflect clinical practice for the induction of remission in patients with ANCA-associated vasculitis and includes up to three courses of induction therapy, for whole ITT Population as well as for the four subgroups of patients, separately.

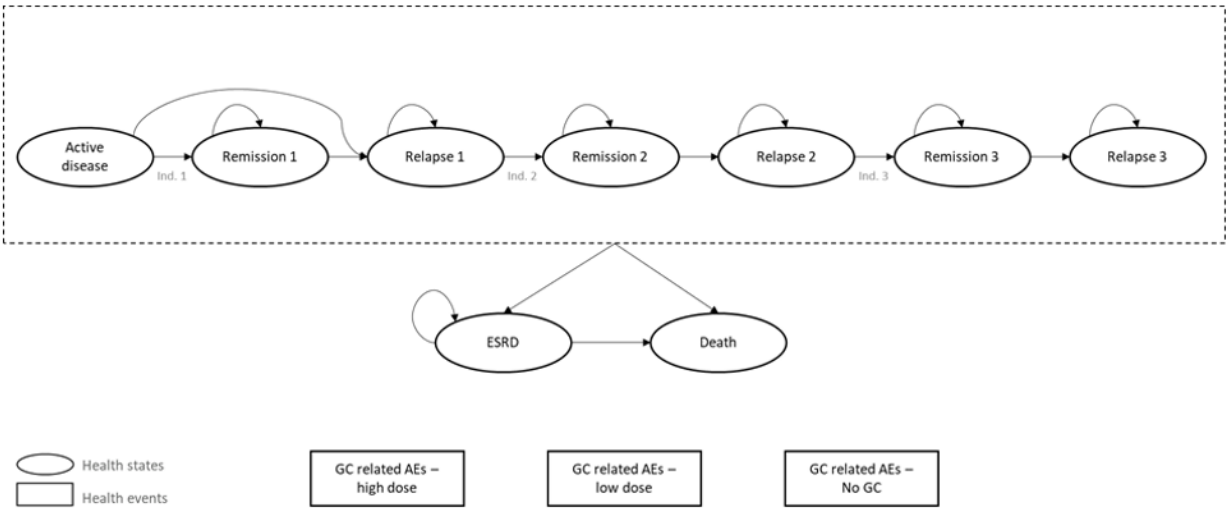
The model is structured around three pair-wise comparisons based on the induction treatment of the first course which is fixed in the model. The induction treatment chosen for the 2nd. and the 3rd. induction is the same in both treatment arms.

- AVA+CYC vs. CYC+GC + (CYC+GC) + (CYC+GC)
- AVA+RTX vs. RTX+GC + (RTX+GC) + (RTX+GC)

The model follows the clinical management of ANCA-associated vasculitis, with four different disease stages: remission induction, remission maintenance, disease relapse and refractory disease [188,189].

The model contains nine mutually exclusive health states: one active disease state, three remission states, three relapse states, an end-stage-renal disease (ESRD) state and a death state (Figure 29**Fejl! Henvisningskilde ikke fundet.**). In addition to the nine health-states, patients can experience health events such as adverse events (AEs).

Figure 29 Scematic diagram of the cost-effectiveness model for Tavneos®

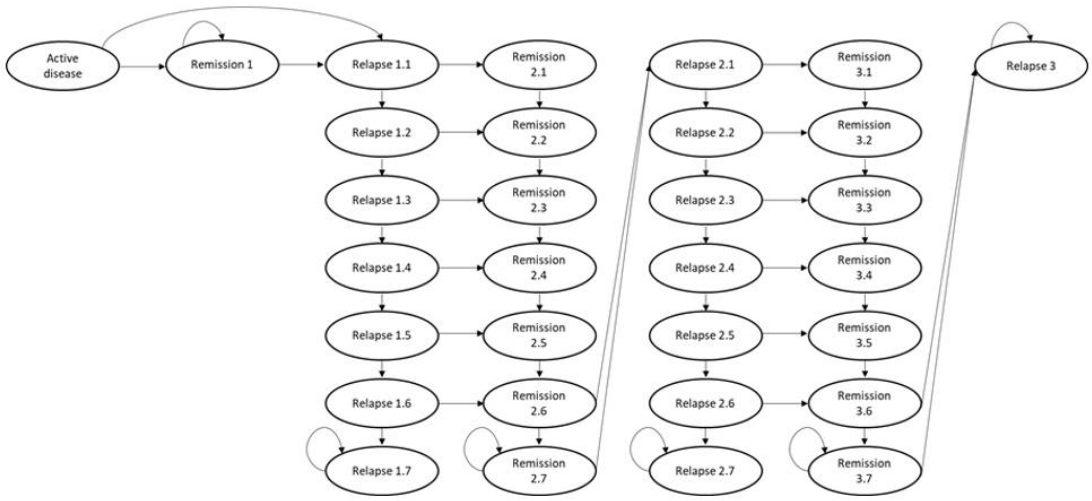


The cost-effectiveness model was conceptualized as a Markov model. Markov models are appropriate for handling longer term outcomes and chronic diseases because cycles explicitly account for time [215,216].

8.1.2.1 Markov state and tunnel state in the model

- Induction courses are spread over a 6-month period, as per the ADVOCATE protocol [155], which was simplified to six cycles in the model. Patients therefore have six cycles to move to a remission state and each of the six cycles is associated with different costs.
- Patients in remission can only relapse after having completed the full six cycles on the induction therapy.
- Patients transition from “Active disease” to “Remission 1” in the first six cycles of the model and patients in “Remission 1” receive maintenance therapy from cycle seven. The model cycles allow to appropriately follow patients through the first induction course.
- Patients can relapse and therefore reach the “Remission 2” and “Remission 3” health states at any point (from cycle seven).
- “Remission 2” and “Remission 3” have seven tunnel states to appropriately follow patients. The first five tunnel states are for the second to sixth cycle of the induction period (the first cycle of treatment being given in the relapse states).
- From the sixth tunnel state, patients receive maintenance therapy for 24 months.
- Health states, “Relapse 1” and “Relapse 2” both have six tunnel states, one for each cycle of the (re-)induction therapy, plus a seventh health state for patients who do not respond to the induction treatment and therefore stay in the relapse state for the remainder of the time horizon, these patients are defined as refractory patients. Therefore, the health state Relapse 1.7, Relapse 2.7, and Relapse 3 are the refractory health states referred to in the dossier (see Figure 30). This solution is necessary as the model is flexible in the number of inductions which makes one refractory health state difficult to implement.
- The model allows transition to ESRD state from all health states (active, relapse, and remission)
- A half-cycle correction is applied to the calculation of costs and health effects accrued throughout each cycle, to account for the transition of patients from one health state to another, representing an average transition halfway through a cycle (i.e., not at the beginning or end of a cycle).

Figure 30 Scematic diagram of the cost-effectiveness model for Tavneos®



- As ANCA-associated vasculitis is a chronic relapsing autoimmune disease that can lead to life-threatening kidney damage in the long run, a lifetime perspective is required to capture these costs and consequences (eg, future need for dialysis and repeated induction therapy in case of relapse). In the base case analysis, no difference in mortality is assumed between the addition of avacopan to CYC/RTX and SOC (GC+CYC/RTX) - on the other hand, the difference in proportion in remission and the risk of relapse is modelled. The effect avacopan achieves over 52 weeks is propagated through the time horizon of the analysis by a greater proportion of patients achieving remission and a smaller proportion of patients experiencing relapses – this in turn leads to a reduced risk of irreversible kidney damage and the costs and quality of life losses linked to this – something that follows the patient for life.

This means that although the direct effect of avacopan (proportion in remission and relapse) is not extrapolated (instead the avacopan arm has the same transition probabilities as the comparison arm), the initial effect of avacopan will be significant over the patient's lifetime, which justifies the chosen the lifetime horizon (40 years).

8.1.1.2 Definition of Health states and events

Remission

Remission is the primary goal in the management of ANCA-associated vasculitis [188,189]. The remission health state is defined in accordance with the ADVOCATE trial as patients achieving a Birmingham vasculitis activity score (BVAS) of 0 and not taking GCs within four weeks of the end of the 6-month induction period [155].

Active disease

The active disease state is defined as patients with a BVAS>0.

Relapse

Based on the ADVOCATE trial protocol and in line with Danish practice, a relapse is defined as a worsening of disease, after having previously achieved remission [188,189], that involves:

- one or more major item in the BVAS, or
- three or more minor items in the BVAS, or
- one or two minor items in the BVAS recorded at two consecutive study visits.

ESRD

Patients are considered to have ESRD if they have an estimated glomerular filtration rate (eGFR) < 15 ml/min and present a chronic need for renal replacement therapy (RRT) (proxied as three dialysis care visits within a 6-month period) [217].

Adverse events

Treatment for ANCA-associated vasculitis may be associated with AEs, most notably with the use of GCs. There are currently two ways to account for AEs in the model. Either, using the AE rates as reported in the ADVOCATE trial – each event is costed separately (**Fejl! Henvisningskilde ikke fundet.**) or, in an alternative setting, cost associated with AEs are assumed to be included in the cost of hospitalization based on data from ADVOCATE.

In the base case analysis AEs are believed to be included in the cost of hospitalization as seen in ADVOCATE and it is chosen in the model settings “Include hospitalizations data from Advocate”.

8.1.1.3 Treatment pathway

Treatment arms in the model

The model is structured around three pair-wise comparisons based on the induction treatment of the first course, which is fixed in the model. The first two comparisons are:

- AVA+CYC vs. CYC+GC (prednisolone in Denmark)
- AVA+RTX vs. RTX+GC (prednisolone in Denmark)

The user has the possibility to implement a second and a third induction in the model by defining the treatment pathways. The induction treatment chosen for the 2nd and the 3rd induction is the same in the Tavneos® and SoC arm.

Additionally, a comparison of AVA+CYC/RTX vs. CYC/RTX+GC is possible, considering a mix of induction therapy with CYC and RTX based on what is expected in clinical practice. The assumption in the base-case (Danish population) is that 20% of patients would receive RTX in combination with GCs or AVA and 80% would receive CYC in combination of GCs or AVA. Based on the Danish Treatment Guidelines [188,189].

The user has a possibility to choose patient population: Danish Population (base case); ADVOCATE ITT-population as well as the pre-defined subgroups from the ADVOCATE-study.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

8.2.1.1 Population

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

The population in the analysis reflects the indication and was based on the Danish Patient population in ADVOCATE study settings [155]. The population has been confirmed to be very similar to the population believed eligible for treatment with Tavneos® in Denmark [185,188,189], although the patient population in Denmark have a higher proportion of women (48 %) [185] and a lower proportion of MPA (prevalence approximately 11% and incidens approximately 14%, LPR3 2020). Selected baseline characteristics from ADVOCATE are presented in Table 30. The key demographics and clinical characteristics of the patient baseline ADVOCATE ITT Population are compared to the Danish Patient Population in Appendix C.

Table 30 Selected baseline characteristics in ADVOCATE [155]

Category	**Prednisone (N=164)**	**Tavneos® (N=166)**
Age (years) at Screening, mean ± SD	60.5 ± 14.50	61.2 ± 14.56
Gender, n (%)		

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

ANCA: Anti-neutrophil cytoplasmic antibody, BMI: Body mass index, BVAS: Birmingham vasculitis activity score, eGFR: Estimated glomerular filtration rate, IV: Intravenous, MDRD: Modification of Diet in Renal Disease, VDI: Vasculitis Damage Index.

By selecting the Danish patient population in the "model setting: population", the Danish distribution of gender has been implemented. The distribution of the GPA/MPA is the same for the choices of the "Danish population" and the "ADVOCATE ITT population".

The distribution of GPA/MPA can be manually changed in the model in the modelsetting.

In the scenario analysis, the cost-effectiveness in key pre-defined subgroups of ADVOCATE has been explored (see section 8.2.2). The subgroups are:
GPA
MPA
Relapsed
Treatment naïve

8.2.2 relationship between the clinical documentation, data used in the model and the Danish clinical practice

The duration of induction treatment in the model was 6 months whereas the ADVOCATE-trial patients received treatment for 52 weeks. We therefore wish to clarify that in the health economic model the duration of avacopan treatment was 52 weeks in accordance with the ADVOCATE-trial. During the first six months, avacopan treatment was modelled as induction treatment, and during the following six months as maintenance treatment. The duration of azathioprine maintenance treatment (24 months) in the model was in line with EULAR/ERA-EDTA recommendations and Danish guidelines [1,188,189]. Tavneos is intended to be used as one part of a regimen consisting of either rituximab or cyclophosphamide followed by azathioprine (EPAR). There is no clinical evidence to support the use of Tavneos in the long-term maintenance treatment (i.e., beyond 52 weeks) and it is not expected to be used as off-label treatment for that purpose. This is endorsed by the soon published updated EULAR/ERA-EDTA guidelines.

8.2.2.1. Intervention

Tavneos® (avacopan), in combination with a RTX or CYC regimen, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) [8]. Tavneos® is a small molecule drug that selectively inhibits C5aR1, thereby inhibiting the C5a receptor [9].

The recommended dose is 30 mg Tavneos® (3 hard capsules of 10 mg each) taken orally twice daily, morning and evening, with food. Tavneos® should be administered in combination with a RTX or CYC regimen as follows:

- rituximab for 4 weekly intravenous doses or,
- intravenous or oral cyclophosphamide for 13 or 14 weeks, followed by oral azathioprine or mycophenolate mofetil and,
- glucocorticoids as clinically indicated.

The compliance is in the calculations assumed to be:

- 100 % for the two hospital dispensed medicines CYC and RTX administrated in the hospital department.
- 86,4 % for avacopan tablets because the patients administrated it at home twice daily [155].

Clinical study data are limited to 52 weeks of exposure followed by 8 weeks of observation [8]. A summary of the intervention characteristics is presented in Table 31below.

Table 31 Summary of intervention characteristics

Intervention	Clinical Documentation	Used in the model	Expected Danish Clinical Practice
Posology	30 mg twice daily, Oral administration, morning and evening [154]	30 mg twice daily, Oral administration, morning and evening	30 mg twice daily, Oral administration, morning and evening
Length of treatment	6 months (duration of induction period) + 6 months maintenance: Total of 52 weeks [188,189]	6 months (duration of induction period) + 6 months maintenance: Total of 52 weeks	6 months (duration of induction period) + 6 months maintenance: Total of 52 weeks
Indication	Adults with ANCA-associated vasculitis (GPA or MPA) [154]	Adults with ANCA-associated vasculitis (GPA or MPA)	Adults with ANCA-associated vasculitis (GPA or MPA)
Position in clinical practice	Tavneos® in combination with rituximab or cyclophosphamide followed by azathioprine	Tavneos® in combination with rituximab or cyclophosphamide followed by azathioprine	Tavneos® in combination with rituximab or cyclophosphamide followed by azathioprine
ANCA-associated vasculitis: Anti-neutrophil cytoplasmic antibody - associated vasculitis; GPA Granulomatosis polyangitis; MPA: Microscopic polyangitiis			

8.2.2.2 Comparator

Current SoC for induction in Demark is immunosuppressants (RTX/CYC) combined with GC (prednisolone) which was considered the most relevant comparator for Tavneos® [188,189].

In Danish treatment guidelines [188,189], the current SoC for ANCA-associated vasculitis is CYC (administered via intermittent intravenous [IV] pulse therapy) combined with GCs (prednisolone). RTX can be administered in place of CYC, when CYC is contraindicated.

In the base case analysis Tavneos® is compared to a 50% mix of CYC+GC and RTX+GC and in key scenario analysis Tavneos® is compared to CYC+GC and RTX+GC, respectively. In all cases GC is assumed to be prednisolone.

8.2.2.3 Outcomes

The model estimates total costs for the treatment with Tavneos® and for SoC (CYC+GC or alternatively, RTX+GC). Benefit (or harm) of treatments were measured using life-years gained (LYs) and QALYs. Incremental differences are reported and summarized using ICERs.

8.2.2.4 Time horizon and cycle length

The time horizon of the analysis must be long enough for all the important future differences in costs and health effects between alternatives to be captured. That is, the time horizon must be such that making it longer would not affect the results in any meaningful way. With patients in the ADVOCATE trial having a mean age of 60 when receiving the treatment in both arms, a lifetime horizon (40 years) was considered appropriate. Different time horizons are tested in sensitivity analyses.

8.2.2.5 Discounting

A discount rate of 3,5% (year 0-35) and 2,5% (year 36-70) was applied to both cost and outcomes in the model see Table 32. The rate was based on the Danish Ministry of Finance 2022.

Table 32 Discounting rate used in the health economic analysis

Denmark	Discount rates: costs, outcomes	Comment/source
Year 0-35	3,5%,3,5%	The Danish Ministry of Finance 2022
Year 36-70	2,5%,2,5%	The Danish Ministry of Finance 2022

8.2.2.6 Uncertainty

To account for uncertainty, both a one -way sensitivity analysis and a probabilistic sensitivity analysis (PSA) were performed see section 8.7.

8.3 Extrapolering af relevant efficacy

8.3.1 Patient population

The patient population used in the analysis was based on patient characteristics in ADVOCATE [155] and the Danish Nationwide study of incidence and survival Nelveg-Kristensens et al [185]. Patient characteristics used in the analysis are presented in (Table 33) and compared to values in ADVOCATE.

Table 33 Patient characteristics used in the analysis

Characteristic	Used in analysis	Source	ADVOCATE	User changeable
Age	60	Nelveg-Kristensen [185]/Advocate [155]	61	Yes
Mean body weight (kg)	77	ADVOCATE [155]	77	Yes
Mean body surface (m^2)	1.92	ADVOCATE [155]	1.92	Yes

8.3.2 Effectiveness

The main inputs for effectiveness were sourced from the pivotal trial ADVOCATE. The key inputs are:

- Probability of remission
- Probability of relapse
- Probability of ESRD
- Adverse event rate

In addition to ADVOCATE, studies sourced from literature were used to inform the model.

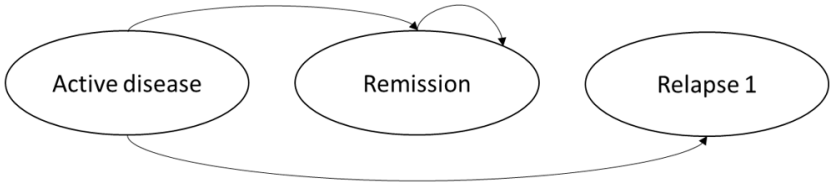
8.3.3 Transition probabilities

8.3.3.1Transition probability - Remission

In the analysis, all patients enter the model in the health state 'Active disease'. The probability of achieving first remission (**Fejl! Henvisningskilde ikke fundet.**Figure 31) is based on remission rates observed in ADVOCATE at week 26 (see Table 34) [155].

Patients In the ADVOCATE study have only received one course of treatment and in the model patients that fail to achieve remission will remain with active disease but will transfer to the health state 'Relapse 1'. In the model patients will only be broad to remission one time.

Figure 31 First remission



It was assumed that there is no difference in remission rates between RTX and CYC based on non-inferiority of RTX in the RAVE clinical trial [109].

Table 34 Remission rates observed in the ADVOCATE trial at week 26 for the ITT population

	Tavneos®	RTX (SoC)	CYC (SoC)
	% (95 % CI)	% (95 % CI)	% (95 % CI)
Remission rates at 26 weeks	72.3% (64.8,78.9)	70.1% (62.5,77.0)	70.1% (62.5,77.0)
Remission rates at 52 weeks	65.7% 57.9,72.8)	54.9% (46.9,62.2)	54.9% (46.9,62.2)

RTX: Rituximab, CYC: Cyclophosphamide, SoC: Standard of care

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 [155]. 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 [109].

Based on the observed remission rates in Table 34, the 4-week cycle probability of remission for Tavneos® and the comparator was calculated based on the exponential distribution:

Tavneos®

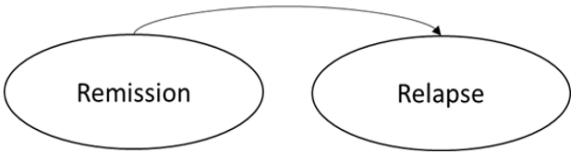
$$1 - e^{-\left(-\frac{\ln(1-0.723)}{26}\right)\cdot 4} = 0.179$$

And for SoC:

$$1 - e^{-\left(-\frac{\ln(1-0.701)}{26}\right)\cdot 4} = 0.170$$

8.3.3.2 1Transition probability - Relapse

Figure 32 Transition probability of a relaps



The relapse rate from remission was estimated as the difference in remission rates at week 26 and week 52 in ADVOCATE. For SoC (RTX/CYC arm in ADVOCATE):

$$r(4\,weeks) = -ln\left(\frac{p(52\,weeks)}{p(26\,weeks)}\right)\cdot\frac{4}{26} = (\ln(0.701) - \ln(0.549))\cdot\frac{4}{26} = 0.0376.$$

The corresponding four-week rate for Tavneos®:

$$r(4\,weeks) = -ln\left(\frac{p(52\,weeks)}{p(26\,weeks)}\right)\cdot\frac{4}{26} = (\ln(0.723) - \ln(0.657))\cdot\frac{4}{26} = 0.0147.$$

The relative treatment effect of Tavneos® may be expressed as a hazard ratio (HR):

$$HR = \frac{0.0147}{0.0376} = 0.39.$$

From week 52 and onwards the HR is assumed to be one. Based on a real-world study using the Clinical Practice Research Datalink (CPRD), the probability of moving from remission to relapse is assumed to decrease with time [217]. The transition probability from remission to relapse after two years in remission is assumed to be 20% of the transition probability in the first two years – i.e., the rate of relapse was divided by five [188]. The resulting risk (probability) of relapse per time-period is presented below in (Table 35). Please note that the above calculated rates have been transformed to probabilities assuming an exponential distribution.

Table 35 Probability of relapse per time period

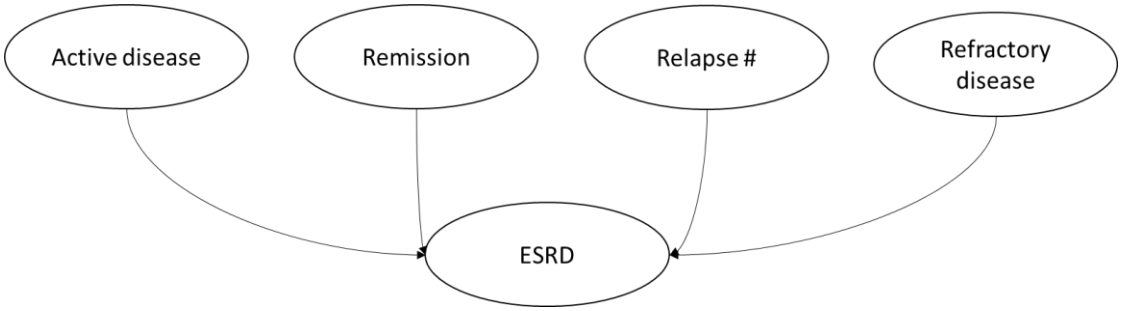
	Tavneos®	SoC
Transition probability - 1st and 2nd year, week 26-52	0.0146	0.0369
Transition probability - 1st and 2nd year, week 52-60	0.0369	0.0369
Transition probability - 1st and 2nd year, week 60+	0.0369	0.0369
Transition probability - 2+ years in remission	0.0075	0.0075

SoC: Standard of Care

8.3.3.3 End stage renal disease (ESRD)

The risk of ESRD is assumed to be different depending on treatment and disease status: active disease (or relapse), remission and refractory disease**Fejl! Henvisningskilde ikke fundet.**.

Figure 33 End stage renal disease



The effect of Tavneos® is modelled by adjusting the risk of ESRD based on eGFR data from ADVOCATE at week 26 and 52, respectively.

Based on a study by Robson *et al.* [44], patients are at a higher risk of developing ESRD in the first six months following disease onset compared to subsequent years [189]. The transition probability in the active disease or relapse health states is assumed to correspond to the probability in the first six months after diagnosis reported in the Robson *et al.* study. The 4-week transition probability based on long-term data up to seven years of follow-up is used as a proxy for probability of ESRD in remission, see (Table 36) for the rates reported by Robson *et al* [44].

Table 36 ESRD transition probability based on literature

Time point	Proportion with ESRD	4-week rate	Source
6-months	6.4%	0.0101	[44]
7.1 years	13.9%	0.0009	[44]

ESRD: End stage renal disease

No evidence for the rate of ESRD for patients with refractory disease was identified from the literature, therefore this probability is informed by adjusting the long-term probability of remission reported by Robson *et al.* [44]. Refractory patients are assumed to have the same risk of ESRD as patients with active disease (relapse).

In the Danish base case ESRD rates per health state are adjusted based on eGFR data from ADVOCATE (Table 37) at week 26 (induction) and week 52 (remission) to consider the relative treatment effect of Tavneos® compared to SoC.

Table 37 Recovery of eGFR points at induction observed in ADVOCATE

	Tavneos®	SoC	Source
eGFR points – week 26	5.8	2.9	[155]
eGFR points – week 52	7.3	4.1	

eGFR: Estimated glomerular filtration rate, SoC: Standard of care

The ESRD rate is adjusted by a HR estimated based on the difference in eGFR improvement between Tavneos® and SoC in ADVOCATE in combination with a HR (0.90) for the risk of ESRD per unit increase in eGFR from a study by Gercik *et al.* [224], for the first induction period:

$$HR_{Tavneos} = 0.90^{5.8} = 0.54.$$

The corresponding HR for SoC:

$$HR_{SoC} = 0.90^{2.9} = 0.74.$$

And for the first remission:

$$HR_{Tavneos} = 0.90^{7.3} = 0.46.$$

$$HR_{SoC} = 0.90^{4.1} = 0.65.$$

These calculations can be found in the "AE calculations" sheet of the model, where different HRs associated with an improvement in eGFR may be selected, identified from other studies than Gercik *et al.* [224] in a pragmatic literature search [225-227].

Gercik et al 2020 [224]

Brix et al 2018 [225]

Menez et al 2018 [226]

Ford et al 2014 [227]

Gercik et al 2020 [224] was one of the latest publication regarding this kind of data and it was endorsed by Key Opinion Leaders in UK, Sweden and Norway as clinical relevant and valid to be used in the model.

In the Model Settings the other sourses of data can be chosen, if scenario analysis to base-case to be done.

The four studies were identified based on pragmatic literature searches to inform specific parts of the model (ESDR, probability of death due to infections), for which no studies were identified in the clinical SLRs.

PHMR conduct systematic literature reviews to inform the NICE submission. This includes SLR for clinical and HRQoL studies (see attached report for each which was published in the NICE committee papers).

The SLR did not identify all the inputs needed for the model and these had to be sourced using pragmatic literature searches and hand searches of key papers and NICE TA reports, which is a standard approach in economic modelling. Most of the papers identified below were obtained from pragmatic searches, so there is no record of the search procedure. The papers cover the following areas of the model:

Utility values in the ESRD health state (specifically dialysis) (Fletcher BR et al 2022 [236])

Probability of ESRD (Robson et al 2015 [44])

Probability of death due to GC infection (Little et al 2010 [64])

Impact of change in eGFR and the probability of ESRD (Gercik et al 2020 [224])

Considering that the above parameters have a substantial impact on the model results. A more formal approach to identifying the studies could make the model and HTA dossiers which it informs more robust.

The risk of ESRD in relapse is assumed to be the same for Tavneos® and SoC, based on the rates in Robson *et al.* [44] and adjusted using the change in eGFR points observed in ADVOCATE.

For each relapse a loss of eGFR of 10 ml/min is assumed based on Karras *et al*. [214]. In the study, the drop is associated with a renal relapse but in the model, this value is assumed for all relapses in ANCA-associated vasculitis.

A summary of the final transition probabilities to ESRD are presented below in Table 38.

Table 38 Final transition probabilities to ESDR per health state in the model

Health state	Arm	Probability per cycle **of ESRD**	Comment	Source
Active disease, model cycles 1-7+: Induction 1	SoC	0.0075	Based on first six- month rates reported in Robson *et al.* and eGFR point reductions in ADVOCATE.	Robson *et al. [44]* ADVOCATE [155]
Active disease, model cycles 1-7+: Induction 1	Tavneos®	0.0055	Based on first six- month rates reported in Robson *et al.* and eGFR point reductions in ADVOCATE.	Robson *et al. [44]* ADVOCATE [155]
Remission, model cycles 1-6: Remission 1	SoC	0.0066	Based on first six- month rates reported in Robson *et al.* and eGFR point reductions in ADVOCATE.	Robson *et al. [44]* ADVOCATE [155]
Remission, model cycles 1-6: Remission 1	Tavneos®	0.0047	Based on first six- month rates reported in Robson *et al.* and eGFR point reductions in ADVOCATE.	Robson *et al. [44]* ADVOCATE [155]
Remission, model cycles 7+: Remission 1	SoC and Tavneos®	0.0006	Based on 7.1-year rates reported in Robson *et al.* and eGFR point reductions in ADVOCATE.	Robson *et al. [44]* ADVOCATE [155]
Relapse, model cycles 1-7+: Induction 2	SoC	0.0158	Based on first six- month rates reported in Robson *et al.* and eGFR point reductions in ADVOCATE and estimated drop in eGFR after relapse.	Robson *et al. [44]* ADVOCATE [155]
Relapse, model cycles 1-6: Induction 2	Tavneos®	0.0116	Based on first six- month rates reported in Robson *et al.* and eGFR point reductions in ADVOCATE and estimated drop in eGFR after relapse.	Robson *et al. [44]* ADVOCATE [155]
Relapse, model cycles 7+: Induction 2	Tavneos®	0.0158	Assumption – same as for SoC	
Remission, model cycles 1-6: Remission 2	Tavneos®	0.0088	Based on first six- month rates reported in Robson *et al.* and eGFR point reductions in ADVOCATE and estimated drop in eGFR after relapse.	Robson *et al. [44]* ADVOCATE [155]
Remission, model cycles 1-6: Remission 2	SoC	0.00123	Based on first six- month rates reported in Robson *et al.* and eGFR point reductions in ADVOCATE and estimated drop in eGFR after relapse.	Robson *et al. [44]* ADVOCATE [155]
Remission, model cycles 7+: Remission 2	SoC and Tavneos®	0.0011	Based on 7.1-year rates reported in Robson *et al.* and eGFR point reductions in ADVOCATE and estimated drop in eGFR after relapse.	Robson *et al. [44]* ADVOCATE [155]
Relapse, model cycles 1-6: Induction 3	SoC	0.0330	Based on first six- month rates reported in Robson *et al.* and eGFR point reductions in ADVOCATE and estimated drop in eGFR after relapse.	Robson *et al. [44]* ADVOCATE [155]
Relapse, model cycles 1-6: Induction 3	Tavneos®	0.0244	Based on first six- month rates reported in Robson *et al.* and eGFR point reductions in ADVOCATE and estimated drop in eGFR after relapse.	Robson *et al. [44]* ADVOCATE [155]
Relapse, model cycles 7+: Induction 3	Tavneos® and SoC	0.0330	Based on first six- month rates reported in Robson *et al.* and eGFR point reductions in ADVOCATE and estimated drop in eGFR after relapse.	Robson *et al. [44]* ADVOCATE [155]
Remission, model cycles 1-6: Remission 3	SoC	0.0227	Based on first six- month rates reported in Robson et al. and eGFR point reductions in ADVOCATE and estimated drop in eGFR after relapse.	Robson *et al. [44]* ADVOCATE [155]
Remission, model cycles 1-6: Remission 3	Tavneos®	0.0163	Based on first six- month rates reported in Robson *et al.* and eGFR point reductions in ADVOCATE and estimated drop in eGFR after relapse.	Robson *et al. [44]* ADVOCATE [155]

Remission, model cycles 7+: Remission 3	Tavneos® and SoC	0.0020	Based on 7.1-year rates reported in Robson *et al.* and eGFR point reductions in ADVOCATE and estimated drop in eGFR after relapse.	Robson *et al. [44]* ADVOCATE [155]

eGFR: Estimated glomerular filtration rate, ESRD: End stage renal disease, SoC: Standard of care

8.3.3.4 Mortality

For the background mortality, Danish life tables for women and men, respectively, was used, provided in the Excel Model, sheet: Danish Inputs [228]. To account for the increased mortality for individuals with ANCA-associated vasculitis and in individuals with ESRD, compared to the general population, a relative risk is applied to the life table.

For the relative risk, data from the literature is used. Mortality rates in the active disease, remission and relapse health states are assumed to be equal and are based on a study by Jayne *et al*, [229].

8.3.3.5 Literature based mortality adjustment

Wallace *et al.* investigated mortality trends in patients diagnosed with GPA between 1992 and 2013, using the Health Improvement Network (THIN) in the UK [82]. They showed that mortality in the first year following diagnosis is higher than in subsequent years. The HR for mortality in the first year was reported to be 6.31 (95% CI 3.62-10.98), while the HR is 2.51 (95% CI 1.88-3.36) over 10 years follow-up.

Nelveg-Kristensen et al found the overall risk of death associated with ESDR was 1,74 (CI 1,29-2,37, P<0,001) and the risk of dead and ESDR were decreasing over time in the Danish cohort study [185].

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 39.

Table 39 Summary of Studies reporting the cumulative incidence of ESRD in AAV

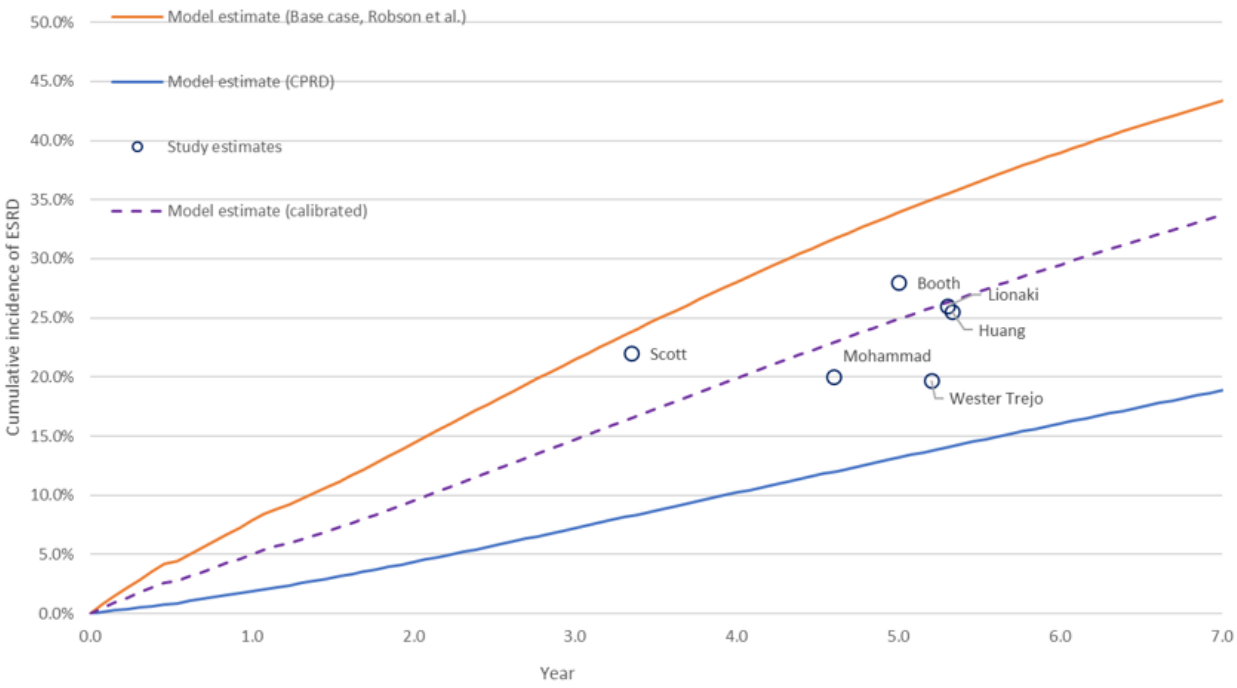
Study	Country	Recruitment period	N	Median full-up	Cumulative incidence
Booth et al. 2003 [204]	UK	1995-2000	246	5.0	28.0%
Huang et al. 2021 [243]	China	2003-2017	141	5.3	25.5%
Lionaki et al. 2009 [59]	USA	1986-2007	523	5.3	26.0%
Mohammad et al. 2014 [50]	Sweden	1997-2009	183	4.6	20.2%
Scott et al. 2021 [244]	Ireland	2012-2020	332	3.4	22.0%
Wester Trejo et al. 2019 [63]	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. [44] and CPRD) in Figure 34.

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 34.

Figure 34 Comparison of cumulative incidence of ESRD reported in published studies in AVV and the model



Due to the lack of a proper source, the Swedich Kidney Register [230] data for 2020 were used to calculate the standardized Mortality Ratio (SMR). This was achieved by extracting the total number of patients in 2020 (10.297) and the mortality probability (9,8%) for that year. Using the average age of the male and female patients, we calculated what the mortality was for the general population of the same age, in Sweden. Next we calculated what expected deaths for a kidney patients would be based on the general population mortality (i.e. 56,6). Lastly, we divided the observed numbers of deaths in the kidney registry (i.e., 1009) by the number of expected deaths based on the general population (i.e., 56,6) and reached an SMR of 17,83. For the detailed calculation see the table below.

Table Calculation of SMR based on the Swedich Kidney Registry Data [230]

Mortality in 2020 (SNR)	9,80%	divide by expected mortality			
Total patients in 2020 (SNR)	10297	https://www.medscinet.net/snr/rapporterdocs/SNR_arsrapport%202021_webversion.pdf			
	Men	Women	Total		
Percentage	65%	35%	1		
Average age	60,68	59,54	60,28		
Total patients	6693	3604	10297		
Deaths in 2020	656	353	1009		
Population	Deaths	Population	Deaths/population	SNR population	Expected deaths in SNR
Men 61 years old in 2020	375	57804,5	0,006487384	6693	43,42038682
Women 60 years old in 2020	209	57112,5	0,003659444	3604	13,18845349
Total	584	114.917	0,010146828	10297	**56,60884031**
SMR=observed deaths/expected deaths	**17,82594369**				
SD SMR	0,561156679	1,09986709			
Upper CI	18,92581078				
Lower CI	16,7260766				

The SMR for patients with ESRD is taken from the Swedish Kidney Register [230]. The estimated SMR for ANCA-associated vasculitis patients is approximately 17.83 [95%CI 16.73,18.93]. The SMR is calculated using the observed mortality for the population in the Swedish kidney register, DNLS, Nelveg Kristensen et al and the expected number of deaths for the general population [185,190,230].

Dansk Nefrologisk Selskabs Landsregister (DNSL) works with 4 Indicators all around mortality and patient survival (Indicator 3, 5A, 5B and 7) calculated for patients in dialysis and kidney transplanted, respectively [190]. The four indicator results from DNSL are comparable with the Swedish Kidney Registry [190, 230].

Table 40 Hazard ratios and standard mortality ratios for ANCA-associated vasculitis

	Literature based
First year	6.31 [82]
Subsequent years	2.51 [82]
ESRD*	17.83 [230]

ESRD: End-stage renal disease. *Calculated using the observed mortality for the population in the Swedish kidney register, DNLS, Nelveg Kristensen et al and the expected number of deaths for the general population [185, 190,230].

8.3.3.6 Mortality adjustment for Tavneos®

Treatment with immunosuppressants in ANCA-associated vasculitis is associated with a significantly increased risk of infections [105,128]. Around half of all deaths in the first year following an ANCA-associated vasculitis diagnosis are caused by infections [3,64]. To reflect the reduced burden of infection-related deaths through the GC sparing capacity of Tavneos®, the HR for mortality from literature was adjusted in the first year. 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 literature
HR_{yr2+} = HR of death in subsequent years in AAV from literature

α = Proportion of deaths attributed to GC
β = Proportion of infections avoided using Tavneos®

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 [64]. 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 one), the equation reduces to $HR_{adj} = HR_{yr2+}$, i.e., all excess infection-related deaths in first year are avoided and the rate equals to the HR applied in subsequent years of treatment. If we assume that no infections can be avoided by using Tavneos® (β is set to zero), the equation reduces to $HR_{adj} = HR_{yr1}$, i.e., the probability of death with Tavneos® is equal to GC-based treatments.

The calculation of the betavalue in the model is calculated based on serious infection-related AE from the ADVOCATE-study, which the investigators have accessed as being related to the study treatment, cf. Appendix S Table 14.3.1.6.2 Treatment-Emergent Serious Adverse Events possible related to Study Treatment (Prednisone/Placebo) by system Organ Class and Preferred term (Safety Population). The table reports Serious Infections-Related AEs that investigators have considered related to the prednisone/placebo in each treatment group to estimate the proportion of infections avoided using avacopan. It means that 1,8 % (3/166) of the patients who received avacopan+SOC experienced a serious infection event related to prednisone and 6,7 % (11/164) of the patients who received Prednisone+SOC experienced a serious infection event related to Prednisone. The relative reduction in the incidence the beta value was (6.7%-1.8%)/6.7% = 73.1%).

8.3.3.7 Adverse events

Glucocorticoid therapies are associated with numerous side effects and the toxicity increases with daily and cumulative dose. AEs can be considered in the analysis in two distinct ways: the direct use of AE rates as seen in Table 41 or by including the costs associated with hospitalisation – rates of hospitalisation were taken directly from ADVOCATE. In the base case analysis, AEs are assumed to be covered by hospitalisations as captured in ADVOCATE (see section 8.5 Hospitals costs).

8.3.3.8 Adverse events from ADVOCATE

Grade 3 or 4 AEs reported in the Tavneos® and SoC arm of the ADVOCATE trial were derived from the CSR, see Table 41.

Table 41 Adverse events reported in ADVOCATE

Adverse event	SoC	Tavneos®
AAV	12.2%	7.2%
Pneumonia	3.7%	4.8%
GPA	0.6%	3.0%
Acute kidney injury	0.6%	1.8%
Urinary tract infection	1.2%	1.8%
Angina pectoris	0.0%	1.2%

Cardiac failure	0.0%	1.2%
Device-related infection	0.0%	1.2%
Drug hypersensitivity	1.2%	1.2%
Hepatic enzyme increased	1.8%	1.2%
Hepatic function abnormal	0.0%	1.2%
Hyperglycaemia	0.6%	1.2%
Influenza	0.6%	1.2%
Pyrexia	1.8%	1.2%
Acute myocardial infarction	1.2%	0.6%
Agranulocytosis	1.2%	0.6%
Blood creatinine increased	1.2%	0.6%
Lymphopenia	1.8%	0.6%
Pulmonary alveolar haemorrhage	1.2%	0.6%
Anaemia	1.2%	0.0%
Dehydration	1.2%	0.0%
Diarrhoea	1.8%	0.0%
Epistaxis	1.2%	0.0%
Herpes zoster	1.2%	0.0%
Infectious pleural effusion	1.2%	0.0%
Large intestinal polyp	1.2%	0.0%
Microscopic polyangiitis	1.2%	0.0%
Mononeuropathy multiplex	1.2%	0.0%
Neutropenia	1.2%	0.0%
Pneumonia bacterial	1.2%	0.0%
Prostate cancer	1.2%	0.0%
Pulmonary embolism	1.8%	0.0%
Respiratory syncytial virus infection	1.2%	0.0%
Thrombocytopenia	1.2%	0.0%
Vomiting	1.2%	0.0%

AAV: antibody – associated vasculitis, GPA: Granulomatosis polyangiitis (Wegener's), SoC: Standard of care

8.4 Documentation of health-related quality of life (HR-QoL)

8.4.1 Overview of Health-state utility values

In the ADVOCATE-study Health-related Quality of Life was assessed with the Medical Outcomes Study Short Form 36 version 2 survey [220] and the EQ-5D-5L [158]. These assessments were completed on day 1 (pre-dosing) and week 4, 10, 16, 26, 39, 52, and 60 [155,155a] and Appendix AE Confidential table TDK 4.

In the Health-Economic model the utilities were devided from EQ-5D-5L data from ADVOCATE and valued using the 5L to 3L cross-walk algorithm from the van Hout paper [231] and associated Stada code is attached the confidential Appendix AI England cross walk stata and the Appendix AJ Costom Analysis (12) table e988 itt UK.

8.4.2 Health state utility values used in the health economic model

The model uses health-state utility values (HSUV) from EQ-5D-5L data from ADVOCATE stratified by health state (active disease, remission, and relapse) according to remission and relapse definitions in the trial. Utility values corresponding to EQ-5D-3L states are based on the van Hout cross-walk [231]. The HSUVs are presented in Table 43.

The data for EQ-5D-5L were collected at baseline, week 26 and 52 from ADVOCATE study [155, 155a]. Number of patients evaluated, and change compared to baseline can be seen in the Table 42 below.

The utilities are calculated based on the combination of answers on the five dimensions (EQ-5D, index scale).

Table 42 Score on EQ-5D-5L, index [155a]

	Avacopan	Prednisone	Different
	N=166	N=164	(95% CI)
Baseline			
Patient Evaluated	166	160	
Mean + SEM	0,75±0,018	0,77±0,018	
Change from baseline to week 26			
Patient Evaluated	152	146	
Least -squares mean (LSM+SEM)	0,02±0,014	0,00±0,015	0,02 (-0,01 to 0,06)
Change from baseline to week 52			
Patient Evaluated	149	145	
Least -squares mean (LSM+SEM)	0,05+0,015	0,00+0,015	0,05 (0,01 to 0,09)

LSM = Least squares mean; = standard error of the mean

It is not possible to make the calculation with the Danish Preference Weighs without individual patient data. Vifor have no access to individual patient data, due to the contract between Vifor and Chemocentrix. The UK preference weight have been used – it was the only possibility.

Table 43 Health-state utility values used in the base case analysis

Health-state	**HSUV Tavneos®**	**HSUV SoC**	**Comment/Source**
Active disease	0.708	0.697	Cross-walked [155,231]
Remission	0.790	0.766	Cross-walked [155,231]
Relapse	0.738	0.678	Cross-walked [155,231]

HSUV: Health state utility value, SoC: Standard of care

In the base case, health state utilities are assumed to be treatment-specific (e.g., separate estimations for the two arms of ADVOCATE). Any difference in the utility values between treatments for the same health state is assumed to be attributed to reduced use of GCs with Tavneos®. Therefore, when treatment-specific utilities are selected, utility decrements for individual AEs are automatically switched off in the model to avoid double counting.

In addition to the HSUV for active disease, remission, and relapse the analysis also captures the utility of the ESRD health-state. The HSUV for ESRD is dependent on the treatment received. See table 39.

Table 44 Health state utility values for end stage renal disease (ESRD)

ESRD	HSUV	Comment/Source
Dialysis	0,774 (0,767-0,781)	Fletcher BR et al 2022 [236]
Renal transplant	0.840 (0,821-0,59)	Fletcher BR et al 2022 [236]

ESRD: End stage renal disease, HSUV: Health state utility value

HSUV for ESDR was identified from Fletcher BR et al 2022. Detailed information of the ad-on literature review of the published literature reporting HSUV for patients in dialysis or transplanted (June 2021 to October 2022) is provided in appendix Q.

Treatment independent HSUV and disutilities associated with AEs are presented in Table 45.

Table 45 Treatment Independent HSUV and disutility associated with AE

Health state	**HSUV**	**Source**
Active disease	0.702	ADVOCATE [155]
Remission	0.778	
Relapse	0.696	

8.4.2 Quality of Life – age adjustment

In order to account for age during the time horizon, HR QoL was adjusted for the decrease of utility with age based on EQ-5D-3L values presented by DMC in "Appendix: Aldersjustering for sundhedsrelateret livskvalitet". The multiplicative method was used to adjust the index score per age group Table 46.

Table 46 Age-adjustment, weight used by age group

Age group	EQ-5D-3L index score (SD)
20-29	0,871
30-39	0,848
40-49	0,834
50-59	0,818
60-69	0,818
70-79	0,813
80-88	0,721
>88*	0,721

8.5 Resource use and costs

8.5.1 pharmaceutical costs

8.5.1.1 Intervention

Tavneos® is administered as, 30 mg (3 hard capsules of 10 mg each) taken orally, twice daily for a period of 52 weeks [154,155]. As Tavneos® is administered orally, no costs are assumed to be incurred. Table 47 details the cost for the intervention and Table 48shows the treatment costs of Tavneos®.

Table 47 Tavneos® cost

Drug	Strength	Pack size	PPP (DKK)	Compliance/Relative dose intensity
Tavneos®	10 mg	180	52.033,97	86.4%

PPP: Pharmacy purchasing price, PSP

As Tavneos® is given alongside rituximab or cyclophosphamide, and with maintenance, azathioprine is added, these treatment costs are also considered and added in both treatment arms. For details see section 8.5.1.2.

Table 48 Tavneos® treatment cost

Treatment duration	Administration plan	Total dose	Total cost (DKK)
Daily	Twice daily	60 mg	1.734,47
Monthly	28 days	1.680 mg	48.565,44
Annual	52 weeks	21. 840 mg	631.345,50

8.5.1.2 Comparator

The comparator presented in the CEM for the induction stage is rituximab or cyclophosphamide alongside glucocorticoids. For maintenance, azathioprine is added.

The pharmacy purchase prices from www.medicinpriser.dk (06/04/2022) are used. The cheapest packaging or combinations of packaging are used for the calculation. If there is generic competition the cheapest brand is used.

Table 49 RTX/CYC treatment cost

Drug	Strength	Pack size	PPP (DKK)	Treatment duration	Total cost (DKK)
Cyclophosphamide	1,000 mg 200 mg	1 1	307,50 61,50	15 mg/kg, 4 cycles*	2.214,00
Rituximab	500 mg/ 50 ml 100 mg/vial	1 3	8.194,58 1.638,92	375mg/m^2, 1 cycle**	52.445,36
Azathioprine¥	50 mg 25 mg	100 50	55,45 107,50	Started at week 15 until week 52***	719,00
Prednisone¥	25 mg 5 mg 2,5 mg	100 100 100	399,00 38,42 80,54	Day 1 to 140¥¥	633,22

*Cyclophosphamide administration - cycle 1: days 1 & 15, cycle 2: days 29 & day 49, cycle 3: Day 70, cycle 4: Day 91. ** Rituximab administration – cycle 1: days 1, 8, 15, 22. *** Azathioprine administration - Titration up to 2mg/kg/day over 2 weeks. ¥¥ Tapered to 60mg/day ¥Compliance rate is 98.4%; PPP: Pharmacy purchasing price

As descriped in section 8.2.2 the model includes maintenance treatment with Azathioprine from week 15 to 52, starting with a tritation up to 2 mg/kg/day over 2 weeks. The costs is included in the pharmaceutical cost in both treatment arms.

8.5.2 Hospitals costs

Certain drugs were offered intravenously and hence incurred administration costs. It was assumed no administration costs were incurred for oral treatments. Costs were sourced from the department of “InteraktiveDRG 2022” from Sundhedsdatastyrelsen Table 50.

In the calculation the DRG gruppe tariffs for hospital costs, as an average estimates rather than dividing into subelements and it is assumed the monitoring and maintenance tests lab-tests are included in the DRG group tariffs.

Table 50 Total administration costs

Therapy	Procedure SKS kode	DRG gruppe DRG gruppe kode	DRG takst	Number of infusions	Drug costs	Total costs (DKK)

Cyclophosphamide IV	BOHJ3 Cytostatisk behandling med immunomodulerende virkning	08MA12 Generaliseret bindevævs sygdom	43.621	6	3.723	258.003
Rituximab IV	BOHJ11 Behandling med CD20 antistof	08MA12 Generaliseret bindevævs sygdom	43.621	4	57.690	116.794

IV: Intravenous

In the application the cost for the medicines is calculated separately. This is the reason for deducting the drug price in the calculation, so that it does not count twice.

Costs associated with ESRD

Patients in ESRD health state incur more costs associated with this debilitating state. These are associated with treatments specific to the disease such as hemodialysis and transplant. The proportion of patients receiving peritoneal dialysis, hemodialysis, and renal transplant) for ESRD were estimated using the data from DNSL Årsrapport [190] and are presented in Table 51.

Table 51 Distribution of ESRD treatment

Item	Estimate	Reference
Peritoneal dialysis	9,2 %	Prevalent patients, DNSL [190]
Haemodialysis	36,4 %	Prevalent patients, DNSL [190]
Renal transplant	54,4 %	Prevalent patients, DNSL [190]

The costs for maintenance dialysis and ongoing treatment for renal transplant were sourced for InteraktiveDRG 2022.

Table 52 ESRD-assocoation cost

Item	Cost (DKK)	Comment/Reference
Maintenance dialysis, per annum	101.953	08MP68 Medicinske sygdomme I muskel-skeletsystemet og bindevæv med dialyse
Renal transplant, first year, per annum	546.270	Nyretransplantation, kompliceret
Renal transplant, ongoing, per annum	101.953	08MP68 Medicinske sygdomme I muskel-skeletsystemet og bindevæv med dialyse

InteraktivDRG 2022

Hospital cost related to management of ANCA-associated vaskulitis patients

Hospital admissions are considered a significant cost item in the management of ANCA-associated vasculitis patients. The mean number of hospitalisations and length of stay were sourced from the ADVOCATE trial and tariffs from the Danish DRG were used to estimate the cost. The DRG takst and the trimpoint was based on the DRG for non-complicated/complicated hospitalisation due to ANCA-associated vasculitis. Frequency of hospitalisation as seen in ADVOCATE is presented in Table 55.

Table 53 Hospital length of stay from ADVOCATE study and Cost for patients with ANCA-associated vasculitis [155]

Patient population	DRG gruppe	DRG takst 2022*1	Hospital length of stay days*2	Trimpunkt*1	langliggertakst/dag*3	In total
Avacopan	08MA12 Generaliserende Bindevævssygdomme	43.621	13,8	14	2.185	43.621

GC SoC	08MA12 Generaliserende Bindevævssygdomme	43.621	19,6	14	2.185	56.731

*1 DRG-takster 2022

*2 Post Hoc analyse done for modelling Hospitalization Length of stay ADVOCATE study, Appendix L, [156]

*3 Langliggertaksten, Sundhedsdatastyrelsen Takstsystem 2022, Vejledning

Table 54 Calculation Mean Number of Hospitalisations

	Tavneos	SoC
ADVOCATE Intent to Treat Population [155]	166	164
Number of Hospitalisations*1	78	111
Mean number of hospitalisations	0,47	0,68

***1** Post Hoc analyse done for modelling Hospitalization Length of stay ADVOCATE study, Appendix L, [156]

Table 55 Frequency, length, and cost of hospital admission (DRG) in the ADVOCATE [155]

	Tavneos®	SoC
Mean number of hospitalisations	0.47	0.68
Mean length of stay	13.80	19.60
Mean annual cost of hospitalisation (DKK)	20.496,61	37.805,65
Mean cycle cost of hospitalisation (DKK)	1.576,66	2.908,13

Soc: Standard of careT

In addition to the HSUV for active disease, remission, and relapse the

8.5.3 Transport costs and time spend by patients and relatives

Patients' and relatives´ time, as well as travel costs were included in the base case. Patients' and relatives´ time is estimated based on resource use and average income 181 DKK per hour [DMC Værdisætning af omkostninger version 1.6.]

DMC estimate a roundtrip to the hospital in average to 40 km * 3,51 DKK = average costs 140 DKK DMC Værdisætning af omkostninger version 1.6.].

Table 56 Frequency, length, and cost of hospital admission (DRG) in the ADVOCATE [155]

	Patients' & relatives' time spend excl. Transport time	Patients' and relatives' time spent transport	Kilometers
Patients' and relatives' time spend hours	131,5	46	
roundtrip km.			1.300
Costs included in the model DKK	23.802	8.326	4.563

The calculation of the cost is done in the excel model in the sheets "Patient & relatives Costs - Avacopan" and "Patient & relatives Costs – Comparator". No differences in the patient- and relative cost are included in the calculations.

The costs are referred to the four Engines into the colomns hospitalisatios

Sheet: Engine AVA + CYC to column HP hospitalization

Sheet: Engine AVA + RTX to column HK hospitalization

Sheet: Engine CYC + GC to column HP hospitalization

Sheet: Engine RTX + GC to column HL hospitalization

Adverse events costs

The costs of AEs were sourced from the DRG price list of 2022 see table 53 next page.

Table 57 Costs of Adverse events

Adverse events	DRG takst	DRG gruppe	Aktionsdiagnose, tillægsdiagnose
Anti-neutrophil cytoplasmic antibody positive vasculitis	43.621	08MA12	DM318 Anden nekrotoserende vaskulitis
Pneumonia	40.070	04MA13	DJ189 Pneumoni UNS; DM317 Mikroskopisk polyangiitis
Granulomatosis with polyangiitis	43.621	08MA12	DM313 Wegeners granulomatose
Acute kidney injury	17.746	11MA10	DN288 Anden sygdom i nyre eller urinleder; DM313 Wegeners granulomatose
Urinary tract infection	27.401	11MA07	DN390 Urinvejsinfektion uden angivelse af lokation; DM313 Wegeners granulomatose
Angina pectoris	11.170	05MA02	DI200 Ustabil angina pectoris; DM313 Wegeners granulomatose
Cardiac failure	33.447	05MA04	DI509 Hjertesvigt: DM313 Wegeners granulomatose
Device-related infection	40.002	18MA08	DT802G CVK-relateret; DM313 Wegeners granulomatose
Drug hypersensitivity	3.888,0	21MA01	No additional cost assumed
Hepatic enzyme increased	32.187	07MA05	DR945 Abnorm levertfunktionsundersøgelse; DM313 Wegners granulomatose
Hepatic function abnormal	32.187	07MA05	DR945 Abnorm levertfunktionsundersøgelse; DM313 Wegners granulomatose
Hyperglycaemia	4.460	23MA03	DR739 Hyperglykæmi UNS; DM313 Wegeners granulomatose
Influenza	19.883	03MA05	DJ091 Influenza med påvist influenza virus A; DM313 Wegeners granulomatose
Pyrexia	18.647	18MA04	DR508B Vedvarende feber af ukendt årsag; DM313 Wegeners granulomatose
Acute myocardial infarction	19.850	05MA01	DI219 Akut myokardieinfackt UNS; DM313 Wegeners granulomatose
Agranulocytosis	38.408	16MA03	DD709A Neutropeni og Agranulocytose forårsaget af lægemiddel; DM313 Wegeners granulomatose
Blood creatinine increased	33.289	11MA02	DN088 Glomerulonefropati ved anden sygdom klassificeret andet sted; DM313 Wegeners granulomatose
Lymphopenia	25.419	16MA10	No additional cost assumed
Pulmonary alveolar haemorrhage	20.541	04MA23	DR048A Blødning fra lunger; DM313 Wegeners granulomatose
Anaemia	41.278	16MA05	DD590 Autoimmun hæmolytisk anæmi forårsaget af lægemiddel; DM313 Wegeners granulomatose
Dehydration	27.155	10MA06	DE869A Dehydrering; DM313 Wegeners granulomatose
Diarrheoia	6.756	06MA11	DK529B1 Kemoterapi-induceret diaré; DM313 Wegeners granulomatose

Epistaxis	17.437	03MA03	DR040 Næseblod; DM313 Wegeners granulomatose
Herpes zoster	19.518	09MA03	DB029 Herpes zoster-infektion uden komplikation; DM313 Wegeners granulomatose
Infectious pleural effusion	40.002	18MA08	DA499 Bakteriel infektion UNS; DJ909 Pleuraeffusion IKA
Large intestinal polyp	26.019	06MA14	DK635 Colonpolyp UNS; DM313 Wegeners granulomatose
Microscopic polyangiitis	43.621	08MA12	DM317 Mikroskopisk polyangiitis
Mononeuropathy multiplex	28.237	01MA04	DG587 Neuropati samtidig i flere enkelte nerver; DM313 Wegeners granulomatose
Neutropenia	38.408	16MA03	DD709A Neutropeni og Agranulocytose forårsaget af lægemiddel; DM313 Wegeners granulomatose
Pneumonia bacterial	40.070	04MA13	DJ159 Pneumoni UNS; DM313 Wegeners granulomatose
Prostate cancer	32.964	11MA08	Long-term AE - not captured in short-term AE cost
Pulmonary embolism	30.269	04MA04	DI260 Lungeemboli med akut cor pulmonale; DM313 Wegeners granulomatose
Respiratory syncytial virus infection	29.940	18MA06	DB974 Respiratory syncytial (RS) virus som årsag til sygdom; DM313 Wegeners granulomatose
Thrombocytopenia	27.168	16MA09	DD689 Koagulationsdefekt UNS; DM313 Wegeners granulomatose
Vomiting	6.756	06MA11	DR119C Opkastning; DM313 Wegeners granulomatose

8.6 Results

Base case the Danish Patient population

8.6.1 Base case overview

Table 58 *p*resent the base case settings of the cost-effectiveness model

Table 58 Base case overview

Variable	Assumed value	Justification
Settings		
Time horizon	40 years	Patients entering the model have a mean age of 60 years [155,185]. Based on average life expectancy we do not expect any patients to live past 100 years old.
Perspective	Payer perspective	DMC guidelines
Markov assumption	NA	Patients will move through the health states as disease relapses. This is a reasonable assumption as the health states describe the patients' disease path.
Baseline characteristics	Whole cohort: Age (years) = 60 Weight (kg) = 77	The baseline characteristics were based on ADVOCATE trial and Nelveg-Kristensen.
Discount costs and effects	3,5 % (year 0-35) 2,5 % (year 36-70)	In accordance with Finansministeriets Notat 2. March 2021 Nøgletalskataloget
Data Sources		
Mortality data source	SNR	SNR report
Efficacy data source	ADVOCATE/literature	Trial data for efficacy. CHMP Assessment report
ESRD data source	Literature and ADVOCATE	ESRD rate are adjusted using eGFR estimates from ADVOCATE + HRs*1 from literature.
Adverse events source	ADVOCATE	
Clinical inputs		
Treatment duration	Tavneos® treatment + 6 months maintenance	Based on ADVOCATE data.
Induction courses	3 induction courses	Based on maximum lifetime dosage for cyclophosphamide.
Reinduction courses	0 reinduction courses	Based on ADVOCATE data.
Drug wastage cyclophosphamide	Yes	
Drug wastage rituximab	Yes	
Therapy for 2nd induction AVA+CYC	Rituximab	Danish treatment guidelines

Therapy for 2nd induction AVA+RTX	Cyclophosphamide	Danish treatment guidelines
Therapy for 3rd induction AVA+CYC	Cyclophosphamide	Danish Treatment guidelines
Therapy for 3rd induction AVA+RTX	Rituximab	Danish Treatment guidelines
Number of cycles on GC	5	ADVOCATE CSR.
Tavneos® infection mortality	Reduced mortality	Based on ADVOCATE.
Treatment specific utilities	Yes	Captures disease severity.

*1 Gercik et al 2020 [224] was one of the latest publications regarding this kind of data and it was endorsed by key Opinion Leaders in UK, Sweden and Norway as clinical relevant and valid to be used in model.

8.6.2 Base case results

The base case results are presented in table 60. In the Danish setting, from a payer perspective, the use of Tavneos® in combination with RTX and CYC for the treatment of adults with ANCA-associated vasculitis compared to SoC (GCs + RTX and CYC) was associated with higher costs DKK 386.713 but resulted in 0.29 additional QALYs.

Table 59 Results of the base case analysis

	Tavneos® + RTX/CYC	SoC (GC + CYC/RTX)	Incremental
Costs (DKK)	1.496.353	1.109.640	386.713
QALYs	6,54	6,25	0,29
ICER (DKK/QALY)	1.350.207		

CYC: Cyclophosphamide, GC: Glucocorticoids, ICER: Incremental cost-effectiveness ratio, QALYs: Quality-adjusted life years, RTX: Rituximab, SoC: Standard of care

In Table 60 the disaggregated costs are presented. Most additional costs associated with the use of Tavneos® were found to be drug costs. The additional drug costs are partly offset by lower costs associated with hospitalisations and ESRD for Tavneos® compared to SoC.

Table 60 Disaggregated costs for the base case analysis, all costs in DKK

Cost category	Tavneos® + RTX/CYC	SoC (GC + CYC/RTX)	Incremental
Drug costs	937.536	510.710	426.826
Active disease	11.320	11.559	-239
Remission	46.328	42.672	3.656
Relapse	42.747	42.165	583
Hospitalisations	91.625	103.156	-11.531
ESRD	366.796	399.379	-32.583
Total costs	**1.496.353**	**1.109.640**	**386.713**

CYC: Cyclophosphamide, ESRD: End stage renal disease, GC: Glucocorticoids, RTX: Rituximab, SoC: Standard of care

Table 61 Drug-, hospital-, adverse reaction- and patient costs for the base case analysis, all costs in DKK

Unit Costs Summary			
Total cost per 1st year	**Avacopan**	**Prednisolon**	**Incrementelle costs**
Costs of pharmaceuticals	645.948	15.397	630.551
Hospital costs	254.822	267.058	-12.236
Adverse reaction costs Avacopan + RTX/CYC	77.887	99.059	-21.172
Transport costs and time spent by patients and relative	36.691	36.691	0
General practitioners and practicing medical specialists	2.451	2.451	0
Total	**1.017.799**	**420.656**	**597.143**

Scenario analysis

The results for the scenario analyses of comparing Tavneos® in combination with CYC to CYC+GC and Tavneos® in combination with RTX compared to RTX+GC are presented in Table 62 and Table 63, respectively.

Table 62 Senario analysis – Tavneos + CYC vs. GC+CYC

	Tavneos® + CYC	SoC (GC + CYC)	Incremental
Costs (DKK)	1.531.041	1.143.177	387.865
QALYs	6,54	6,25	0,29
ICER (DKK/QALY)	1.354.230		

CYC: Cyclophosphamide, GC: Glucocorticoids, ICER: Incremental cost-effectiveness ratio, QALYs: Quality-adjusted life years, SoC: Standard of care

Table 63 Senario analysis – Tavneos + RTX vs. GC+RTX

	Tavneos® + RTX	SoC (GC + RTX)	Incremental
Costs (DKK)	1.460.045	1.082.044	378.000
QALYs	6,54	6,25	0,29
ICER (DKK/QALY)	1.319.787		

GC: Glucocorticoids, ICER: Incremental cost-effectiveness ratio, QALYs: Quality-adjusted life years, RTX: Rituximab, SoC: Standard of care

Results for the two scenario analyses were similar to the base case analysis.

Scenario analyses based on Danish guidelines were also conducted. See Table 65 for the key variables used in the scenario analyses and the respective results.

Table 64 Senario analyses – key variables and results

Base case	Scenario	Incremental cost	Incremental QALY	New ICER	Delta ICER
Base case		386.713	0,286	1.350.207	
Time horizon - lifetime	5 years	376.221	0,075	5.035.904	3.685.698
Time horizon - lifetime	10 years	376.979	0,163	2.306.031	955.824
Time horizon - lifetime	20 years	385.581	0,273	1.410.938	60.731
Time horizon - lifetime	30 years	386.703	0,286	1.350.854	647
Discount costs and effects	5%,5%	385.069	0,250	1.537.774	187.568
Discount costs and effects	0%,0%	392.815	0,402	978.141	-372.066
Population	Newly diagnosed AAV	383.308	0,232	1.650.161	299.954
Population	Relapsed AAV	424.783	0,386	1.100.337	-249.870
Population	GPA	411.122	0,211	1.946.093	595.886
Population	MPA	363.977	0,428	849.462	-500.745
Number of induction courses 3	1	394.899	0,212	1.863.864	513.658
Number of induction courses 3	2	389.396	0,285	1.366.137	15.930
Drug waste CYC: No	Yes	388.091	0,314	1.234.598	-115.608
Drug waste RTX: No	Yes	388.123	0,314	1.234.701	-115.505
Avacopan infection mortality: reduced based on ADVOCATE	Equal to CYC/RTX	378.220	0,249	1.518.112	167.905
Include hospitalization data from ADVOCATE: Yes	No	395.835	0,314	1.259.234	-90.973
Treatment specific utilities: Yes	No	388.091	0,294	1.318.516	-31.691
ESRD method: eGFR drop with relapse	No eGFR decrease with relapse	387.299	0,258	1.498.443	148.237
eGFR drop at relapse (ml/min): 10	8	388.837	0,303	1.281.907	-68.299
eGFR drop at relapse (ml/min): 10	12	387.383	0,325	1.193.754	-156.452
Treatment effect after 52 weeks: None	Persists	305.310	0,637	479.298	-870.909
Treatment effect after 52 weeks: None	Waning effect	383.016	0,334	1.145.807	-204.400

Population

Results for the subgroups in ADVOCATE is presented in Table 65.

Table 65 Results of Tavneos + CYC/RTX compared to GC + CYC/RTX in subgroups

Subgroup	AVA+CYC vs. CYC+GCs			AVA+RTX vs. RTX+GCs			AVA+CYC/RTX vs. CYC/RTX+GCs		
	Δ Costs	Δ QALYs	ICER	Δ Costs	Δ QALYs	ICER	Δ Costs	Δ QALYs	ICER
ADVOCATE ITT population	387.865 kr	0,29	1.354.230 kr	378.000 kr	0,29	1.319.787 kr	386.713	0,29	1.350.207
Newly diagnosed AAV	383.943 kr	0,21	1.812.573 kr	376.887 kr	0,21	1.779.263 kr	382.641	0,21	1.806.426
Relapsed AAV	422.863 kr	0,36	1.187.547 kr	406.481 kr	0,36	1.141.542 kr	421.604	0,36	1.184.010
GPA	411.816 kr	0,19	2.153.310 kr	400.990 kr	0,19	2.096.705 kr	410.225	0,19	2.144.993
MPA	362.533 kr	0,39	921.889 kr	353.659 kr	0,39	899.323 kr	361.798	0,39	920.020
Danish Population	387.865 kr	0,29	1.354.230 kr	373.463 kr	0,29	1.303.945 kr	387.404	0,29	1.352.620
Danish Population Newly diagnosed AAV	383.943 kr	0,21	1.812.573 kr	374.225 kr	0,21	1.766.695 kr	383.422	0,21	1.810.115
Danish Population Relapsed AAV	422.863 kr	0,36	1.187.547 kr	398.158 kr	0,36	1.118.167 kr	422.359	0,36	1.186.133
Danish Population GPA	411.816 kr	0,19	2.153.310 kr	396.417 kr	0,19	2.072.792 kr	411.180	0,19	2.149.983
Danish Population MPA	362.533 kr	0,39	921.889 kr	349.201 kr	0,39	887.988 kr	362.239	0,39	921.141
Live values	387.865 kr	0,29	1.354.230 kr	378.000 kr	0,29	1.319.787 kr	386.713 kr	0,29	1.350.207 kr

The subgroup analysis predicted the use of Tavneos® to be most cost-effective in the MPA subpopulation of ADVOCATE and the least cost-effective in the GPA subpopulation. Results of the subgroup analysis should be interpreted with caution as inputs in the analysis are for the ITT population and differences in cost-effectiveness between the subgroups are driven by differences in relapse rates from ADVOCATE, which may be affected by small sample sizes for some of the groups.

8.7 Sensitivity analyses

There are several model parameters which are expected to be key drivers in the model:

- The rate of relapse
- Length of treatment effect
- The transition probabilities to the ESRD state
- Adjustment for GC-related infection mortality
- Probability of ESRD in refractory disease
- Source of adverse event data
- Treatment-specific utility values

Exploratory scenarios have been conducted to understand the impact of each on the model results.

Deterministic sensitivity analyses were conducted to assess uncertainty in the model parameters and to identify the most influential variables. Deterministic sensitivity analyses were conducted by varying the model input parameters ± 10 %. For scenario analyses, different model inputs were derived from alternative sources and/or multiple model parameters were varied simultaneously. Different parameter values and/or sources of values to inform the model were tested in the scenario sensitivity analyses. The performed deterministic sencitivity and scenario analysis are described in Table 66. Sensitivity and scenario analyses.

Table 66 Sensitivity and scenario analyses

Scenario	Description
Time horizon	a) 2 years b) 5 years c) 10 years
Avacopan treatment effect	a) GC effect to 1st year mortality ±10% b) eGFR recovery in induction ±10 % c) HR of relapse ±10 %
Costs	a) ESRD costs ±10 % b) Adverse event costs ±10 % c) Monitoring costs ±10 %
Utility values	a) All utility values ±10 % b) ESRD utility values ±10 % c) Utility values for remission state ±10 %

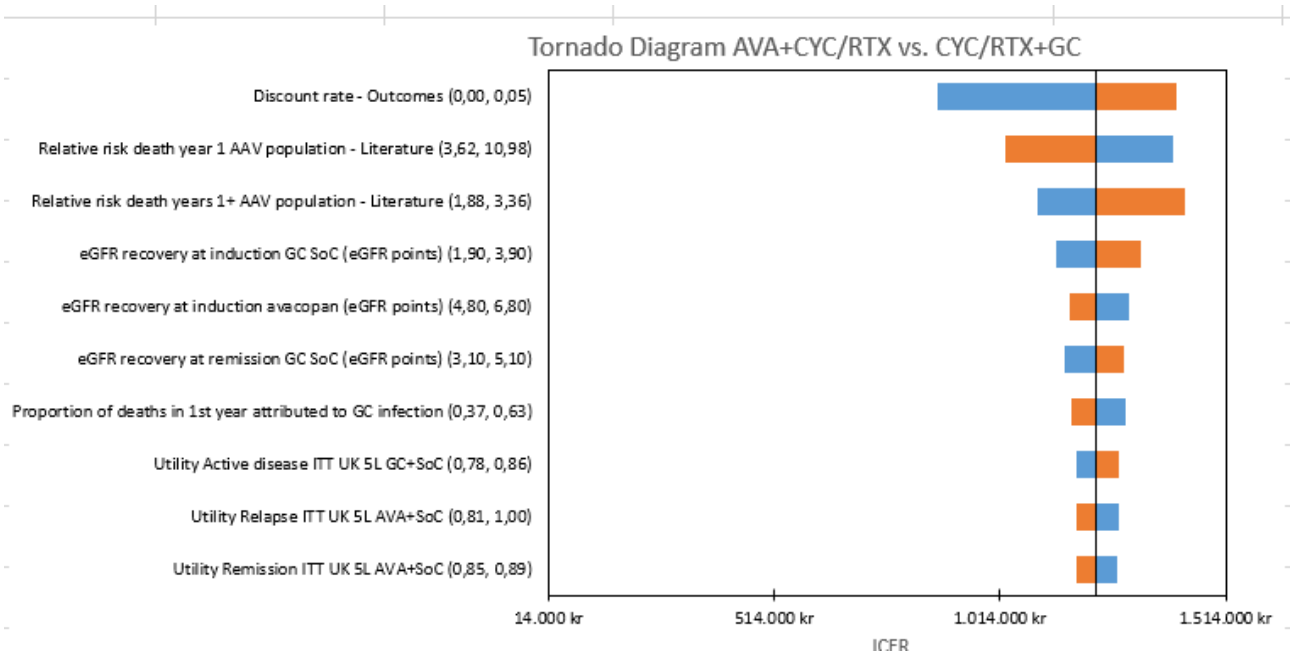
A one-way sensitivity analysis was performed where key parameters were varied. The results are presented in *Table 67* and *Figure 35*.

Table 67 One-way sensitivity analysis AVA+CYC/RTX vs. CYC/RTX+GC

Avacopan + CYC/RTX vs. CYC+RTX + GC		1.350.207 kr
Parameter	**ICER at lower value of parameter**	**ICER at upper value of parameter**
Discount rate - Outcomes (0,00, 0,05)	875.197	1.404.678
Relative risk death year 1 AAV population - Literature (3,62, 10,98)	1.395.335	1.026.607
Relative risk death years 1+ AAV population - Literature (1,88, 3,36)	1.097.888	1.425.270
eGFR recovery at induction GC SoC (eGFR points) (1,90, 3,90)	1.138.286	1.325.016
eGFR recovery at induction avacopan (eGFR points) (4,80, 6,80)	1.299.870	1.168.066
eGFR recovery at remission GC SoC (eGFR points) (3,10, 5,10)	1.158.430	1.289.873
Proportion of deaths in 1st year attributed to GC infection (0,37, 0,63)	1.290.600	1.170.543
Utility Active disease ITT UK 5L GC+SoC (0,78, 0,86)	1.182.036	1.276.232
Utility Relapse ITT UK 5L AVA+SoC (0,81, 1,00)	1.275.641	1.182.543
Utility Remission ITT UK 5L AVA+SoC (0,85, 0,89)	1.274.175	1.183.805

3L: Third line, AAV: antibody - associated vasculitis, AVA: Avacopan, eGFR: Estimated glomerular filtration rate, GC: Glucocorticoids, ICER: Incremental cost-effectiveness ratio, ITT: Intention to treat, SoC: Standard of care, UK, United Kingdom

Figure 35 Tonado diagram – one-way sensitivity analysis



The parameters that had the largest effect on the ICER were found to be the discount rate of the outcomes and the relative risk of death in subsequent years (i.e. after first year). Overall, the results of the one-way sensitivity analysis demonstrated that the base case results of the analysis were stable for variations in key model parameters.

The driver of the cost/effectiveness differences between the two subpopulations GPA and MPA are mainly the week 26 and and 52 remission rates as reported in ADVOCATE [155, 155.a], and a very minor drug cost impact in the RTX and CYC background therapy subgroup.

Table 68 Week 26 and 52 remission in ADVOCATE subgroups patients with MPA [155,155a]

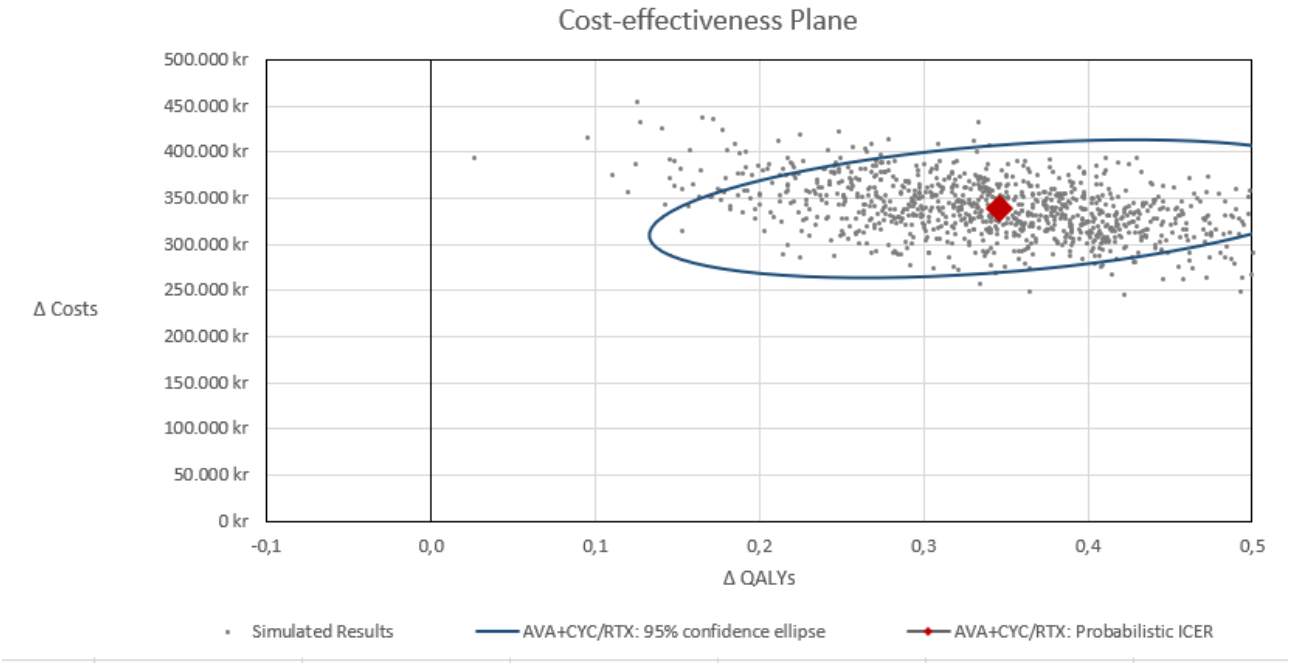
Subgroup	In remission at week 26 (95% CI)		In remission at week 52 (95% CI)	
Treatment arm	**AVA+CYC/RTX**	**CYC/RTX+GC**	**AVA+CYC/RTX**	**CYC/RTX+GC**
ADVOCATE ITT (base case)	72.3 (64.8,78.9)	70.0 (62.5,77.0)	65.7 (57.9,72.8)	54.9 (46.9,62.6)
Relapsed AAV	86.3 (73.7,94.3)	78.0 (64.0,88.5)	76.5 (62.5,87.2)	48.0 (33.7,62.6)
Newly diagnosed AAV	66.1 (56.7,74.7)	66.7 (57.2,75.2)	60.9 (51.3,69.8)	57.9 (48.3,67.1)
MPA	73.3 (61.9,82.9)	67.6 (55.7,78.0)	70.7 (59.0,80.6)	51.4 (39.4,63.1)
GPA	71.4 (61.0,80.4)	72.2 (61.8,81.1)	61.5 (50.8,71.6)	57.8 (46.9,68.1)
MPO positive	73.4 (63.3,82.0)	69.1 (58.8,78.3)	70.2 (59.9,79.2)	53.2 (42.6,63.6)
PR3 positive	70.8 (58.9,81.0)	71.4 (59.4,81.6)	59.7 (47.5,71.1)	57.1 (44.7,68.9)
RTX background therapy	77.6 (68.5,85.1)	75.7 (66.5,83.5)	71.0 (61.5,79.4)	56.1 (46.1,65.7)
CYC background therapy	62.7 (49.1,75.0)	59.6 (45.8,68.8)	55.9 (42.4,68.8)	52.6 (39.0,66.0)

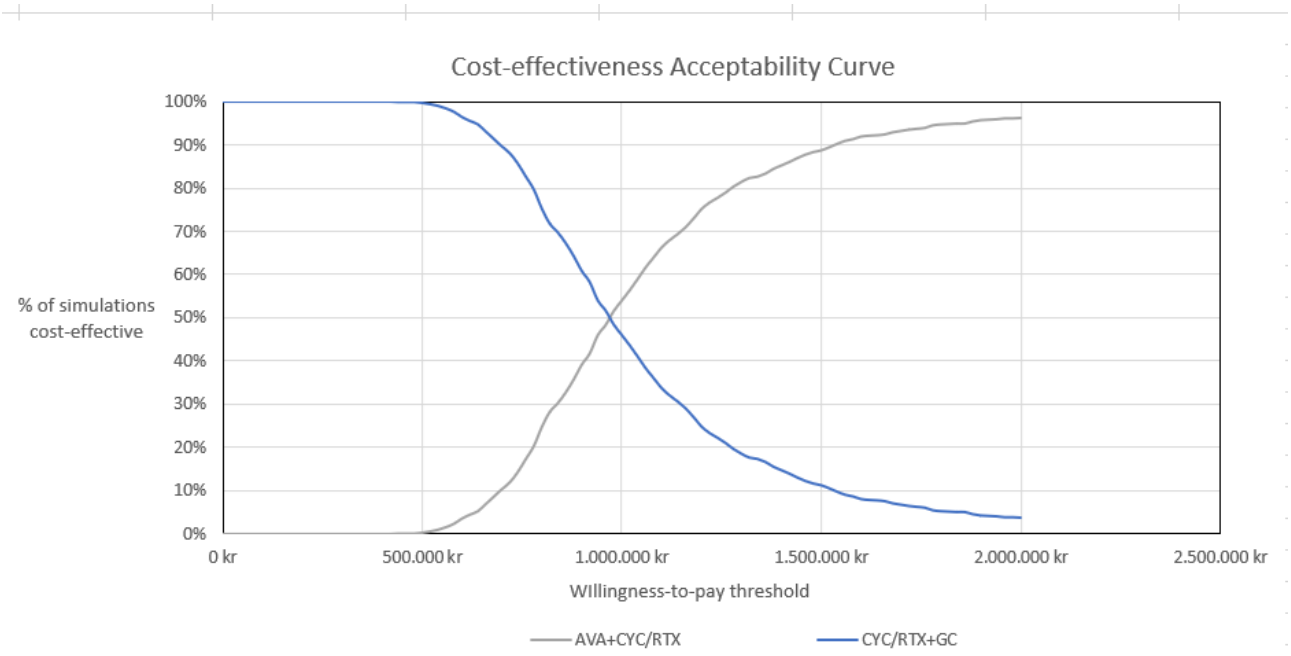
8.7.2 Probabilistic sensitivity analyses

A probabilistic sensitivity analysis (PSA) was performed verifying model parameters according to their associated variance and assumed distribution. The cost-effectiveness plane and cost effectiveness acceptability curve (CEAC) for Avacopan + cyclophosphamide/rituximab are presented in figure 37. The Cost-effectiveness Planes for Avacopan + cyclophosphamide respectively Avacopan + rituximab are shown in the model.

Remission rates at week 26 and 52 were assumed to be closely correlated within each treatment arm and subgroup. We assumed a correlation coefficient of 0.8. The remission rates were adjusted using the Cholesky decomposition. The calculations can be found in the 'Correlation adjustment' sheet of the model. If required, scenario analyses can be conducted by varying the coefficient in the 'Clinical data' sheet.

Figure 36 Cost-effectiveness plane and Cost-effectiveness Acceptability Curve Avacopan + cyclophosphamide/rituximab





9. BUDGET IMPACT ANALYSIS

The number of patients expected to be treated with Tavneos – Tavneos will be recommend or not recommend see Table 71 and Table 70. For details regarding the calculation and documentation see section 5.1.4.1 patient population relevant for this application.

Table 69 Number of patients expected to be treated over the next five years period-if Tavneos is recommend as standard treatment

	Year 1	*Year 2*	*Year 3*	*Year 4*	*Year 5*
Tavneos	*130*	*249*	*258*	*266*	*275*
Prednisolon	*214*	*107*	*110*	*114*	*117*
Toral number of patients	*344*	*356*	*368*	*380*	*392*

Table 70 Number of patients expected to be treated over the next five years period – if Tavneos isn't recommend as standard treatment

	Year 1	*Year 2*	*Year 3*	*Year 4*	*Year 5*
Tavneos	*0*	*0*	*0*	*0*	*0*
Prednisolon	*344*	*356*	*368*	*380*	*392*
Toral number of patients	*344*	*356*	*368*	*380*	*392*

Table 71 Cost per patient/year – for incident or prevalent patients in the treatment if Tavneos is recommended

Cost per patient/year					
Incident, Avacopan	***Year 1***	***Year 2***	***Year 3***	***Year 4***	***Year 5***
Costs of pharmaceutical	645.948	645.948	645.948	645.948	645.948
Hospital costs	254.822	254.822	254.822	254.822	254.822
Adverse reaction costs	53.513	69.502	81.651	88.518	89.314
Costs per patient Incident, Avacopan	954.284	970.273	982.421	989.289	990.085
Prevalent, Avacopan					
Costs of pharmaceutical	645.948	645.948	645.948	645.948	645.948
Hospital costs	43.621	43.621	43.621	43.621	43.621
Adverse reaction costs	53.513	69.502	81.651	88.518	89.314
costs per patient prevalent, Avacopan	743.083	759.072	771.221	778.088	778.884
Incident, Prednisolon					
Costs of pharmaceutical	15.397	15.397	15.397	15.397	15.397
Hospital costs	267.058	267.058	267.058	267.058	267.058
Adverse reaction costs	71.954	84.256	93.673	97.477	95.928
Costs per patient Incident, Prednisolon	354.409	366.711	376.129	379.932	378.383
Prevalent, Prednisolon					
Costs of pharmaceutical	15.397	15.397	15.397	15.397	15.397
Hospital costs	43.621	43.621	43.621	43.621	43.621
Adverse reaction costs	71.954	84.256	93.673	97.477	95.928
costs per patient, prevalent , Prednisolon	130.972	143.274	152.692	156.496	154.946

Table 72 Expected budget impact of recommending Tavneos® for the treatment of ANCA-associated vasculitis

TAVNEOS® RECOMMENDED					
Incident, Avacopan recommanded (Avacopan + prednisolon)	***Year 1***	***Year 2***	***Year 3***	***Year 4***	***Year 5***
Costs of pharmaceutical	45.645.286	82.250.690	82.314.250	82.366.841	82.687.662
Hospital costs	47.174.148	46.503.777	46.534.295	46.559.547	46.713.589
Adverse reaction costs	11.680.408	13.298.748	15.347.235	16.427.348	16.498.547
Total costs Incident, Avacopan recommended	104.499.842	142.053.214	144.195.779	145.353.736	145.899.798
Prevalent, Avacopan recommanded (Avacopan + prednisolon)	***Year 1***	***Year 2***	***Year 3***	***Year 4***	***Year 5***
Costs of pharmaceutical	41.602.874	80.439.504	85.966.579	91.356.620	96.563.947
Hospital costs	7.132.034	7.681.658	8.209.472	8.724.200	9.221.479
Adverse reaction costs	10.621.371	13.018.817	16.045.513	18.241.225	19.300.497
Total costs prevalent, Avacopan recommended	59.356.278	101.139.979	110.221.565	118.322.045	125.085.923
Prevalent + incident Avacopan recommended (Avacopan + prednisolon)	***Year 1***	***Year 2***	***Year 3***	***Year 4***	***Year 5***
Costs of pharmaceutical	87.248.160	162.690.194	168.280.829	173.723.461	179.251.609
Hospital costs	54.306.181	54.185.435	54.743.767	55.283.747	55.935.069
Adverse reaction costs	22.301.778	26.317.565	31.392.748	34.668.572	35.799.043
Total costs Incident + prevalent, Avacopan recommended	163.856.120	243.193.194	254.417.344	263.675.780	270.985.721
TAVNEOS® NOT RECOMMENDED					
Incident, Avacopan not recommanded (prednisolon)	***Year 1***	***Year 2***	***Year 3***	***Year 4***	***Year 5***
Costs of pharmaceutical	2.767.804	2.770.106	2.771.935	2.773.448	2.782.678
Hospital costs	48.006.196	48.046.117	48.077.833	48.104.076	48.264.165
Adverse reaction costs	12.934.352	15.158.433	16.863.831	17.558.199	17.336.635
Total costs Incident, Avacopan not recommended	63.708.353	65.974.656	67.713.598	68.435.722	68.383.478
Prevalent, Avacopan not recommanded (prednisolon)	***Year 1***	***Year 2***	***Year 3***	***Year 4***	***Year 5***
Costs of pharmaceutical	2.517.452	2.711.457	2.897.764	3.079.452	3.254.980
Hospital costs	7.132.034	7.681.658	8.209.472	8.724.200	9.221.479
Adverse reaction costs	11.764.417	14.837.497	17.629.348	19.495.453	20.279.173
Total costs prevalent, Avacopan not recommended	21.413.902	25.230.612	28.736.584	31.299.105	32.755.633
Prevalent + incident Avacopan not recommended (prednisolon)	***Year 1***	***Year 2***	***Year 3***	***Year 4***	***Year 5***
Costs of pharmaceutical	5.285.256	5.481.563	5.669.699	5.852.899	6.037.658
Hospital costs	55.138.229	55.727.775	56.287.305	56.828.276	57.485.645
Adverse reaction costs	24.698.769	29.995.931	34.493.178	37.053.652	37.615.808
Total costs Incident + prevalent, Avacopan not recommended	85.122.255	91.205.269	96.450.182	99.734.827	101.139.111
Budget impact of recommandation for Tavneous®	**78.733.865**	**151.987.925**	**157.967.162**	**163.940.953**	**169.846.611**

10 DISCUSSION ON THE SUBMITTED DOCUMENTATION

An avacopan-based regimen reduces the overall number of relapses

An Avacopan-based regimen sustains more patients in remission than is possible with the current SOC, with the potential to save the additional costs of relapses. At Week 52 of the ADVOCATE trial, 65.7% subjects achieved sustained remission with an Avacopan-based regimen compared with 54.9% with SOC (p=0.0066) [155, 156]. An Avacopan-based regimen also reduced the relative risk of relapse by 54% compared with SOC in patients who achieved BVAS = 0 (regardless of GC use in prior 4 weeks) at any point during the trial (p< 0.01) [155, 156].

An avacopan-based regimen reduces the hospitalizations

In the ADVOCATE trial, hospitalization was captured and analysed as part of safety monitoring. The data demonstrated that an Avacopan-based regimen could decrease both the number of hospitalisations and the duration of hospital stay by approximately one third compared to SOC, (GC-based regimen) in the treatment of ANCA-AV [155, 156].

The objective of the health economic analysis was to evaluate the cost-effectiveness of avacopan+SOC compared to SOC for patients with ANCA-AV over a lifetime horizon (40 years) from a Danish payer perspective. SOC encompassed GC+RTX or GC+CYC. Key model inputs were sourced from the pivotal phase 3 trial ADVOCATE with the effect of avacopan and SOC estimated from the direct head-to-head comparison. The ADVOCATE study and the Systematic Literature Search did not identified all the inputs needed in the model and these had to be sourced using pragmatic literature searches and hand search of key papers, which is a standard approach in economic modelling. Considering that the above parameters have a substantial impact on the model results, we agree that a more formal approach to identifying the studies could make the model and HTA dossier which is informs more robust.

According to the base case results of the model, avacopan is associated with a gain of 0.36 life years compared to Standard of Care (SoC) with comparator prednisolon. This additional survival translates into 0.29 additional QALYs compared to SOC in Denmark. Treatment with avacopan increases treatment costs by an additional DKK 386.713 compared to SOC, resulting in an ICER of DKK 1.350.207 per QALY gained over a lifetime horizon.

The deterministic sensitivity analysis demonstrates that these model outcomes were relatively stable to changes in inputs and assumptions. The discount rate for outcomes and the eGFR recovery at induction had the largest effect on the ICER.

Provided that Tavneos will standard treatment - the number af patients eligible for treatment with Tavneos® will the first year (2023) amount to approximately 130 patients and in 2027 to approximately 275 patients.

Table 73 The budget impact during the next 5 years

	2023	2024	2025	2026	2027
Budget impact of recommandation for Tavneous®	78.733.865	151.987.925	157.967.162	163.940.953	169.846.611

11 LIST OF EXPERTS

N/A

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APPENDIX A – LITTERATURE SEARCH FOR EFFICACY AND SAFETY OF INTERVENTION AND COMPARATOR

Search strategy

Systematic review aims and objectives

The objective of this project was to perform an update of the previously completed SLR of RCTs to identify the clinical evidence for avacopan and any relevant comparator interventions.

A systematic review attempts to assemble all available relevant evidence using explicit, valid, and replicable methods to minimise the risk of bias in the selection of studies (CRD 2009; Higgins 2011; NICE 2013). The National Institute for Health and Care Excellence (NICE) defines a systematic review as "systematically locating, including, appraising and synthesising the evidence to obtain a reliable and valid overview of the data related to a clearly formulated question" (NICE 2013).

Systematic review research question

The research question for this review was, "What is the clinical efficacy and safety of avacopan, in combination with CYC or RTX (with/without steroids) compared with relevant comparator therapies for adult patients with GPA or MPA?"

Literature review methods

This review was conducted using a review protocol approved by Vifor Pharma Group before the start of the systematic review. The following established international guidelines for conducting systematic reviews and submitting technology appraisals to NICE were consulted throughout this project:

- The National Institute for Health and Care Excellence: *Guide to the methods of technology appraisal* (NICE 2013) (https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781)
- Single technology appraisal: User guide for company evidence submission template Updated April 2017. (https://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-technology-appraisal-guidance) (NICE 2017)
- The Centre for Reviews and Dissemination's guidance for undertaking systematic reviews in health care (CRD 2009), which is cited by NICE
- The Cochrane Handbook for Systematic Reviews of Interventions, version 5.1 (Higgins & Green, 2011)
- Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement (Moher et al. 2009)

Identification and selection of relevant studies

A full SLR was undertaken to identify all studies that provide information on the clinical efficacy, safety, and tolerability of avacopan in combination with CYC or RTX (with/without GCs) compared

with relevant comparator therapies for adult patients with GPA or MPA. This review was conducted in 3 stages: a comprehensive and systematic search of the published literature to identify all potentially relevant studies, a systematic selection of relevant studies based on explicit inclusion and exclusion criteria, and an extraction of relevant data from eligible studies to assess comparative clinical evidence.

The searches were designed to meet the requirements of health technology assessment agencies including NICE and the Scottish Medicines Consortium and following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (Moher et al. 2009).

Literature searches

The search strategies broadly had 2 sets of terms:

1. Terms to search for the health condition of interest
2. Terms to search the subject area of interest

Search terms included a number of MeSH indexing and free-text terms to ensure that the highest proportion of relevant articles were captured. The key characteristics for the searches were the following:

- Language: English
- Scope countries: No limit
- Publication type/status: Randomised Controlled Trial filter
- Time frame: 1998 to present

Electronic databases

The search plan included both electronic searching and hand-searching. The following electronic databases were for citations of interest:

- Embase (OvidSP)
- MEDLINE epub ahead of print, in-process and other non-indexed citations, MEDLINE Daily, MEDLINE <1946 to present>, MEDLINE in-process citations, and Daily Update (OvidSP)
- Cochrane Central Register of Controlled Trials (Wiley): http://www.thecochranelibrary.com
- National Institutes of Health Clinicaltrials.gov: http://www.clinicaltrials.gov/
- World Health Organization International Clinical Trials Registry Platform: http://www.who.int/ictrp/en/
- Cochrane Database of Systematic Reviews (Wiley): http://www.thecochranelibrary.com
- Database of Abstracts of Reviews of Effects (Wiley): http://www.thecochranelibrary.com
- Health Technology Assessment Database (Wiley): http://www.thecochranelibrary.com
- Epistemonikos Database: https://www.epistemonikos.org/

The search strings are shown in tables 1A for the search 2018; 1B for the update 2020 and 1C for the update 2021 and were translated as necessary for each of the resources searched. The search strategies and the searches were designed and run by an experienced information specialist.

Table 1A to 1C Search strings. 1A 2018; 1B 2020 and 1C 2021

Table 1A Electronic search strings: 2018 searches

Cochrane Library (includes CDSR, DARE, CENTRAL, NHSEED, HTAD) Searched 04 June 2018 (http://www.cochranelibrary.com/)			
S. no.	**Query**	**Facet**	**Hits**
1	MeSH descriptor: [Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis]	This term only	52
2	(("anca associated" or anca-associated or "anti neutrophil cystoplasmic antibody" or "anti-neutrophil cystoplasmic antibody" or "pauci-immune" or pauci-immune) near/2 (vasculitis or vasculitide*))	Ti,ab	229
3	MeSH descriptor: [Granulomatosis with Polyangiitis]	This term only	61
4	((wegener* or polyangiitide* or polyangiitis) near/2 granulomatos*)	Ti,ab	198
5	MeSH descriptor: [Microscopic Polyangiitis]	This term only	24
6	microscopic polyangiiti*	Ti,ab	
7	#1 or #2 or #3 or #4 or #5 or #6		379
Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects; HTAD, Health Technology Assessment Database; NHSEED, National Health Service Economic Evaluations Database			

MEDLINE (Ovid MEDLINE epub ahead of print, in-process, and other non-indexed citations; Ovid MEDLINE daily; and Ovid MEDLINE 1946 to present) Searched 04 June 2018 via OvidSP interface			
S. no.	**Query**	**Facet**	**Hits**
1	Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis		1269
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$))	Ti,ab	2060
3	Granulomatosis with Polyangiitis		6525
4	((wegener$ or polyangiitide$ or polyangiitis) adj2 granulomatos$)	Ti,ab	6975
5	Microscopic Polyangiitis		422
6	microscopic polyangiiti$.	Ti,ab	1405
7	1 or 2 or 3 or 4 or 5 or 6		10944
8	randomized controlled trial.pt. or randomized.mp. or placebo.mp.		802492
9	7 and 8		277

Embase (Embase <1974 to 2018 week 23>) Searched 04 June 2018 via OvidSP interface			
S. no.	Query	Facet	Hits
1	ANCA associated vasculitis		4518
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$))	Ti,ab	3700
3	Wegener granulomatosis		12,069
4	((wegener$ or polyangiitide$ or polyangiitis) adj2 granulomatos$)	Ti,ab	9468
5	microscopic polyangiitis		2539
6	microscopic polyangiiti$.	Ti,ab	2246
7	or/1-6		18,297
8	random$.tw. or placebo$.mp. or double-blind$.tw.		1,554,734
9	7 and 8		902

ClinicalTrials.gov (in advanced search/targeted search terms entered into condition field. No other limits applied. Two searches required for condition terms as too long for single search) Searched 04 June 2018 via https://clinicaltrials.gov 103 unique results found after 130 results de-duplicated against each other			
S. no.	**Query**	**Facet**	**Hits**
1	(("anca associated" OR anca-associated OR "anti neutrophil cystoplasmic antibody" OR "anti-neutrophil cystoplasmic antibody" OR "pauci-immune" OR pauci-immune) AND (vasculitis OR vasculitide OR vasculitides))		43
2	((wegener OR wegeners OR polyangiitide OR polyangiitides OR polyangiitis) AND (granulomatosis OR granulomatoses OR microscopic))		87

World Health Organization International Clinical Trials Registry Platform (in advanced search terms entered into condition field) Recruitment status: all (no other limits applied) Searched 13 June 2017 via http://apps.who.int/trialsearch/AdvSearch.aspx 205 records for 130 trials found			
S. no.	Query	Facet	Hits
1	(("anca associated" OR anca-associated OR "anti neutrophil cystoplasmic antibody" OR "anti-neutrophil cystoplasmic antibody" OR "pauci-immune" OR pauci-immune) AND vasculiti*) OR ((wegener* OR polyangiiti*) AND (granulomatos* OR microscopic))		205

S. no.	Database/ website	Provider/interface	Filter used for study design	Coverage	Hits
1	**CDSR**	http://www.cochranelibrary.com/	-	-	3
	DARE				7
	CENTRAL				365 (326 unique)
	NHSEED				-
	HTAD				2
2	**MEDLINE**	OvidSP interface	randomized controlled trial.pt. or randomized.mp. or placebo.mp.	Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>	277 (276 unique)
3	**Embase**	OvidSP interface	random$.tw. or placebo$.mp. or double-blind$.tw	Embase <1974 to 2018 week 23>	902 (660 unique)
4	**ClinicalTrials.gov**	https://clinicaltrials.gov	-		130 (103 unique)
5	**WHO ICTRP**	http://apps.who.int/trialsearch/AdvSearch.aspx	-	In advanced search terms entered into condition field. Recruitment status: all. No other limits applied.	205 records for 130 trials (55 unique)
				TOTAL	**1789 (1432 unique)**

No publication time limit was applied.
Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials; CDSR, Cochrane Database of Systematic Reviews; DARE, Database of Abstracts of Reviews of Effects; HTAD, Health Technology Assessment Database; NHSEED,National Health Service Economic Evaluations Database; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform

Table 1B Electronic search strings: 2020 searches

Includes Cochrane Database of Systematic Reviews, Cochrane Central Trials Register Searched 16 June 20 at http://www.cochranelibrary.com/			
S. no.	**Query**	**Facet**	**Hits**
1	MeSH descriptor: [Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis]	This term only	69
2	(("anca associated" or anca-associated or "anti neutrophil cystoplasmic antibody" or "anti-neutrophil cystoplasmic antibody" or "pauci-immune" or pauci-immune) near/2 (vasculitis or vasculitide*)	Ti,ab	335
3	MeSH descriptor: [Granulomatosis with Polyangiitis]	This term only	84
4	((wegener* or polyangiitide* or polyangiitis) near/2 granulomatos*	Ti,ab	272
5	MeSH descriptor: [Microscopic Polyangiitis] this term only	This term only	41
6	microscopic polyangiiti*:	Ti,ab	159
7	#1 or #2 or #3 or #4 or #5 or #6		534

Epistemonikos database Searched 16/ June 2020 at https://www.epistemonikos.org/			
S. no.	**Query**	**Facet**	**Hits**
1	(title:((title:((("anca associated" OR anca-associated OR "anti neutrophil cystoplasmic antibody" OR "anti-neutrophil cystoplasmic antibody" OR "pauci-immune" OR pauci-immune) AND (vasculitis OR vasculitide*))) OR abstract:((("anca associated" OR anca-associated OR "anti neutrophil cystoplasmic antibody" OR "anti-neutrophil cystoplasmic antibody" OR "pauci-immune" OR pauci-immune) AND (vasculitis OR vasculitide*))))) OR abstract:((title:((("anca associated" OR anca-associated OR "anti neutrophil cystoplasmic antibody" OR "anti-neutrophil cystoplasmic antibody" OR "pauci-immune" OR pauci-immune) AND (vasculitis OR vasculitide*))) OR abstract:((("anca associated" OR anca-associated OR "anti neutrophil cystoplasmic antibody" OR "anti-neutrophil cystoplasmic antibody" OR "pauci-immune" OR pauci-immune) AND (vasculitis OR vasculitide*)))))) OR (title:((title:(((wegener* OR polyangiitide* OR polyangiitis) AND granulomatos*)) OR abstract:(((wegener* OR polyangiitide* OR polyangiitis) AND granulomatos*)))) OR abstract:((title:(((wegener* OR polyangiitide* OR polyangiitis) AND granulomatos*)) OR abstract:(((wegener* OR polyangiitide* OR polyangiitis) AND granulomatos*))))) OR (title:((title:(microscopic polyangiiti*) OR abstract:(microscopic polyangiiti*))) OR abstract:((title:(microscopic polyangiiti*) OR abstract:(microscopic polyangiiti*))))		27

Database of Abstracts of Reviews of Effects no longer updated since original searches, so Epistemonikos searched to identify systematic reviews published since 2018. Restricted to systematic reviews, publication date 2018 onward

Ovid MEDLINE and epub ahead of print, in process, and other non-indexed citations; and daily <1946 to June 15, 2020> Searched 16 June 2020 via OvidSP interface			
S. no.	**Query**	**Facet**	**Hits**
1	Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/		1728
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$))	Ti,ab	2551
3	Granulomatosis with Polyangiitis		6934
4	((wegener$ or polyangiitide$ or polyangiitis) adj2 granulomatos$).	Ti,ab	7612
5	Microscopic Polyangiitis		516
6	microscopic polyangiiti$.	Ti,ab	1586
7	1 or 2 or 3 or 4 or 5 or 6		12,228
8	randomized controlled trial.pt. or randomized.mp. or placebo.mp.		907,307
9	7 and 8		321

Embase <1974 to 2020 **w**eek 24> Searched 16 **June 20**20 via OvidSP interface			
S. **n**o.	**Query**	**Facet**	**Hits**
1	ANCA associated vasculitis		5980
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$)).	Ti,ab	4901
3	Wegener granulomatosis		12,931
4	((wegener$ or polyangiitide$ or polyangiitis) adj2 granulomatos$).	Ti,ab	10,600
5	microscopic polyangiitis		3077
6	microscopic polyangiiti$.	Ti,ab	2707
7	or/1-6		20,850
8	random$.tw. or placebo$.mp. or double-blind$.tw.		1,794,318
9	7 and 8		1052

ClinicalTrials.gov in advanced search/targeted search terms entered into condition field. No other limits applied Two searches required for condition terms as too long for single search Searched 16 June 2020 via https://clinicaltrials.gov 119 unique results found after 152 results de-duplicated against each other			
S. no.	Query	Facet	Hits
1	(("anca associated" OR anca-associated OR "anti neutrophil cystoplasmic antibody" OR "anti-neutrophil cystoplasmic antibody" OR "pauci-immune" OR pauci-immune) AND (vasculitis OR vasculitide OR vasculitides))		54
2	((wegener OR wegeners OR polyangiitide OR polyangiitides OR polyangiitis) AND (granulomatosis OR granulomatoses OR microscopic))		98

WHO ICTRP: Currently unavailable to search because of COVID-19 demand on WHO website (https://www.who.int/ictrp/en/). Content from WHO ICTRP forms part of Cochrane CENTRAL, so it will have been captured in that search			
S. no.	Query	Facet	Hits
1	-		-
Abbreviations: WHO ICTRP, World Health Organization International Clinical Trials Registry Platform			

Table 1C Electronic search strings: 2021 searches

Cochrane library Includes Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Trials Register (CENTRAL). Searched 16/06/21 at http://www.cochranelibrary.com/			
S. no.	Query	Facet	Hits
1	MeSH descriptor: [Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis] this term only		77
2	(("anca associated" or anca-associated or "anti neutrophil cystoplasmic antibody" or "anti-neutrophil cystoplasmic antibody" or "pauci-immune" or pauci-immune) near/2 (vasculitis or vasculitide*)):	ti,ab	391
3	MeSH descriptor: [Granulomatosis with Polyangiitis] this term only		86
4	((wegener* or polyangiitide* or polyangiitis) near/2 granulomatos*):	ti,ab	308
5	MeSH descriptor: [Microscopic Polyangiitis] this term only		42
6	microscopic polyangiiti*:	ti,ab	180
7	#1 or #2 or #3 or #4 or #5 or #6		611

Total	609 total results include 3 from CDSR, 606 from CENTRAL.

Epistemonikos Database
Searched 16/06/21 at https://www.epistemonikos.org/

DARE no longer updated since original searches so Epistemonikos searched to identify systematic reviews published since 2018. Restricted to systematic reviews, publication date 2018 onwards.

S. no.	Query	Hits
1	(title:((title:((("anca associated" OR anca-associated OR "anti neutrophil cystoplasmic antibody" OR "anti-neutrophil cystoplasmic antibody" OR "pauci-immune" OR pauci-immune) AND (vasculitis OR vasculitide*))) OR abstract:((("anca associated" OR anca-associated OR "anti neutrophil cystoplasmic antibody" OR "anti-neutrophil cystoplasmic antibody" OR "pauci-immune" OR pauci-immune) AND (vasculitis OR vasculitide*))))) OR abstract:((title:((("anca associated" OR anca-associated OR "anti neutrophil cystoplasmic antibody" OR "anti-neutrophil cystoplasmic antibody" OR "pauci-immune" OR pauci-immune) AND (vasculitis OR vasculitide*))) OR abstract:((("anca associated" OR anca-associated OR "anti neutrophil cystoplasmic antibody" OR "anti-neutrophil cystoplasmic antibody" OR "pauci-immune" OR pauci-immune) AND (vasculitis OR vasculitide*)))))) OR (title:((title:(((wegener* OR polyangiitide* OR polyangiitis) AND granulomatos*)) OR abstract:(((wegener* OR polyangiitide* OR polyangiitis) AND granulomatos*)))) OR abstract:((title:(((wegener* OR polyangiitide* OR polyangiitis) AND granulomatos*)) OR abstract:(((wegener* OR polyangiitide* OR polyangiitis) AND granulomatos*))))) OR (title:((title:(microscopic polyangiiti*) OR abstract:(microscopic polyangiiti*))) OR abstract:((title:(microscopic polyangiiti*) OR abstract:(microscopic polyangiiti*))))	61

MEDLINE

Searched 16/06/21 via OvidSP interface.

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to June 15, 2021>

S. no.	Query	Facet	Hits
1	Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/		2021

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$)).	ti,ab.	2911
3	Granulomatosis with Polyangiitis/		7187
4	((wegener$ or polyangiitide$ or polyangiitis) adj2 granulomatos$).	ti,ab	8049
5	Microscopic Polyangiitis/		578
6	microscopic polyangiiti$.	ti,ab.	1718
7	1 or 2 or 3 or 4 or 5 or 6		13069
	randomized controlled trial.pt. or randomized.mp. or placebo.mp.		968950
	7 and 8		351

Embase

Searched 16/06/21 via OvidSP interface.

Database: Embase <1974 to 2021 Week 23>

S. no.	Query	Facet	Hits
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$).	ti,ab.	11408
5	microscopic polyangiitis/		3444
6	or/1-6		22847
7	random$.tw. or placebo$.mp. or double-blind$.	tw.	1934122
8	7 and 8		1185

ClinicalTrials.gov
Searched 16/06/21 via https://clinicaltrials.gov

In Advanced Search/Targeted search terms entered into Condition field.
No other limits applied.
Two searches required for condition terms as too long for single search

S. no.	Query	Hits
1	In Condition field; (("anca associated" OR anca-associated OR "anti neutrophil cystoplasmic antibody" OR "anti-neutrophil cystoplasmic antibody" OR "pauci-immune" OR pauci-immune) AND (vasculitis OR vasculitide OR vasculitides))	59

2	In Condition field; ((wegener OR wegeners OR polyangiitide OR polyangiitides OR polyangiitis) AND (granulomatosis OR granulomatoses OR microscopic))	98
Total		127 unique results found after 157 results de-duplicated against each other

WHO ICTRP **Searched 16/06/21 via ICTRP Search Portal Advanced Search (ictrptest.azurewebsites.net)** **In Advanced Search terms entered into Condition field.** **Recruitment Status- All. No other limits applied.**			
S. no.	**Query**	**Facet**	**Hits**
	In Condition field; (("anca associated" OR anca-associated OR "anti neutrophil cystoplasmic antibody" OR "anti-neutrophil cystoplasmic antibody" OR "pauci-immune" OR pauci-immune) AND vasculiti*) OR ((wegener* OR polyangiiti*) AND (granulomatos* OR microscopic))		259 records for 187 trials found.

Hand-searching and validation of the search strategies

An internal validation was performed to ensure that the relevant citations were identified by the electronic searches. This consisted of cross-checking the following resources:

- The Peer Review of Electronic Search Strategies evidence-based checklist was used to quality assess all searches used in the literature review [A].
- Relevant SLRs previously performed in this area were used to compare the search strategies and included references in this study
- Several relevant studies that were expected to be identified by the search strategy were identified by hand-searching; the search strategy was checked to see that it included them
- The publication lists of any included RCTs were checked on clinicaltrials.org to ensure that all relevant linked publications were included in the review

In addition to prespecified hand searches, general hand searches were also performed to identify further studies of interest; this included searching review articles, the reference lists of included full-text publications, and free text.

Systematic selection of studies

Study selection criteria

To be selected, the publication had to fulfil all inclusion criteria and none of the exclusion criteria table 4. Records retrieved during the searches were added to an EndNote library and duplicate records were removed (de-duplicated) in preparation for screening. After de-duplication, every record retrieved in the search was be independently reviewed by 2 analysts and marked as *include* or *exclude* after review of the study title and abstract (where the latter was available). Full-text articles were obtained for records that met the criteria for inclusion. Each record was then re-evaluated in a full-text review by 2 independent analysts. Any disagreements were resolved through discussion until a consensus was reached. If a consensus could not be achieved, a third reviewer was consulted. All records excluded based on the review of the full text were documented along with the reason for exclusion.

Table 4 PICO elements, inclusion criteria, and exclusion criteria for the systematic literature review

PICOS element	Inclusion criteria	Exclusion criteria
Population	Patients aged ≥18 years with GPA or MPA and renal-limited vasculitis	▪ Paediatric patients ▪ Patients without GPA or MPA
Interventions		
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	Any outcome not listed in the inclusion criteria

	▪ Disease progression (end-stage renal disease) ▪ Dialysis ▪ Renal replacement therapy ▪ Cardiovascular outcomes	
Study type	▪ Randomised controlled trials ▪ English language articles only	▪ 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 ▪ Non-English language at full text
Abbreviations: GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; PICOS, patient, intervention, comparison, outcomes, and study design and type		

Data extraction and management

Data from records meeting criteria for inclusion were extracted by 1 reviewer into a focused data extraction table developed and standardised for this project. A draft data extraction sheet was shared with the Vifor Pharma Group team, who reviewed and provided comments for specific fields to be added or removed. As development of the data extraction tables is an iterative process, the PHMR team tested the draft data extraction tables via practice extraction of several papers identified in the literature review. Thereafter, the final standardised data extraction table was produced, and data from the relevant publications were extracted by 1 reviewer into the data extraction table.

To ensure that the final Excel spreadsheet is of the highest quality and reflects the needs of the client, the PHMR team 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.

Results

Identified studies

The literature was systematically reviewed to identify RCTs reporting data on the clinical efficacy, safety, and tolerability of avacopan in combination with CYC or RTX (with or without steroids) compared with relevant comparator therapies for adult patients with GPA or MPA. The original literature searches were conducted in electronic databases on 4 June 2018 and retrieved a total of 1789 citations with potentially useful content, which was reduced to 1432 after de-duplication. The literature searches were conducted again on 16 June 2020. These searches retrieved a total of

480 citations, reduced to 226 following de-duplication. A further literature search was undertaken on 18 June 2021 which retrieved 467 citations, reduced to 208 on de-duplication. A summary of the citations identified in each of the searches is shown in table 5.

Table 5 Electronic database search results (2018, 2020 and 2021 searches combined)

Source	2018	2020 update	2021 update	Total
Cochrane Database of Systematic Reviews	3	0	1	4
Database of Abstracts of Reviews of Effects[a]	7	N/A	N/A	7
Health Technology Assessment Database	2	N/A	N/A	2
Epistemonikos[a]	N/A	26	33	59
Medline	276	38	21	335
Embase	660	134	100	894
Cochrane Central Trials Register	326	16	10	352
Clinicaltrials.gov	103	12	14	129
WHO ICTRP[b]	55	N/A	29	84
Total	**1432**	**226**	**208**	**1866**

[a]DARE no longer updated since original searches (2018; Epistemonikos was searched to identify systematic reviews published since 2018. Restricted to systematic reviews, publication date 2018 onwards
Bwho ICTRP was unavailable for the 2020 update.

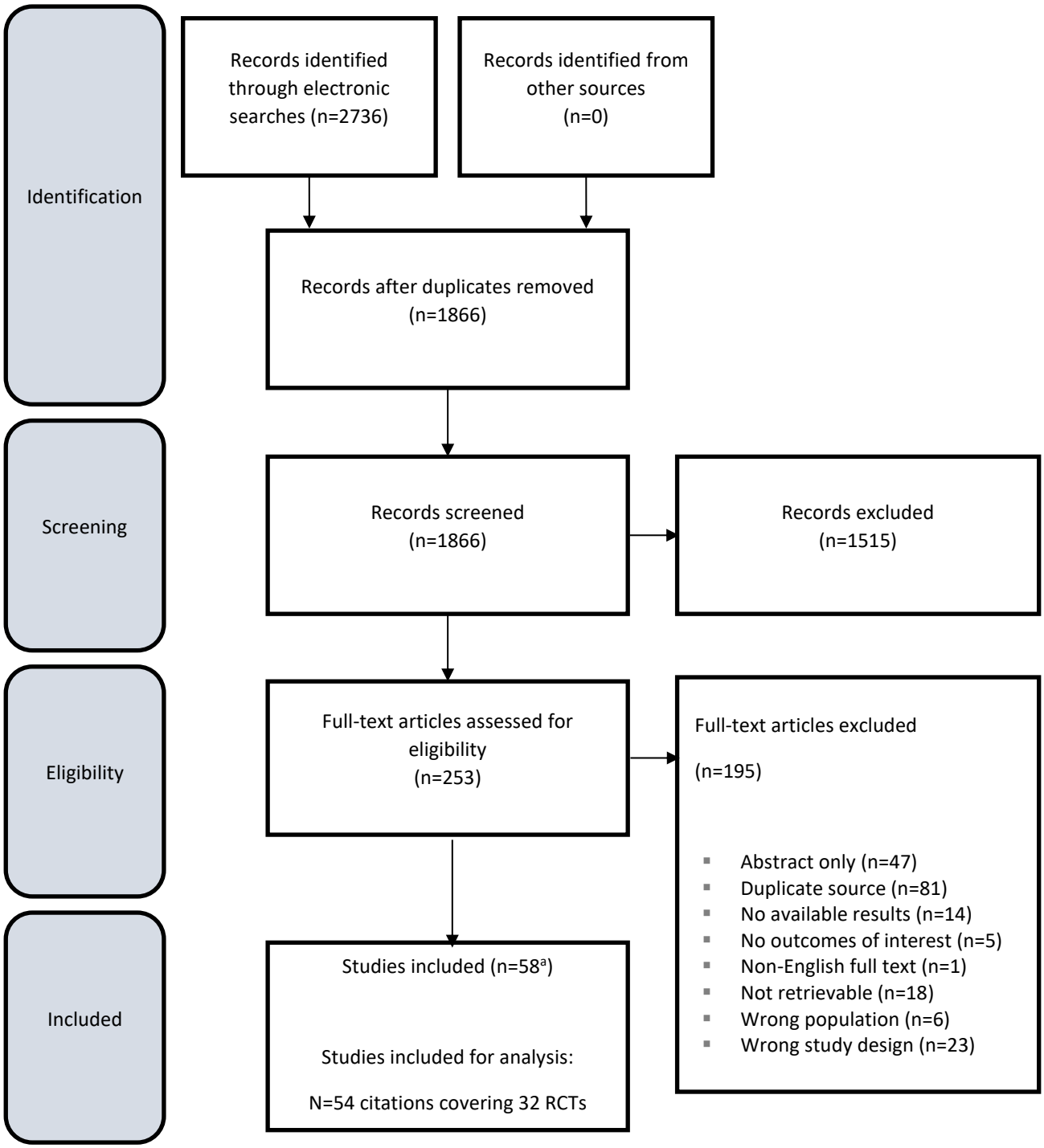
The titles and abstracts of all 1866 citations were reviewed by 2 independent analysts against an updated PICOS to determine whether they met the inclusion criteria and none of the exclusion criteria. A total of 1515 citations were excluded at title and abstract screening, leaving 253 citations that were reviewed at full-text screening.

Of the 253 citations, 195 were excluded following full-text screening (Table 6).

Of the 58 included citations, 4 used a non-PICOS comparator as a treatment arm, so data for these studies were not extracted into the data extraction; information on these studies can be found in Table 9**Fejl! Henvisningskilde ikke fundet.Fejl! Henvisningskilde ikke fundet.**. Therefore, 54 citations reporting data for 32 different RCTs were deemed to be relevant to the research question and were extracted for analysis table 7 og 8.

A flow diagram of the included/excluded citations at each stage is shown in **Fejl! Henvisningskilde ikke fundet.**. Summary of which citations are linked to each study is outlined in Table 7. A full-citation reference list for all the excluded references along with the reason(s) for their exclusion is outlined in table 6.

Figure 1 PRISMA flow diagram for 2018, 2020 and 2021 searches combined, adapted form Moher et al (2009)



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

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

Table 6 List of excluded references/full text papers with a short reason

Authors (year)	Title	Reason for exclusion
(2005)	Etanercept plus standard therapy for Wegener's granulomatosis	Duplicate
Abdulahad et al. (2017)	B-cell depletion by rituximab affects the distribution of effector th-cell subsets in patients with ANCA associated vasculitis	Abstract only
Adu et al. (1997)	Controlled trial of pulse versus continuous prednisolone and cyclophosphamide in the treatment of systemic vasculitis	Wrong population
Adu et al. (1997)	Controlled trial of pulse versus continuous prednisolone and cyclophosphamide in the treatment of systemic vasculitis	Duplicate
Anonymous (2015)	Rituximab (MABTHERA) and severe polyangiitis. An option for patients informed of the uncertainties	Abstract only
Anonymous (2015)	Rituximab (MABTHERA) and severe polyangiitis. An option for patients informed of the uncertainties	Duplicate
Assistance Publique - Hôpitaux de Paris	Efficacy and Safety of Rituximab in the Treatment of Good Prognosis Microscopic Polyangiitis	No outcome of interest
Assistance Publique - Hôpitaux de Paris (2021)	Study of Salvage Therapy to Treat Patients With Granulomatosis With Polyangiitis	No outcome of interest
B. University Hospital (2021)	PRediction Of DIverse Glucocorticoids toxIcity OUtcomeS	Wrong study design
Bekker et al. (2012)	Oral C5A receptor antagonist CCX168 in a phase 2 clinical trial in ANCA-associated renal vasculitis	Duplicate
Bekker et al. (2014)	CCX168, an orally administered C5aR inhibitor for treatment of patients with antineutrophil cytoplasmic antibody-associated vasculitis	Abstract only
Berti et al. (2018)	Serum interleukin-6 levels in antineutrophil cytoplasmic antibody-associated vasculitis	Abstract only
Berti et al. (2018)	Serum interleukin-6 levels in antineutrophil cytoplasmic antibody-associated vasculitis	Duplicate
Berti et al. (2018)	Serum interleukin-6 levels in antineutrophil cytoplasmic antibody-associated vasculitis	Duplicate
Berti et al. (2018)	Serum interleukin-6 levels in antineutrophil cytoplasmic antibody-associated vasculitis	Abstract only
Booth et al. (2004)	Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis	Study design
Booth et al. (2004)	Infliximab improves endothelial dysfunction in systemic vasculitis: A model of vascular inflammation	No outcome of interest
Bruchfeld et al. (2013)	C5aR inhibitor on leukocytes exploratory ANCA associated renal vasculitis (CLEAR) clinical trial with orally administered CCX168	Abstract only
Bruchfeld et al. (2013)	C5aR inhibitor on leukocytes exploratory ANCA associated renal vasculitis (CLEAR) clinical trial with orally administered CCX168	Abstract only
C. University (2014)	Low-dose Glucocorticoid Vasculitis Induction Study	No outcome of interest

Cartin-Ceba (2015)	Diffuse alveolar hemorrhage secondary to ANCA-associated vasculitis: Predictors of respiratory failure and clinical outcomes	Abstract only
Center, National Institute of Allergy; Infectious Diseases; National Institutes of Health Clinical (1999)	Etanercept to treat Wegener's granulomatosis	Study design
Charles (2016)	Comparison of systematic vs individually tailored rituximab regimen to maintain anca-associated-vasculitis remission: Results of a prospective, randomized-controlled, phase 3 trial	Duplicate
Charles (2016)	Comparison of systematic vs individually tailored rituximab regimen to maintain anca-associated-vasculitis remission: results of a prospective, randomized-controlled, phase 3 trial	Duplicate
Charles (2017)	Comparison of systematic vs individually tailored rituximab regimen to maintain ANCA associated vasculitis remission	Abstract only
Charles (2019)	Reducing the number of rituximab infusions at onset of maintenance therapy for ANCA-associated vasculitides: Results of a post hoc Analysis from a Randomized-controlled Trial	Abstract only
Charles (2019)	Comparison between long-term and conventional rituximab-maintenance treatments: Results of a placebo-controlled randomized trial	Abstract only
Charlies (2017)	Comparison of individually tailored vs systematic rituximab regimens to maintain ANCA-associated vasculitis remissions: results of a prospective, randomized-controlled, phase 3 trial	Duplicate
ChemoCentryx (2011)	A study to evaluate the safety and efficacy of CCX168 in subjects with ANCA-associated vasculitis	Duplicate
ChemoCentryx (2014)	Clinical trial to evaluate safety and efficacy of CCX168 in ANCA-associated vasculitis	No results
ChemoCentryx (2016)	A phase 3 clinical trial of CCX168 (avacopan) in patients with ANCA-associated vasculitis	No results
ChemoCentryx (2017)	A Phase 3 Clinical Trial of CCX168 (Avacopan) in Patients With ANCA-Associated Vasculitis	Duplicate
Chen et al. (2012)	A randomized controlled trial of mycophenolate mofetil versus cyclophosphamide for induction therapy in ANCA associated systemic vasculitis with renal involvement	Not retrieved
ChiCTR-TRC-10000991 (2010)	Mycophenolate mofetil versus cyclophosphamide for remission induction therapy in ANCA associated systemic vasculitis with renal involvement	Duplicate
Clowse et al. (2009)	Oral cyclophosphamide therapy diminishes ovarian reserve in women with Wegeners granulomatosis	No outcome of interest
Cortazar (2017)	Design of the maintenance of anca vasculitis remission by intermittent rituximab dosing based on b cell reconstitution versus a serologic anca flare (Maintancavas) trial	Abstract only
de Menthon et al. (2009)	Infliximab (IFX) vs rituximab (RTX) for refractory Wegener's granulomatosis (WG): A prospective, randomized, multicenter study on 21 patients	Duplicate
Development, National Institute of Arthritis; Musculoskeletal; Skin Diseases; FDA Office of Orphan Products (2000)	Etanercept for Wegener's granulomatosis	Duplicate
DRKS00023771 (2020)	Prospective investigation of diagnostics and therapy of vasculitis in Rhineland-Palatinate/Saarland	Wrong study design

EUCTR2005-003610-15-GB (2005)	An international, randomised, open trial comparing a rituximab based regimen with a standard cyclophosphamide/azathioprine regimen in the treament of 'generalised' ANCA associated vasculitis. – RITUXVAS	Duplicate
EUCTR2006-001663-33-GB (2006)	A randomised clinical trial of mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA associated vasculitis – MYCYC	Duplicate
EUCTR2006-001859-35-GB (2007)	Abatacept in ANCA associated vasculitis ABAVAS – ABAVAS	Duplicate
EUCTR2008-002846-51'FR (2009)	Etude de l'efficacité du Rituximab versus Azathioprine en traitement d'entretien au cours des vascularitis associées aux ANCA: Etude prospective, multicentrique, contrôlée, radomisée – MAINRITSAN	Study design
EUCTR2008-004138-26-IT (2008)	Use of abatacept in ANCA-associated vasculitis – ABAVAS	Duplicate
EUCTR2016-001121-14-SE (2016)	A clinical trial to evaluate the safety and efficacy of CCX168 (avacopan), a new drug for the treatment of vasculitis of a certain type, called ANCA-associated vasculitis (AAV)	Abstract only
EUCTR2017-004645-24-GB (2019)	COMBIVAS: A trial of rituximab versus rituximab and belimumab for time to remission in ANCA vasculitis	No outcome of interest
EUCTR2018-000637-12-FR (2019)	Efficacy and safety of rituximab in the treatment of good prognosis microscopic polyangiitis	No outcome of interest
EUCTR2018-003588-69-NL (2018)	The ENDURRANCE-1 Study: Exploring durable remission with rituximab in ANCA associated vasculitis	No outcome of interest
Faurschou et al. (2012)	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	Duplicate
Faurschou et al. (2012)	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	Duplicate
Gapud et al. (2018)	Long-term clinical course of antineutrophil cytoplasmic antibody-associated vasculitis patients off maintenance therapy	Study design
Geetha et al. (2012)	The efficacy of rituximab vs cyclophosphamide for treatment of renal disease in anca-associated vasculitis	Abstract only
Geetha et al. (2015)	Rituximab versus cyclophosphamide for ANCA-associated vasculitis with renal involvement	Duplicate
Groningen et al. (2012)	Rituximab for ANCA-associated vasculitis (RAVE) long-term follow-up study	Study design
Groot et al. (1996)	Therapy for the maintenance of remission in sixty-five patients with generalized Wegener's granulomatosis. Methotrexate versus trimethoprim/sulfamethoxazole	Duplicate
Groot et al. (2009)	Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: A randomized trial	Duplicate
Guillevin et al. (1997)	A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis	Duplicate
Guillevin et al. (2012)	Rituximab versus azathioprine for maintenance in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis	Abstract only
Guillevin et al. (2013)	Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. A prospective study in 117 patients	Not retrievable
Guillevin et al. (2013)	Relationship between infectious side effects and immunoglobulin levels in the maintenance rituximab vs azathioprine for anca-associated vasculitides	Not retrievable

Guillevin et al. (2013)	Relationship between infectious side effects and immunoglobulin levels in the maintenance rituximab vs azathioprine for anca-associated vasculitides	Not retrievable
Guillevin et al. (2014)	Rituximab versus azathioprine for maintenance in anca-associated vasculitis. A prospective study in 117 patients	Not retrievable
Guillevin et al. (2014)	Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis	Duplicate
Han et al. (2011)	Effects of mycophenolate mofetil combined with corticosteroids for induction therapy of microscopic polyangiitis	Duplicate
Harper et al. (2011)	Pulse versus daily oral CyP for induction of remission in ANCA-associated vasculitis. A European, multi-centre randomized controlled trial: Long-term follow-up	Duplicate
Harper et al. (2012)	Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up	Duplicate
Harper et al. (2009)	Pulse vs daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: A randomized controlled trial	Duplicate
Haubitz et al. (1998)	Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement: a prospective, randomized study	Duplicate
Hellmich (2014)	Remission induction in ANCA-associated vasculitis: follow-up data of the RAVE study	Non-English
Hiemtra et al. (2010)	Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial	Duplicate
Isrctn (2006)	A randomised controlled trial of Infliximab in ANCA associated systemic vasculitis	Population
Isrctn (2020)	Biologics in refractory vasculitis	No outcome of interest
ISRCTN03001669 (2006)	European Community SYStemic VASculitis TRIALs group	Duplicate
ISRCTN07757494 (2009)	Plasma exchange and glucocorticoid dosing in the treatment of antineutrophil cytoplasm antibody associated vasculitis	Duplicate
ISRCTN28528813 (2006)	An international, randomised, open label trial comparing a rituximab-based regimen with a standard cyclophosphamide/azathioprine based regimen in the treatment of active, generalised anti-neutrophilic cytoplasmic antibodies associated vasculitis	Duplicate
Jarrousse et al. (1993)	Increased risk of Pneumocystis carinii pneumonia in patients with Wegener's granulomatosis. [Erratum appears in Clin Exp Rheumatol 1994 Jan-Feb;12(1):117]	Abstract only
Jayne (2005)	An international, randomised open label trial comparing a rituximab based regime with a standard cyclophosphamide/azathioprine regimen in the treatment of active 'generalised' ANCA-associated vasculitis	Duplicate
Jayne (2020)	A randomized, double-blind, active controlled study of avacopan in anti-neutrophil cytoplasmic antibody-associated vasculitis	Abstract only
Jayne (2021)	Avacopan in Anca-Associated Vasculitis: Evidence for Elimination of Daily Prednisone Therapy and Reduction in Glucocorticoid-Related Toxicity from the Phase 3 Advocate Trial	Abstract only
Jayne et al. (2000)	Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity	Duplicate

Jayne et al. (2003)	A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies	Duplicate
Jayne et al. (2007)	Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis	Duplicate
Jayne et al. (2013)	An international, open label, randomised controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing ANCA-associated vasculitis (RITAZAREM)	Not retrievable
Jayne et al. (2014)	Oral C5A receptor antagonist CCX168 phase 2 clinical trial in ANCA-associated renal vasculitis	Abstract only
Jayne et al. (2014)	Oral C5A receptor antagonist CCX168 phase 2 clinical trial in ANCA-associated renal vasculitis	Abstract only
Jayne et al. (2014)	Phase 2 randomised trial of oral C5A receptor antagonist CCX168 in ANCA-associated renal vasculitis	Duplicate
Jayne et al. (2014)	Phase 2 randomised trial of oral C5A receptor antagonist CCX168 in ANCA-associated renal vascul	Duplicate
Jayne et al. (2016)	Successful steroid replacement in ANCA-associated vasculitis with c5a receptor inhibitor CCX168 in phase 2 randomised trial (clear)	Abstract only
Jayne et al. (2016)	Successful steroid replacement in ANCA-associated vasculitis with c5a receptor inhibitor CCX168 in phase 2 randomised trial (clear)	Duplicate
Jayne et al. (2017)	Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis	Duplicate
Jayne et al. (2018)	Adverse events with glucocorticoid standard of care versus avacopan in anca-associated vasculitis: Observations from the clear trial	Abstract only
Jones et al. (2008)	Randomised trial of rituximab versus cyclophosphamide for ANCA associated renal vasculitis: RITUXVAS	Duplicate
Jones et al. (2009)	Randomized trial of rituximab vs cyclophosphamide for ANCA-associated renal vasculitis: Rituxvas	Duplicate
Jones et al. (2010)	Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis	Duplicate
Jones et al. (2010)	Two year follow-up results from a randomised trial of rituximab versus cyclophosphimide for generalized' ANCA-associated vasculitis: Rituxvas	Duplicate
Jones et al. (2011)	Two-year follow-up results from a randomized trial of RTX versus CyP for ANCA- associated renal vasculitis: RITUXVAS	Duplicate
Jones et al. (2013)	A randomized trial of mycophenolate mofetil versus cyclophosphamide for remission induction of ANCA-associatedd vasculitis: "MYCYC". On behalf of the European vasculitis study group	Abstract only
Jones et al. (2013)	A randomized trial of mycophenolate mofetil versus cyclophosphamide for remission induction of ANCA-associated vasculitis: "MYCYC". On behalf of the European vasculitis study group	Duplicate
Jones et al. (2014)	Randomized trial of enteric-coated mycophenolate sodium versus mycophenolate mofetil in multi-system autoimmune disease	Duplicate
Jones et al. (2014)	Randomized trial of enteric-coated mycophenolate sodium versus mycophenolate mofetil in multi-system autoimmune disease	Wrong population
Jones et al. (2015)	Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial	Duplicate
Jones et al. (2018)	Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: A randomised, non-inferiority trial	Not retrievable
Jones et al. (2018)	Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: A randomised, non-inferiority trial	Duplicate
JPRN-UMIN000007076 (2012)	Rituximab treatment for patients with Wegener's granulomatosis	Duplicate

JPRN-UMIN000020329 (2016)	Remission induction with rituximab in Japanese patients with ANCA-associated vasculitis	Abstract only
Karras et al. (2017)	Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis	Study design
Karras et al. (2017)	Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis	Study design
L. L. U. H. U. M. C. G. F. C. B. Cambridge University Hospitals NHS Foundation Trust University Hospital Birmingham Imperial College London London North West Healthcare NHS Trust University Hospitals (1995)	Plasma Exchange for Renal Vasculitis	Duplicate
L. N. U. U. o. G. U. o. C. C. U. H. N. F. T. (2019)	Rituximab and Belimumab Combination Therapy in PR3 Vasculitis	No outcome of interest
Lind, van Wijngaarden et al. (2006)	Clinical and histologic determinants of renal outcome in ANCA-associated vasculitis: a prospective analysis of 100 patients with severe renal involvement	Wrong study design
Maritati et al. (2013)	Methotrexate vs cyclophosphamide as maintenance therapy in severe eosinophilic granulomatosis with polyangitiis: A subanalysis of the powercime trial	Not retrievable
Maritati et al. (2013)	Methotrexate vs cyclophosphamide as maintenance therapy in severe eosinophilic granulomatosis with polyangitiis: A subanalysis of the powercime trial	Duplicate
Maritati et al. (2017)	Methotrexate versus cyclophosphamide for remission maintenance in ANCA-associated vasculitis: a randomised trial	Duplicate
Medicine, Nanjing University School of (2003)	MMF versus CTX in the induction treatment of ANCA associated vasculitis	No results
Menthon et al. (2011)	Infliximab or rituximab for refractory Wegener's granulomatosis: Long-term follow-up. A prospective randomised multicentre study on 17 patients	Duplicate
Merkel (2020)	A randomized, double-blind, activecontrolled study of avacopan in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis	Abstract only
Merkel et al. (2016)	A randomized clinical trial of CCX168, an orally administered C5AR inhibitor for treatment of patients with ANCA-associated vasculitis	Abstract only
Merkel et al. (2016)	A randomized clinical trial of CCX168, an orally administered C5AR inhibitor for treatment of patients with ANCA-associated vasculitis	Duplicate
Miloslavsk et al. (2013)	Clinical outcomes of remission induction therapy for severe antineutrophil cytoplasmic antibody-associated vasculitis	Duplicate
Miloslavsky et al. (2013)	Safety of remission induction with rituximab versus cyclophosphamide in patients 65 and older with severe ANCA-associated vasculitis	Abstract only
Miloslavsky et al. (2013)	Retreatment with rituximab in the rituximab in ANCA-associated vasculitis (RAVE) trial	Abstract only
Miloslavsky et al. (2013)	Safety of remission induction with rituximab versus cyclosphosphamide in patients 65 and older with severe ANCA-associated vasculitis	Duplicate
Miloslavsky et al. (2014)	Rituximab for the treatment of relapses in antineutrophil cytoplasmic antibody-associated vasculitis	Study design

Miloslavsky et al. (2015)	Outcomes of nonsevere relapses in antineutrophil cytoplasmic antibody-associated vasculitis treated with glucocorticoids	Duplicate
Miloslavsky et al. (2015)	Outcomes of nonsevere relapses in antineutrophil cytoplasmic antibody-associated vasculitis treated with glucocorticoids	Duplicate
Moiseev et al. (2013)	Severe adverse events from treatment with genetically engineered biological agents in patients with rheumatic diseases	Non-English
Montante et al. (2017)	Economic evaluation of rituximab versus azathioprine for maintenance treatment of ANCA associated vasculitis: The mainritsan trial	Abstract only
Montante et al. (2017)	Economic evaluation of rituximab versus azathioprine for maintenance treatment of ANCA-associated vasculitis. A prospective, multicenter study	Abstract only
Montante et al. (2017)	Economic evaluation of rituximab versus azathioprine for maintenance treatment of ANCA-associated vasculitis. A prospective, multicenter study	Duplicate
Morgan et al. (2011)	Addition of infliximab to standard therapy for ANCA-associated vasculitis	Study design
Nachman et al. (1996)	Treatment response and relapse in antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis	Study design
National Institute of Allergy; Infectious Diseases; Immune Tolerance Network; Genentech, Inc. (2005)	Rituximab for the treatment of Wegener’s granulomatosis and microscopic polyangiitis	Duplicate
Nct (2004)	Comparative study of the efficacy of induction therapy with cyclophosphamide or mycophenolate mofetil for non-life-threatening relapses of PR3- or MPO-ANCA associated vasculitis	No results
Nct (2006)	MMF versus CTX in the induction treatment of ANCA associated vasculitis	Duplicate
Nct (2006)	A randomised clinical trial of mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA associated vasculitis	Duplicate
Nct (2007)	Abatacept in ANCA associated vasculitis	No results
Nct (2011)	A study to evaluate the safety and efficacy of CCX168 in subjects with ANCA-associated vasculitis	No results
Nct (2014)	Clinical trial to evaluate safety and efficacy of CCX168 in ANCA-associated vasculitis	No results
Nct (2016)	A phase 3 clinical trial of CCX168 (avacopan) in patients with ANCA-associated vasculitis	No results
Niaid (2004)	Phase I/II trial of TNFR: fc (etanercept) in patients with Wegener’s granulomatosis	Study design
Niles et al. (2017)	Safety following initiation of rituximab in granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA): Interim analysis of the rituximab in ANCA-associated vasculitis registry (RAVER)	Abstract only
NL7658 (2019)	Exploring durable remission with rituximab in ANCA associated vasculitis	No outcome of interest
Nowack et al. (1999)	Mycophenolate mofetil for maintenance therapy of Wegener's granulomatosis and microscopic polyangiitis: A pilot study in 11 patients with renal involvement	Study design
Pagnoux et al. (2008)	Azathioprine or methotrexate maintenance for ANCA-associated vasculitis	Duplicate
Pagnoux et al. (2012)	Treatment of systemic necrotizing vasculitides in patients >65 years old: Results of the multicenter randomized cortage trial	Abstract only

Pagnoux et al. (2012)	Treatment of systemic necrotizing vasculitides in patients >65 years old: Results of the multicenter randomized cortage trial	Duplicate
Pagnoux et al. (2015)	Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: Results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy	Population
Pagnoux et al. (2015)	Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy	Duplicate
Paris, Assistance Publique - Hôpitaux de (2001)	Intravenous Immunoglobulin After Relapse in Vasculitis	No results
Paris,–Assistance Publique – Hôpitaux de (2004)	RATTRAP: Infliximab Versus Rituximab in Systemic Necrotizing Vasculitides	No results
Paris,–Assistance Publique – Hôpitaux de (2008)	Efficacy study of two treatments in the remission of vasculitis	Study design
Paris,–Assistance Publique – Hôpitaux de (2008)	Association corticosteroid/azathioprine in microscopic polyangiitis/polyarteritis nodosa or eosinophilic granulomatosis with polyangiitis (Churg Strauss syndrome)	No results
Peh et al. (2010)	Rituximab versus cyclophosphamide in ANCA associated renal vasculitis	Duplicate
Peh et al. (2010)	Rituximab versus cyclophosphamide in ANCA associated renal vasculitis	Duplicate
Pepper et al. (2013)	Intravenous cyclophosphamide and plasmapheresis in dialysis-dependent ANCA-associated vasculitis. [Erratum appears in Clin J Am Soc Nephrol. 2013 Apr;8(4):701 Note: Caisian, Alina (corrected to Casian, Alina)]	Population
Pharma, Cambridge University Hospitals NHS Foundation Trust; Aspreva Pharmaceuticals; Vifor (2007)	Clinical trial of mycophenolate versus cyclophosphamide in ANCA vasculitis	Abstract only
Puechal et al. (2014)	Granulomatosis with polyangiitis or microscopic polyangiitis: Long-term outcomes of the prospective wegent trial comparing azathioprine vs methotrexate for remission-maintenance in 126 patients	Abstract only
Puechal et al. (2015)	Granulomatosis with polyangiitis or microscopic polyangiitis: Long-term outcomes of the prospective WEGENT trial comparing azathioprine vs methotrexate for remission-maintenance in 126 patients	Wrong study design
Puechal et al. (2016)	Does adding azathioprine to glucocorticoid induction increase the remission rate and prevent relapses in patients with systemic necrotizing vasculitides without poor-prognosis factors? A multicenter, double-blind randomized controlled trial	Abstract only
Puechal et al. (2016)	Long-term outcomes Among Participants in the WEGENT Trial of Remission-Maintenance Therapy for Granulomatosis With Polyangiitis (Wegener's) or Microscopic Polyangiitis	Duplicate
Puechal et al. (2017)	Risk of serious infection in granulomatosis with polyangiitis or microscopic polyangiitis: Long-term outcomes of 126 wegent trial patients	Abstract only
Puechal et al. (2017)	Risk of serious infection in granulomatosis with polyangiitis or microscopic polyangiitis: Long-term outcomes of 126 wegent trial patients	Duplicate

Puechal et al. (2017)	Adding azathioprine to remission-induction glucocorticoids for eosinophilic granulomatosis with polyangiitis (Churg-Strauss), microscopic polyangiitis, or polyarteritis nodosa without poor prognosis factors: A randomized, controlled trial	Population
Pugnet et al. (2014)	Rituximab versus azathioprine for ANCA-associated vasculitis maintenance therapy: Impact in health-related quality of life	Abstract only
Pugnet et al. (2016)	Rituximab versus azathioprine for ANCA-associated vasculitis maintenance therapy: impact on global disability and health-related quality of life	Duplicate
Ribi et al. (2010)	Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: a prospective randomized study of one hundred twenty-four patients	Duplicate
Roche, Hoffmann-La (2015)	A Study Evaluating the Safety and Efficacy of Rituximab in Combination With Glucocorticoids in Participants With Wegener's Granulomatosis or Microscopic Polyangitis	No results
Romand (2020)	An increase in serum calprotectin level in ANCA-associated vasculitides patients during maintenance therapy is associated with more relapse and accelerated renal function decline	Abstract only
Roubaud-Baudron et al. (2012)	Rituximab maintenance therapy for granulomatosis with polyangiitis and microscopic polyangiitis	Study design
Samson et al. (2014)	Long-term follow-up of non-HBV polyarteritis nodosa and microscopic polyangiitis with poor-prognosis factors	Not retrievable
Seo et al. (2005)	Damage caused by' Wegener's granulomatosis and its treatment: prospective data from the Wegener's Granulomatosis Etanercept Trial (WGET)	Outcome
Seror et al. (2010)	Treatment strategies and outcome of induction-refractory Wegener's granulomatosis or microscopic polyangiitis: analysis of 32 patients with first-line induction-refractory disease in the WEGENT trial	Population
Shimoyama et al. (2017)	Efficacy and safety profile of intravenous cyclophosphamide treatment in elderly patients with systemic vasculitis	Abstract only
SIwy et al. (2015)	Urinary proteomics identifies marker peptides in patients with anca-associated vasculitis (AAV), IGA nephropathy (IGAN), and henoch-schonlein purpura nephritis (HSPN)	Wrong study design
Smith (2019)	A randomized, controlled trial of rituximab versus azathioprine after induction of remission with rituximab for patients with ancaassociated vasculitis and relapsing disease	Abstract only
Smith (2019)	A randomized controlled trial of Rituximab (RTX) vs. Azathioprine (AZA) after induction of remission with RTX for patients with ANCA-associated vasculitis (AAV) and relapsing disease	Duplicate
Smith (2020)	Extended Follow-Up of Patients Recruited to a Randomized, Controlled Trial of Rituximab versus Azathioprine after Induction of Remission with Rituximab for Patients with ANCA-Associated Vasculitis and Relapsing Disease	Abstract only
Smith (2020)	A randomized, controlled trial of rituximab versus azathioprine after induction of remission with rituximab for patients with ANCA-associated vasculitis and relapsing disease	Duplicate
Smith (2020)	A randomized, controlled trial of rituximab versus azathioprine after induction of remission with rituximab for patients with ANCA-associated vasculitis and relapsing disease	Duplicate
Smith (2020)	Extended Follow-up of patients recruited to a randomized, controlled trial of rituximab vs. Azathioprine, after rituximab remission induction for patients with relapsing ANCA-associated vasculitis	Abstract only
Specks et al. (2011)	Immunoglobulin concentrations and infection risk among patients with ANCA-associated vasculitis treated with rituximab or cyclophosphamide	Abstract only

Specks et al. (2011)	Immunoglobulin concentrations and infection risk among patients with ANCA-associated vasculitis treated with rituximab or cyclophosphamide	Duplicate
Specks et al. (2013)	Efficacy of remission-induction regimens for ANCA-associated vasculitis	Duplicate
Stone et al. (2001)	Etanercept combined with conventional treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety	Wrong study design
Stone et al. (2001)	Etanercept combined with conventional'treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety	Study design
Stone et al. (2009)	Rituximab versus cyclophosphamide for induction of remission in ANCA-associated vasculitis: A randomized controlled trial (RAVE)	Duplicate
Stone et al. (2009)	Rituximab versus cyclophosphamide for induction of remission in ANCA-associated vasculitis: A randomized controlled trial (RAVE)	Abstract only
Stone et al. (2010)	Rituximab versus cyclophosphamide for ANCA-associated vasculitis	Duplicate
Stone et al. (2011)	Extended follow-up of treatment with rituximab versus cyclophosphamide for remission-induction of anca-associated vasculitis: Which subsets are at greatest risk for flare?	Abstract only
Stone et al. (2011)	Extended follow-up of treatment with rituximab versus cyclophosphamide for remission-induction of anca-associated vasculitis: which subsets are at greatest risk for flare?	Duplicate
Szpirt et al. (2011)	Plasma exchange for induction and cyclosporine A for maintenance of remission in Wegener's granulomatosis--a clinical randomized controlled trial	Duplicate
Terrier et al. (2013)	Rituximab versus azathioprine for maintenance in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (mainritsan): Follow up at 34 months	Abstract only
Terrier et al. (2013)	Rituximab versus azathioprine for maintenance in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (mainritsan): Follow up at 34 months	Duplicate
Terrier et al. (2013)	Rituximab versus azathioprine for maintenance in antineutrophil cytoplasmic antibodies-associated vasculitis: Follow up at 39 months	Abstract only
Terrier et al. (2014)	Factors predictive of ANCA-associated vasculitis relapse in patients given rituximab-maintenance therapy: Data from the extended follow-up of MAINRITSAN trial patients	Duplicate
Terrier et al. (2015)	Factors predictive of ANCA-associated vasculitis relapse in patients given rituximab-maintenance therapy: Data from the extended follow-up of MAINRITSAN trial patients	Abstract only
Terrier et al. (2016)	Rituximab versus azathioprine to maintain remission of ANCA associated vasculitides (MAINRITSAN): Follow-up at 60 months	Abstract only
Terrier et al. (2016)	Rituximab versus azathioprine to maintain remission of ANCA associated vasculitides (MAINRITSAN): Follow-up at 60 months	Duplicate
Tomasson et al. (2011)	Optimal definition for the duration of sustained remission in anca-associated vasculitis	No outcome of interest
Tomasson et al. (2012)	Assessment of health-related quality of life as an outcome measure in granulomatosis with polyangiitis (Wegener's)	Duplicate

Trust, University Hospital Birmingham NHS Foundation (2003)	Anti-Cytokine Therapy for Vasculitis	Study design
Tuin et al. (2017)	Mycophenolate mofetil versus cyclophosphamide for the induction of remission in non-life-threatening relapses of PR3 and mpoanca associated vasculitis	Not retrievable
Tuin et al. (2017)	Mycophenolate mofetil versus cyclophosphamide for the induction of remission in non-life-threatening relapses of PR3 and mpoanca associated vasculitis	Not retrievable
University of Pennsylvania;Cambridge University Hospitals NHS Foundation Trust; University of Birmingham; National Institute of Arthritis (2010)	Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody (ANCA) – Associated Vasculitis	No results
University of South Florida; The Cleveland Clinic; Bristol-Myers Squibb; University of Pennsylvania (2015)	Abatacept for the Treatment of Relapsing, Non-Severe, Granulomatosis With Polyangiitis (Wegener's)	No results
Unizony et al. (2014)	Peripheral CD5⁺ B-cells in ANCA-associated vasculitis	Duplicate
Unizony et al. (2014)	Peripheral CD5+ B-cells in ANCA-associated vasculitis	No available results
Unizony et al. (2014)	Comparison of clinicopathologically-and serologically-based classification systems for ANCA-associated vasculitis	Duplicate
Unizony et al. (2015)	Comparison of clinicopathologically-and serologically-based classification systems for ANCA-associated vasculitis	Abstract only
Unizony et al. (2016)	Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type	Duplicate
Vaglio et al. (2009)	Methotrexate vs cyclophosphamide for remission maintenance in ANCA-associated vasculitides: A randomized, open-label, single-centre trial	Abstract only
Venhoff et al. (2017)	Off-label biologic therapy of ANCA-associated and non-ANCA-associated small-vessel vasculitis: efficacy and safety analysis of a national registry (GRAID2)	Non-English
Wallace et al. (2017)	Effect of Disease Activity, Glucocorticoid Exposure, and Rituximab on Body Composition During Induction Treatment of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis	Duplicate
Wallace et al. (2019)	Disease activity, ANCA-type, and lipid levels in ANCA-associated vasculitis	Duplicate
Walsh (2018)	The effect of plasma exchange and the effect of reduced-dose oral glucocorticoids during remission induction in severe anca-associated vasculitis	Abstract only
Walsh et al. (2009)	Health-related quality of life in ANCA-associated vasculitis treated with a rituximab-based regimen vs Cyclophosphamide	Duplicate
Walsh et al. (2013)	Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear	Duplicate

Walsh et al. (2014)	Long-term follow-up of cyclophosphamide compared with azathioprine for initial maintenance therapy in ANCA-associated vasculitis	Duplicate
Walsh et al. (2017)	Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis: Baseline characteristics of a randomized controlled trial (PEXIVAS)	Abstract only
Walsh et al. (2018)	The effects of plasma exchange and reduced-dose glucocorticoids during remission-induction for treatment of severe ANCA-associated vasculitis	Abstract only
Walsh et al. (2019)	The effect of reduced-dose oral glucocorticoids during induction of remission induction in severe ANCA-associated vasculitis	Abstract only
Wechsler et al. (2017)	Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis	Wrong population

There were 54 citations (covering 32 RCTs) identified for analysis in total (Table 7). All trials reported the dose and route of the primary interventions and the use of additional background corticosteroid therapy. With the exception of three trials [NORAM,(Han et al. 2011; Hu et al. 2008)], all trials also reported the use of additional background immunosuppressive therapy.

Table 7. The 32 RCTs linked to the 54 publications

Trial	Related publications
ADVOCATE	(Jayne et al. 2021)
AZA-ANCA	
CHUSPAN	(Guillevin et al. 2003); (Samson et al. 2017); (Ribi et al. 2010)
CLASSIC	
CLEAR	(Jayne et al. 2017)
CYCAZAREM	(Walsh et al. 2014)
CYCLOPS	(Harper et al. 2012); (de Groot et al. 2009)
IMPROVE	(Hiemstra et al. 2010)
MEPEX	(van Wijngaarden et al. 2006); (Jayne et al. 2007); (Walsh et al. 2013)
MYCYC	(Jones et al. 2019)
MAINRITSAN	(Montante et al. 2019); (Pugnet et al. 2016); (Terrier et al. 2018); (Guillevin et al. 2014)
MAINRITSAN2	(Charles et al. 2018)
MAINRITSAN3	(Charles et al. 2020)
NORAM	(de Groot et al. 2005); (Faurschou et al. 2012)
PEXIVAS	(Walsh et al. 2020)
RAVE	(Berti et al. 2019); (Geetha et al. 2015); (Specks et al. 2013); (Stone et al. 2010); (Unizony et al. 2016); (Miloslavsky et al. 2015); (Miloslavsky et al. 2014); (Miloslavsky et al. 2013); (Wallace et al. 2019)
RITUXVAS	(Jones et al. 2010); (Jones et al. 2015)
VCRC-LS	(Tomasson et al. 2012)[a]
WEGENT	(Pagnoux et al. 2008); (Puéchal et al. 2016); (Seror et al. 2010)
WGET	(Silva et al. 2011); (Stone et al. 2006); (Tomasson et al. 2012)[a]; WGET Group (2005)
de Menthon et al. (2011)	(de Menthon et al. 2011)
LoVAS	(Furuta et al. 2021)
Gottenberg et al. (2007)	(Gottenberg et al. 2007)
Guillevin et al. (1997)	(Guillevin et al. 1997)
Han et al. (2011)	(Han et al. 2011)
Haubitz et al. (1998)	(Haubitz et al. 1998)
Hu et al. (2008)	(Hu et al. 2008)
Jayne et al. (2000)	(Jayne et al. 2000)
Jayne et al. (2003)	(Jayne et al. 2003)
Maritati et al. (2017)	(Maritati et al. 2017)
Szpirt et al. (2010)	(Szpirt et al. 2010)
Tuin et al. (2019)	(Tuin et al. 2019)
[a]Tomasson et al. (2012) reported data from both WGET and VCRC-LS trials separately	

The patient populations that were represented in the RCTs were heterogeneous, varying on the number of patients with renal involvement, disease status, and newly diagnosed or relapsing disease. A summary of trial characteristics, including intervention/comparator(s), baseline population, objectives, and endpoints, can be found in table 8.

Table 8 Summary of trial characteristics

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
ADVOCATE (NCT02994927)	**Prednisone**: 60 mg/d, orally (+ avacopan matchingplacebo 3 capsules morning and 3 capsules evening separated by at least 12 hours)—*primary intervention (n=166)* *Per-protocol immunosuppressants* ▪ **IV CYC** 15 mg/kg/d up to 1.2 g on weeks 2, 4, 7, 10, and 12/oral CYC 2 mg/kg/d (maximum 200 mg/d) followed by oral AZA 2 mg/kg/d from week 15 ▪ **IV RTX** 375 mg/m^2 weekly for 4 weeks (step 3 only) **Avacopan:** 30 mg BID, orally, 3 capsules morning and 3 capsules evening separated by at least 12 hours (+ prednisone matching placebo)—*primary intervention (n=164)* *Per-protocol immunosuppressants* ▪ **IV CYC** 15 mg/kg/d up to 1.2 g on weeks 2, 4, 7, 10, and 12/oral CYC 2 mg/kg/d (maximum 200 mg/d) followed by oral AZA 2 mg/kg/d from week 15 ▪ **IV RTX** 375 mg/m^2 weekly for 4 weeks (step 3 only)	**Demographics (of total population)** ▪ mITT analysis, 330 patients **Disease status** ▪ Newly diagnosed: 69.4% ▪ Relapsing: 30.6% **Diagnosis:** ▪ GPA: 54.8% ▪ MPA: 45.2% **ANCA type** ▪ PR3: 43.0% ▪ MPO: 57.0% **Renal function** ▪ Serum creatinine: Not reported ▪ eGFR: Not reported **Disease activity (median BVAS score):** 15.0 **Vasculitis damage (median VDI score):** 0	To evaluate the efficacy of avacopan to achieve and sustain remission in subjects with active ANCA-associated vasculitis when used in combination with CYC followed by AZA, or in combination with rituximab	**Primary** ▪ Disease remission defined as BVAS of 0 and no glucocorticoids within 4 weeks of week 26 ▪ Sustained remission defined as BVAS of 0 at week 26 without relapse to week 52 (BVAS of 0 and not taking glucocorticoids for treatment of ANCA-associated vasculitis for 4 weeks prior to week 52) **Secondary** ▪ Rates of GC toxicity using Glucocorticoid Toxicity Index (GTI) ▪ Time to response to treatment ▪ Adverse events ▪ Change in PROs ▪ Changes in renal function (eGFR) ▪ Changes in Vasculitis Damage Index (VDI)	▪ Jayne at al. (2021) ▪ CSR provided by Vifor Pharma Group

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
CLASSIC (NCT02222155)	**Placebo** plus SOC (15 mg/kg IV cyclophosphamide on days 1, 15, 29, 57, and 85 or 375 mg/m^2 IV rituximab on days 1, 8, 15, and 22). All patients also received 60 mg/day oral prednisone, steadily tapering to 10 mg/day by week 11 and to 0 mg/day by week 20. Avacopan-10: avacopan 10 mg orally twice daily plus SOC (see above) Avacopan 30: avacopan 30mg orally twice daily plus SOC (see above).	**Demographics (of total population)** ▪ mITT analysis, 42 patients **Disease status** ▪ Newly diagnosed: 64% ▪ Relapsing: 36% **Diagnosis** ▪ GPA: 69% ▪ MPA: 26% **ANCA type** ▪ PR3: 50% ▪ MPO: 50% **Background treatment** ▪ RTX: 93% ▪ CYC: 7% **Disease assessment scores, mean (SD)** ▪ BVAS: 15.3 (6.6) ▪ VDI score: 0.8 (1.8) **Renal assessments** ▪ eGFR, mean (SD) ml/min/1.73m2: 59.4 (27.2) ▪ Albumin:creatinine ratio, GMR (range), mg/g (n=41): 104.7 (3-5540) ▪ Urinary MCP-1:creatinine ratio, GMR (range), pg/mg creatinine (n=38):522.6 (98-7291)	To evaluate the safety of avacopan, for the treatment of ANCA–associated vasculitis in addition to SOC treatment with glucocorticoids and with cyclophosphamide or rituximab.	**Primary** ▪ Safety: the incidence of AEs ▪ Efficacy: the proportion of patients achieving disease response at day 85 [defined as a 50% or greater reduction of BVAS (version 3) from baseline with no worsening in any body system component]. **Secondary** ▪ The rate of achievement of a BVAS of 0 ▪ BVAS disease activity present within the 28 days prior to the visit ▪ Incidence of infections ▪ Laboratory parameters and vital signs ▪ VDI score ▪ eGFR ▪ Renal response ▪ Haematuria (urinary RBC count) ▪ Albuminuria (morning urinary	▪ Merkel et al. (2021) ▪ CSR provided by Vifor Pharma Group

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
				albumin:creatinine ratio) ▪ Renal inflammatory activity (MCP-1:creatinine ratio and CRP) ▪ HRQoL [SF-36 (v2), EQ-5D	
CLEAR (NCT01363388)	**Avacopan:** 30 mg BID, orally (+ 20mg prednisone)—*primary intervention* *Per-protocol immunosuppressants* ▪ **IV CYC** 15 mg/kg/d up to 1.2 g on weeks 1, 2, 4, 8, and 12 followed by oral AZA 2 mg/kg/d from weeks 14-24 ▪ **IV RTX** 375 mg/m^2 weekly for 4 weeks (step 3 only) *Per-protocol steroids* ▪ Prednisone 20 mg/d orally ▪ Tapering: Reduced to 0 mg by week 15 **Avacopan:** 30 mg BID orally (no prednisone)—*primary intervention* *Per-protocol immunosuppressants* ▪ **IV CYC** 15 mg/kg/d up to 1.2 g on weeks 1, 2, 4, 8, and 12 followed by oral AZA 2 mg/kg/d from weeks 14-24 ▪ **IV RTX** 375 mg/m^2 weekly for 4 weeks (step 3 only) *Per-protocol steroids* ▪ Placebo prednisone **Placebo avacopan:** 30 mg BID orally (+ prednisone)—*primary intervention* *Per-protocol immunosuppressants*	**Demographics (of total population)** ▪ ITT analysis, 67 patients **Disease status** ▪ Newly diagnosed: 73% ▪ Relapsing: 27% **Diagnosis** ▪ GPA: 49% ▪ MPA: 42% ▪ Unknown: 2% **ANCA type** ▪ PR3: 43% ▪ MPO: 52% ▪ Unknown: 5% **Renal function** ▪ Serum creatinine: Not reported ▪ eGFR: 51.6 ± 20.9 mL/min/1.73m^2 ▪ UCAR: 303.8 (24-5962)) mg/g **Disease activity (mean BVAS score):** 13.7 **Vasculitis damage (mean VDI score):** 0.9	To evaluate the safety and tolderability of Avacopan in AAV patients on background cyclophosphamide and rituximab and to evaluate the efficacy of Avacopan based on the BVAS version 3	**Primary** ▪ BVAS decrease from baseline of at least 50% within 12 weeks ▪ No worsening in any body system **Secondary** ▪ BVAS=0 within 12 weeks ▪ Improvement in eGFR ▪ Changes from baseline in renal function, VDI, and PROs	▪ Jayne et al. (2017) ▪ CSR provided by Vifor Pharma Group

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
	▪ **IV CYC**—15 mg/kg/d up to 1.2 g on weeks 1, 2, 4, 8, and 12 followed by oral AZA 2 mg/kg/day from week 14-24 ▪ **IV RTX**—375 mg/m^2 weekly for 4 weeks (Step 3 only) *Per-protocol steroids* ▪ Prednisone 60 mg/d orally ▪ Tapering: Reduced to 5 mg by week 20				
RAVE (NCT00104299)	**IV RTX**: 375 mg/m^2 body surface, weekly for 4 weeks—*primary intervention* *Per-protocol immunosuppressants* ▪ **Placebo CYC** *Per-protocol steroids* ▪ Methylprednisolone 1000 mg (1-3 pulses) taken orally ▪ Prednisone 1 mg/kg/d taken orally ▪ Tapering: Reduced to 0 mg by 20 weeks **IV CYC** 2 mg/kg/d—*primary intervention* *protocol immunosuppressants* ▪ **Placebo RTX** *Per-protocol steroids* ▪ Methylprednisolone 1 g (1-3 pulses) taken orally ▪ Prednisone 1 mg/kg/d taken orally ▪ Tapering: Reduced to 0 mg by 20 weeks	**Demographics (of total population)** ▪ ITT analysis: 197 patients **Disease status** ▪ Newly diagnosed: 49% ▪ Relapsing: 51% **Diagnosis** ▪ GPA: 76% ▪ MPA: 24% **ANCA type** ▪ PR3: 67% ▪ MPO: 33% **Renal function (from Geetha et al. 2015)** ▪ Serum creatinine: Rise in serum creatinine, 30%; mean level, 1.9 mg/dL (165 µmol/L) ▪ eGFR: Not reported **Disease activity (mean BVAS score):** 8.4 **Vasculitis damage (mean VDI score):** 1.2 **Comorbidities** ▪ Cranial-nerve palsy: 0% ▪ Meningitis: 1% ▪ Motor mononeuritis multiplex: 11% ▪ Sensory peripheral neuropathy: 22%	To compare RTX with standard cytotoxic therapy for the induction of complete remission by 6 months in patients with severe ANCA-associated vasculitis. Cohort followed for 18 months after trial start	**Primary** ▪ BVAS/WG of 0 within 6 months and successful completion of prednisone taper ▪ Complete remission at 6, 12, and 18 months **Secondary** ▪ Rates of disease relapse ▪ BVAS/WG of 0 with <10 mg/d of steroids ▪ Cumulative steroid dose ▪ PROs ▪ Adverse events ▪ Treatment failures caused by uncontrolled disease	▪ Stone et al. (2010) ▪ Miloslavsky et al. (2014) ▪ Unizony et al. (2016) ▪ Geetha et al. (2015) ▪ Specks et al. (2013)

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
RITUXVAS (EudraCT number: 2005-003610-15)	**IV RTX** 375 mg/m^2 body surface for 4 weeks—*primary intervention* *Per-protocol immunosuppressants* ▪ **IV CYC** 15 mg/kg with the first and third RTX infusions *Per-protocol steroids* ▪ Prednisolone 1 mg/kg/d taken orally ▪ Tapering: Reduced to 5 mg/d by 6 months **CYC** 15 mg/kg taken every 2 weeks for 3 doses; every 3 weeks until remission—*primary intervention* *Per-protocol immunosuppressants* ▪ Only in cases of relapse *Per-protocol steroids* ▪ Prednisolone 1 mg/kg/d taken orally ▪ Tapering: Reduced to 5 mg/d by 6 months	**Demographics (of total population)** ▪ ITT analysis: 44 patients **Disease status** ▪ Newly diagnosed: 100% **Diagnosis** ▪ GPA: 46% ▪ MPA: 36% ▪ Renal-limited vasculitis: 18% **ANCA type** ▪ PR3: 53% ▪ MPO: 47% **Renal function** ▪ Serum creatinine: Not reported ▪ eGFR: mean rate: 20.5 mL/min/1.73m^2 ▪ Biopsy demonstrating necrotizing glomerulonephritis ▪ Red cell casts on urine microscopy or ≥ ++ haematuria **Disease activity (median BVAS score):** 18.5 **Vasculitis damage (VDI):** Not reported	To test the hypothesis that RTX leads to a higher rate of sustained remission compared with standard therapies (CYC/AZA) with a lower rate of adverse events and reduced CYC exposure as treatments for active, "generalised" AAV	**Primary** ▪ BVAS of 0 (sustained) at 12 months ▪ Rate of SAEs at 12 months **Secondary** ▪ Time to remission ▪ Steroid dose ▪ Change from baseline in GFR, VDI, and PROs	▪ Jones et al. (2010) ▪ Jones et al. (2015)
NORAM (trial number not reported)	**Oral MTX** 15 mg weekly (escalated to 25 mg/week by 12 weeks, maintained for 10 months at that dose and then tapered at discontinued at 12 months)—*primary intervention* *Per-protocol immunosuppressants* ▪ Not reported *Per-protocol steroids* ▪ Prednisolone 1 mg/kg/d taken orally ▪ Tapering: Reduced to 7.5 mg/d by 6 months	**Demographics (of total population)** ▪ ITT analysis: 100 patients ▪ mITT analysis: 95 patients (after withdrawals) **Disease status** ▪ Newly diagnosed: 100% **Diagnosis** ▪ GPA: 94% ▪ MPA: 6% **ANCA type**	To determine whether MTX could replace CYC in the early treatment of AAV	**Primary** ▪ BVAS1 of 0 within 6 months ▪ BVAS2 of 2 within 6 months **Secondary** ▪ Time to disease relapse ▪ Adverse events	▪ de Groot et al. (2005) ▪ Faurschou et al. (2012)

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
	Oral CYC 2 mg/kg taken daily until remission—*primary intervention* *Per-protocol immunosuppressants* ▪ Not reported *Per-protocol steroids* ▪ Prednisolone 1 mg/kg/d taken orally ▪ Tapering: Reduced to 7.5 mg/d by 6 months	▪ PR3: 74% ▪ MPO: 13% ▪ Unknown: 13% **Renal function (from Geetha et al., 2015)** ▪ Serum creatinine: All patients level <150 µmol/L; median level, 84.5 µmol/L ▪ eGFR: Not reported **Disease activity (median BVAS score):** 15 **Vasculitis damage (median VDI score):** 0.5			
MEPEX (NCT01408836)	**PLEX** 60 mL/kg (volume replacement with 5% albumin) ×7 within 14 days of entry—*primary intervention* *Per-protocol immunosuppressants* ▪ CYC 2.5 mg/kg/d taken orally ▪ Tapering: Reduced to 0 mg at 6 months *Per-protocol steroids* ▪ Prednisolone 1 mg/kg/d taken orally ▪ Tapering: Reduced to 10 mg/d by 5 months ▪ ▪ ▪ ▪	**Demographics (of total population)** ▪ ITT analysis: 137 patients **Disease status** ▪ Newly diagnosed: 100% **Diagnosis** ▪ GPA: 31% ▪ MPA: 69% **ANCA type** ▪ PR3: 42% ▪ MPO: 52% ▪ Unknown: 6% **Renal function** ▪ Serum creatinine: All patients level >500 µmol/L; mean level: 736 µmol/L ▪ eGFR: Not reported **Disease activity (median BVAS score):** 21 **Vasculitis damage (median VDI score):** 0	To investigate whether the addition of plasma exchange was more effective than intravenous methylprednisolone in the achievement of renal recovery in those who presented with serum creatinine 500 mol/L (5.8 mg/dL)	**Primary** ▪ Patient survival at 3 months ▪ Dialysis independence at 3 months ▪ Serum creatinine level <500 µmol/L **Secondary** ▪ Patient survival at 12 months ▪ Serum creatinine level at 12 months ▪ End-stage renal disease ▪ Adverse events	Jayne et al. (2007)
WGET (NCT00005007)	**SC etanercept** 25 mg taken twice weekly—*primary intervention* *Per-protocol immunosuppressants*	**Demographics (of total population)** ▪ ITT analysis: 181 patients **Disease status**	To evaluate etanercept for the maintenance of	**Primary**	▪ WGET Group (2005)

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
	▪ **CYC** 2 mg/kg/d for 3-6 months, followed by MTX 0.25 mg/kg/wk for 12 months once remission was obtained ▪ **AZA** 2 mg/kg/d for patients in remission with serum creatinine >2 mg/dL *Per-protocol steroids* ▪ Methylprednisolone 1 g daily for 3 days taken orally ▪ Prednisone 0.5-1.0 mg/kg/d taken orally ▪ Tapering: Reduced to 0 mg by 6 months **SC placebo etanercept** 25 mg twice weekly—*primary intervention* *Per-protocol immunosuppressants* ▪ **CYC** 2 mg/kg/d for 3-6 months, followed by MTX 0.25 mg/kg/wk for 12 months once remission was obtained ▪ **AZA** 2 mg/kg/d for patients in remission with serum creatinine >2 mg/dL *Per-protocol steroids* ▪ Methylprednisolone 1 g for 3 days taken orally ▪ Prednisone 0.5-1.0 mg/kg/d taken orally ▪ Tapering: Reduced to 0 mg by 6 months	▪ Newly diagnosed: 44% ▪ Relapsing: 56% **Diagnosis** ▪ GPA: 100% **ANCA type** ▪ PR3: 73% ▪ MPO: 12% ▪ Unknown: 15% **Renal function** ▪ Serum creatinine: Mean level, 1.7 mg/dL (150.3 µmol/L) ▪ eGFR: Not reported **Disease activity (mean BVAS score):** 7 **Vasculitis damage (mean VDI score):** 1.3	remission in 180 patients with Wegener's granulomatosis	▪ BVAS/WG of 0 sustained at 6 months **Secondary** ▪ Number and rate of disease relapses ▪ Percentage of patients with a sustained low level of disease activity ▪ Percentage of patients with remission ▪ Cumulative area under curve for BVAS/WG ▪ Quality of life ▪ Adverse events	▪ Stone et al. (2006) ▪ Silva et al. (2011)
de Menthon et al. (2011) **(trial number not reported)**	**IV IFX** 3 mg/kg on days 1-14; then 5 mg/kg monthly (until 11 months if partial remission obtained after assessment)—*primary intervention* *Per-protocol immunosuppressants* ▪ Patient-specific **CYC, AZA, MTX,** and **MMF** all used *Per-protocol steroids* ▪ Used but not specified	**Demographics (of total population)** ▪ ITT analysis: 17 patients **Disease status** ▪ Refractory: 100% **Diagnosis** ▪ GPA: 100% **ANCA type** ▪ PR3: 71%	To compare efficacy and tolerance of infliximab versus RTX to treat refractory WG and clarify their	**Primary** ▪ Partial remission within 6 months (remission undefined) ▪ Complete remission within 6 months	de Menthon et al. (2011)

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
	IV RTX 375 mg/m^2 body surface taken weekly for 4 weeks—*primary intervention* *Per-protocol immunosuppressants* ▪ Patient-specific **CYC, AZA, MTX,** and **MMF** all used *Per-protocol steroids* ▪ Used but not specified	▪ MPO: 6% ▪ Unknown: 23% **Renal function** ▪ Serum creatinine: Not reported ▪ eGFR: Not reported **Disease activity (mean BVAS score):** 12.9 **Vasculitis damage:** Not reported	respective indications	(remission undefined) **Secondary** ▪ Adverse events	
LoVAS NCT02198248	**Reduced-dose glucocorticoid group**: (prednisolone 0.5 mg/kg/d). Prednisolone was stopped at 5 months. All patients received 4 doses of rituximab (375 mg/m^2/week) administered via IV infusion.	**Demographics (reduced-dose population)** ▪ Per protocol and post hoc analysis: n=69 **Diagnosis** ▪ MPA: 76.8% ▪ GPA: 23.2% ▪ Renal limited vaculitis: 0.0% **ANCA positivity** ▪ MPO: 86.9% ▪ PR3: 13.0% **eGFR** (median, IQR), ml/min/1.73m^2: 52.0 (31.4-74.6) **BVAS** (median, IQR): 15 (10-19).	To compare the efficacy and adverse events between a reduceddose glucocorticoid plus rituximab regimen and the standard high-dose glucocorticoid plus rituximab regimen in remission induction of ANCA-associated vasculitis.	**Primary** ▪ The risk difference in the remission induction rate at 6 months between the groups (non-inferiority analysis) **Secondary** ▪ Proportion of patients who died ▪ Proportion of patients with relapse ▪ Proportion of patientswith end-stage kidney disease ▪ BVAS (version 3) ▪ Cumulative dose of prednisolone **HRQoL** ▪ SF-36 ▪ VAS	Furuta et al. (2021)
	High-dose glucocorticoid group: (prednisolone 1.0 mg/kg/d). Prednisolone reduced to a total of 10 mg/d by 5 months. All patients received 4 doses of rituximab (375 mg/m^2/week) administered via IV infusion.	**Demographics (high-dose population)** ▪ Per protocol and post hoc analysis: n=65 **Diagnosis** ▪ MPA: 56.9 ▪ GPA: 43.1% ▪ Renal limited vaculitis: 1.5% **ANCA positivity** ▪ MPO: 84.6% ▪ PR3: 15.4% **eGFR** (median, IQR), ml/min/1.73m^2: 55.3 (41.2-72.3) **BVAS** (median, IQR): 13 (8.5-17.5).			

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
Han et al. (2011) **(trial number not reported)**	**Oral MMF** 1.5 g (body weight >70 kg) taken daily—*primary intervention* *Per-protocol immunosuppressants* ▪ Not reported *Per-protocol steroids* ▪ Methylprednisolone 360-500 mg/d for 3 days taken orally ▪ Prednisone 0.6-0.8 mg/kg/d taken orally ▪ Tapering: Gradual (not specified) **IV CYC** 1 g/pulse (0.8 g/pulse for patients <50kg) taken daily—*primary intervention* *Per-protocol immunosuppressants* ▪ Not reported *Per-protocol steroids* ▪ Methylprednisolone 360-500 mg/d for 3 days taken orally ▪ Prednisone 0.6-0.8 mg/kg/d taken orally ▪ Tapering: Gradual (not specified)	**Demographics (of total population)** ▪ ITT analysis: 41 patients **Disease status** ▪ Newly diagnosed: Not reported ▪ Relapsing: Not reported ▪ Refractory: Not reported **Diagnosis** ▪ MPA: 100% **ANCA type** ▪ MPO: 100% **Renal function** ▪ Serum creatinine: Mean level, 312.8 µmol/L ▪ eGFR: Mean rate, 34.5 mL/min/1.73m^2 **Disease activity (mean BVAS score):** 17.7 **Vasculitis damage:** Not reported	To compare the effects of oral MMF or IV CYC combined with corticosteroids for induction therapy of MPA with renal involvement over a follow-up period of 6 months	**Primary** ▪ BVAS of 0 within 6 months ▪ Stable low dose of steroids <7.5 mg/d **Secondary** ▪ Renal function at 6 months ▪ Adverse events	Han et al. (2011)
Szpirt et al. (2010) **(trial number not reported)**	**PLEX** 4 L (3% albumin in Ringer's lactate) × 6 (per-protocol 3-6 sessions if c-ANCA >320 or PR3-ANCA >25 U/mL)—*primary intervention* *Per-protocol immunosuppressants* ▪ Cytosine A 5 mg/kg/d taken orally for 9 months (randomised) ▪ **CYC** 1.5 mg/kg taken orally (100-150 mg daily) for 3 or 12 months (randomised) *Per-protocol steroids* ▪ Prednisolone 80 mg/d taken orally ▪ Tapering: Reduced to 5 mg by 9 months **Oral CYC** 1.5 mg/kg (100-150 mg daily) for 3 or 12 months (randomised)—*primary intervention* *Per-protocol immunosuppressants* ▪ **Cyclosporin A** 5 mg/kg/d taken orally for 9 months (randomised)	**Demographics (of total population)** ▪ ITT analysis: 32 patients **Disease status** ▪ Newly diagnosed: Not reported ▪ Relapsing: Not reported ▪ Refractory: Not reported **Diagnosis** ▪ GPA: 100% **ANCA type** ▪ PR3: Not reported ▪ MPO: Not reported **Renal function** ▪ Serum creatinine: Mean level, 256.3 µmol/L ▪ eGFR: Not reported **Disease activity:** Not reported **Vasculitis damage:** Not reported	To compare the effects of PE versus no PE and of CYC versus cyclosporine A in a randomised controlled trial with a Latin square design	**Primary** ▪ Patient mortality ▪ Dialysis requirement ▪ Relapses ▪ All events combined **Secondary** ▪ Not reported	Szpirt et al. (2010)

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
	Per-protocol steroids ▪ Prednisolone 80 mg/d taken orally ▪ Tapering: Reduced to 5 mg by 9 months				
Jayne et al. (2000) **(trial number not reported)**	**IVIg** 0.4 g/kg/d for 5 days (total dose 2 g/kg)—*primary intervention* *Per-protocol immunosuppressants* ▪ **CYC** (dose not reported) *Per-protocol steroids* ▪ Prednisolone (dose not reported) **Placebo IVIg** 0.4 g/kg/d for 5 days (total dose 2 g/kg)—*primary intervention* *Per-protocol immunosuppressants* ▪ **CYC** (dose not reported) *Per-protocol steroids* ▪ Prednisolone (dose not reported)	**Demographics (of total population)** ▪ ITT analysis: 34 patients **Disease status** ▪ Refractory: 100% **Diagnosis** ▪ GPA: 71% ▪ MPA: 29% **ANCA type** ▪ PR3: Not reported ▪ MPO: Not reported **Renal function** ▪ Serum creatinine: Not reported ▪ eGFR: Not reported **Disease activity (mean BVAS score):** 5.8 **Vasculitis damage:** Not reported **Other** ▪ At least 2 months treatment with prednisolone and CYC or azathioprine	To test the therapeutic efficacy of a single course of high-dose IVIg in reducing disease activity in previously treated patients with persistent AAV	**Primary** ▪ BVAS decrease from baseline >50% within 3 months **Secondary** ▪ CRP and ANCA levels ▪ Relapse frequency between 3 and 12 months ▪ Reduction in immunosuppressant dose ▪ Adverse events	Jayne et al. (2000)
Hu et al. (2008) **(trial number not reported)**	**Oral MMF** 2.0 g (1.5 g for patients <50 kg) daily for 6 months—*primary intervention* *Per-protocol immunosuppressants* ▪ Not reported *Per-protocol steroids* ▪ Methylprednisolone 0.5 g, 3 pulses taken orally ▪ Prednisone 0.6-0.8 mg/kg/d taken orally ▪ Tapering: Reduced by 5 mg/kg/wk to 10 mg/d **IV CTX** 0.75-1.0 g/m^2 body surface taken monthly—*primary intervention*	**Demographics (of total population)** ▪ ITT analysis: 35 patients **Disease status** ▪ Newly diagnosed: 100% **Diagnosis** ▪ GPA: 3% ▪ MPA: 97% **ANCA type** ▪ PR3: 6% ▪ MPO: 80% ▪ Unknown: 14% **Renal function**	To compare the clinical efficacies of MMF and intermittent CYC pulse therapy as induction treatments in patients with AAV and moderate renal involvement	**Primary** ▪ BVAS1 of 0 within 6 months ▪ BVAS2 <1 within 6 months ▪ No clinical signs of vasculitis ▪ Improved renal function ▪ No active urine sediments **Secondary**	Hu et al. (2008)

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
	Per-protocol immunosuppressants ▪ Not reported *Per-protocol steroids* ▪ Methylprednisolone 0.5 g, 3 pulses taken orally ▪ Prednisone 0.6-0.8 mg/kg/d taken orally ▪ Tapering: Reduced by 5 mg/kg/wk to 10 mg/d	▪ Serum creatinine: All patients level <500 µmol/L; mean level, 3.56 mg/dL (315 µmol/L) ▪ eGFR: Not reported **Disease activity (mean BVAS score):** 15.3 **Vasculitis damage:** Not reported		▪ Changes in renal function ▪ Adverse events/side effects	
MYCYC (NCT00414128)	**MTX** 2 g/d *Per-protocol immunosuppressants* **AZA** given when patients attain remission, 5 mg/d **IV CYC** 15 mg/kg taken for 2-3 weeks—*primary intervention* *Per-protocol immunosuppressants* ▪ **AZA** given when patients attain remission, 5 mg/d	**Demographics** ▪ ITT analysis: 70 patients **Disease status** ▪ Newly diagnosed: 100% **Diagnosis** ▪ GPA: MTX 67%, CYC 63% ▪ MPA: MTX 33%, CYC 37% **ANCA type** ▪ PR3: MTX 59%, CYC 60% ▪ MPO: MTX 40%, CYC 37% **Renal function** ▪ Not reported **Disease activity (mean BVAS score)** ▪ MTX: 19 ▪ CYC: 18 **Vasculitis damage:** Not reported	To investigate whether MMF was non-inferior to cyclophosphamide for remission induction in AAV	**Primary** ▪ Rate of remission by 6 months **Secondary** ▪ Time to remission, remission by 6 months regardless of glucocorticoid adherence ▪ Progressive disease ▪ Relapse ▪ Cumulative glucocorticoid dosing, change in eGFR ▪ VDI 19 ▪ ANCA positivity at 6 months	Jones et al. (2019)
AZA-ANCA (NCT00128895)	**Oral AZA 1.5-2.0 mg/kg/d** (standard maintenance: AZA tapered 1 year after diagnosis by 25 mg every 3 months)—*primary intervention* **Oral AZA 1.5-2.0 mg/kg/d** (extended maintenance: AZA dose maintained until 4 years after diagnosis, then tapered thereafter)—*primary intervention*	**Demographics** ▪ ITT analysis: 131 **Disease status** ▪ Newly diagnosed: 100% **Diagnosis** ▪ GPA • Standard c-ANCA -ve: 95% • Standard c-ANCA +ve: 96% • Extended c-ANCA +ve: 90% ▪ MPA	To determine if extended AZA maintenance therapy could reduce the incidence of relapse compared with standard azathioprine regimen	**Primary** ▪ Relapse-free survival (time from remission to first relapse at 4 years after diagnosis) **Secondary** ▪ Cumulative cyclophosphamide dose	Sanders et al. (2016)

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
		• Standard c-ANCA -ve: 2% • Standard c-ANCA +ve: 0% • Extended c-ANCA +ve: 0% **ANCA type** ▪ PR3: 100% ▪ MPO: 0% **Renal function** ▪ Standard c-ANCA -ve: 199 µmol/L ▪ Standard c-ANCA +ve: 144 µmol/L ▪ Extended c-ANCA +ve: 155 µmol/L ▪ eGFR: Not reported **Disease activity (mean BVAS)** ▪ Standard c-ANCA -ve: 20 ▪ Standard c-ANCA +ve: 18 ▪ Extended c-ANCA +ve: 20 **Vasculitis damage:** Not reported		▪ Cumulative prednisone dose ▪ Cumulative AZA dose ▪ Cumulative organ damage ▪ Adverse events/side effects ▪ Severity of relapses	
WEGENT (NCT00349674)	**Oral AZA** 2 mg/kg/d—*primary intervention* **Oral MTX** 0.3 mg/kg/wk (increased every week by 2.5 mg, to 25 mg per week)—*primary intervention*	**Demographics** ▪ ITT analysis: 63 patients **Disease status** ▪ Newly diagnosed: 100% **Diagnosis** ▪ GPA: 76% ▪ MPA: 24% **ANCA type** ▪ PR3: MTX 35%, AZA 41% ▪ MPO: MTX 33%, AZA 29% **Renal function** ▪ Serum creatinine: AZA 1.52 µmol/L; MTX 1.4 µmol/L **Disease activity (mean BVAS)** ▪ AZA: 23.6 ▪ MTX: 21.2 **Vasculitis damage:** Not reported	To determine the safety and efficacy of AZA versus MTX as maintenance therapy for GPA and MPA	**Primary** ▪ Safety/efficacy **Secondary** ▪ Relapse-free survival rate ▪ Health quality assessment	▪ Pagnoux et al. (2008) ▪ Puéchal et al. (2016) ▪ Seror et al. (2010)
PEXIVAS (NCT00987389)	Plasma exchange + glucocorticoids (standard dose) No plasma exchange + glucocorticoids (standard dose)	**Demographics** ▪ ITT analysis: 352 patients **Disease status**	To determine the efficacy of PLEX in addition to	**Primary**	Walsh et al. (2020)

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
	Plasma exchange + glucocorticoids (reduced dose) No plasma exchange + glucocorticoids (reduced dose)	▪ Newly diagnosed: 80% ▪ Relapsing: 20% **Diagnosis** ▪ Not reported **ANCA type** ▪ PR3: 40.6% ▪ MPO: 59.4% **Renal function (serum creatinine)** ▪ Plasma exchange: 327 ▪ No plasma exchange: 336 ▪ Reduced-dose prednisone: 320 ▪ Standard-dose prednisone/prednisolone: 335 **Disease activity:** BVAS, 9 **Vasculitis damage:** Not reported	immunosuppressive therapy and glucocorticoids in reducing death and ESRD, and to determine the non-inferiority of a reduced dose glucocorticoids regimen in reducing death and ESRD	▪ A composite of all-cause mortality or ESRD **Secondary** ▪ All-cause mortality ▪ ESRD ▪ Serious adverse events ▪ Health-related quality of life	
CYCAZAREM	**Oral CYC** (arm 1) 2 mg/kg/d (and a tapering course of daily oral prednisolone, initially at 1 mg/kg/d) until remission—*primary intervention* *Per-protocol immunosuppressants* ▪ **AZA** 2 mg/kg at 3-6 months, then 1.5 mg/kg/d taken orally **Oral CYC** (arm 2) 2 mg/kg/d (and a tapering course of daily oral prednisolone, initially at 1 mg/kg/d) until 12 months—*primary intervention* *Per-protocol immunosuppressants* ▪ **AZA** 1.5 mg/kg/d at 12 months taken orally	**Demographics** ▪ ITT analysis: 144 patients **Disease status** ▪ Not reported **Diagnosis** ▪ GPA: arm 1 65%, arm 2 63% **ANCA type** ▪ PR3: arm 1 62%, arm 2 63% ▪ MPO: not reported **Renal function** (serum creatinine) ▪ Arm 1: 1.6 µmol ▪ Arm 2: 2.35 µmol **Disease activity (BVAS)** ▪ Arm 1: 17.5 ▪ Arm 2: 16 **Vasculitis damage:** Not reported	To determine the effect of replacing daily oral CYC with AZA after induction of remission rather than after 1 year of treatment in patients with generalized AAV and serum creatinine ≤5.6 mg/dL at presentation	**Primary** ▪ Frequency of first relapse **Secondary** ▪ Rate of death ▪ Renal relapse ▪ Medical exposure following the end of trial ▪ Safety (ESRD and frequency of malignancies)	Walsh et al. (2014)
NCT00751517	**Oral CYC** 1.5 mg/kg/d until 12 months—*primary intervention* *Per-protocol steroids* ▪ Prednisone 5 mg/d for 12 months	**Demographics** ▪ ITT analysis: 71 patients **Disease status** ▪ Not reported **Diagnosis**	To compare the efficacy and safety of CYC with that of MTX for remission maintenance in	**Primary** ▪ Relapse frequency by month 12 (from the beginning of maintenance	Maritati et al. (2017)

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
	MTX 15 mg/wk taken orally, increased until dose of 0.3 mg/kg/wk was reached (maximum 20 mg/wk)—*primary intervention* *Per-protocol steroids* ▪ Prednisone 5 mg/d prednisone from 12 months taken orally	▪ GPA: CYC 39%, MTX 37% ▪ MPA: CYC 22%, MTX 18% **ANCA type** ▪ PR3: CYC 24%, MTX 24% ▪ MPO: CYC 39%, MTX 34% **Renal function (serum creatinine)** ▪ CYC: 1.1 mg/dL ▪ MTX: 0.9 mg/dL **Disease activity (BVAS)** ▪ CYC: 19 ▪ MTX: 18 **Vasculitis damage:** Not reported	ANCA-associated vasculitis	treatment) and the time to relapse **Secondary** ▪ Rates of major and minor relapses per group ▪ Change in eGFR and proteinuria ▪ Treatment related toxicity ▪ Mortality	
IMPROVE (NCT00307645)	Oral prednisone + **oral/IV CYC** ± PLEX ± methylprednisolone, then randomised to **AZA**. CYC 2 mg/kg/d intermittent IV 15 mg/kg—*primary intervention* **AZA** 2 mg/kg/d (from remission 3-6 months), 1.5 mg/kg/d after 12 months, 1 mg/kg/d after 18 months *Per-protocol steroids* ▪ IV methylprednisolone up to 300 mg over 3 days ▪ Prednisone 1 mg/kg/d taken orally Oral prednisone + **oral/IV CYC** ± PLEX ± methylprednisolone, then randomised to **MMF**—*primary intervention* **Oral MMF** 2000 mg/d initially (from remission 3-6 months), reduced to 1500 mg/d at 12 months, then 100 mg/d after 18 months *Per-protocol steroids* ▪ IV methylprednisolone up to 300 mg over 3 days ▪ Prednisone 1mg/kg/d taken orally	**Demographics** ▪ ITT analysis: 156 patients **Disease status** ▪ Newly diagnosed: 100% **Diagnosis** ▪ GPA: AZA 68.7%, MMF 59.2% ▪ MPA: AZA 31.3%, MMF 40.8% **ANCA type** ▪ PR3: AZA 61.3%, MMF 53.9% ▪ MPO: AZA 28.8%, MMF 36.8% **Renal function (serum creatinine)** ▪ AZA: 2.9 mg/dL ▪ MMF: 2.7 mg/dL **Disease activity (BVAS)** ▪ AZA: 11 ▪ MMF: 11 **Vasculitis damage** ▪ Not reported	To define the optimal maintenance therapy for AAV by comparing AZA (standard regimen) with MMF in terms of preventing relapses	**Primary** ▪ Relapse-free survival **Secondary** ▪ Adverse event rate	Hiemstra et al. (2010)

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
MAINRITSAN (NCT00748644)	**IV RTX** fixed 500-mg dose on days 0 and 14 after randomisation, and then at months 6, 12, and 18 after the first treatment—*primary intervention* **Oral AZA** 2 mg/kg/d for 12 months, followed by 1.5 mg/kg/d for 6 months and 1 mg/kg/d for 4 months—*primary intervention*	**Demographics** ▪ ITT analysis: 115 patients **Disease status** ▪ Newly diagnosed: 80% ▪ Relapsing: 20% **Diagnosis** ▪ GPA: AZA 69%, RTX 82% ▪ MPA: AZA 26%, RTX 14% **ANCA type** ▪ PR3: AZA 68%, RTX 83% ▪ MPO: AZA 32%, RTX 17% **Renal function** ▪ Serum creatinine: Not reported ▪ eGFR: AZA 59.4 mL/min/1.73 m^2, RTX 68.3 mL/min/1.73 m^2 **Disease activity** ▪ BVAS: Not reported **Vasculitis damage** ▪ AZA: 2.07 ▪ RTX: 1.63	Study of the efficacy of rituximab for maintenance treatment in systemic AAVs: prospective, multicentre, controlled, randomised comparative study of RTX versus AZA	**Primary** ▪ Number of relapses **Secondary** ▪ Adverse events ▪ Mortality ▪ Rates of minor relapse	▪ Guillevin et al. (2014), ▪ Pugnet et al. (2016) ▪ Terrier et al. (2018) ▪ Montante et al. (2019)
MAINRITSAN 2 (NCT01731561)	**IV RTX ITD** 500 mg RTX at randomisation, then administered in response to changes in ANCA and CD19+ B-lymphocyte status (assessed every 3-months). **IV RTX FS** 500 mg RTX days 0 and 14 post-randomisation, then at months 6, 12, and 18 after first infusion.	**Demographics** ▪ ITT analysis: 162 patients **Disease status** ▪ Newly diagnosed: 64% ▪ Relapsing: 36% **Diagnosis** ▪ GPA: ITD 69.1%, FS 75.3% ▪ MPA: ITD 30.9%, FS 24.7% **ANCA type** ▪ PR3: ITD 22.5%, FS 26.2% ▪ MPA: ITD 12.5%, FS 28.7% **Renal function** ▪ Serum creatinine: Not reported ▪ eGFR: ITD 55.6 mL/min/1.73m^2, FS 58.9 mL/min/1.73m^2 **Disease activity (BVAS):** Not reported	To compare individually tailored, based on trimestrial biological parameter monitoring, to FS RTX reinfusion for remission maintenance of AAVs	**Primary** ▪ Number of relapses at month 28 **Secondary** ▪ Number of major relapses ▪ Number of minor relapses ▪ Association of ANCA evolution and CD19+ cell counts with relapses ▪ Glucocorticoid treatment duration and cumulative dose ▪ VDI scores	Charles et al. (2018)

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
		Vasculitis damage (VDI): ITD 1.64, ITD 1.86		▪ Mortality	
MAINRITSAN3 (NCT02433522)	**IV RTX** 500 mg fixed dose + premedication with IV methylprednisolone 100 mg, dexchlorpheniramine 5 mg, and acetaminophen 1 g before all RTX infusions at randomisation months 6, 12, and 18—*primary intervention* **IV placebo:** 500 mg fixed dose of placebo + premedication with IV methylprednisolone (100 mg), dexchlorpheniramine (5 mg), and acetaminophen (1000 mg) before all placebo infusions at randomisation months 6, 12, and 18—*primary intervention*	**Demographics** ▪ ITT analysis: 97 patients **Disease status** ▪ Newly diagnosed: RTX 54%, placebo 64% ▪ Relapsing: RTX 46%, placebo 36% **Diagnosis** ▪ GPA: RTX 64%, placebo 77% ▪ MPA: RTX 36%, placebo 23% **ANCA type** ▪ PR3: RTX 12%, placebo 15% ▪ MPO: RTX 24%, placebo 17% **Renal function (glomerular filtration rate)** ▪ RTX: 55 mL/min/1.73m^2 ▪ Placebo: 64 m:/min/1.73m^2 **Disease activity (BVAS)** ▪ RTX: 0 ▪ Placebo: 0 **Vasculitis damage** ▪ Not reported	To evaluate the efficacy of prolonging the RTX infusion schedule to maintain remission in patients who achieve complete remission after terminating the first phase of rituximab maintenance therapy.	**Primary** ▪ Relapse-free survival **Secondary** ▪ Major and minor relapse-free survival ▪ Damage as evaluated with the VDI ▪ Health-related quality of life	Charles et al. (2020)
Jayne et al. (2003)	**Oral AZA** 2 mg/kg/d for 12 months following randomisation.; beginning at 12 months, AZA 1.5 mg/kg/d + prednisolone 7.5 mg/d—*primary intervention* *Per-protocol steroids* ▪ Prednisone 10 mg/d taken orally **Oral CYC** 1.5 mg/kg (beginning at 12 months, both groups ceased CYC and switched to azathioprine 1.5 mg/kg/d and prednisolone 7.5 mg/d)—*primary intervention* *Per-protocol steroids*	**Demographics** ▪ ITT analysis: 155 patients **Disease status** ▪ Newly diagnosed: 100% **Diagnosis** ▪ GPA: AZA 61%, CYC 62% ▪ MPA: AZA 39%, CYC 38% **ANCA type** ▪ PR3: AZA 54%, CYC 59% ▪ MPO: AZA 39%, CYC 34% **Renal function** ▪ Serum creatinine: ≤500 µmol **Disease activity (BVAS)**	To investigate whether exposure to CYC in patients with generalised vasculitis could be reduced by substitution of AZA at remission	**Primary** ▪ Rate of relapse **Secondary** ▪ Adverse events ▪ Change in GFR	Jayne et al. (2003)

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
	▪ Prednisone 10 mg/d taken orally	▪ AZA: 18 ▪ CYC: 19.9 **Vasculitis damage:** Not reported			
CHUSPAN (NCT00400075)	**Oral AZA** 2 mg/kg/d—*primary intervention* **IV CYC** 600 mg/m^2 every 2 weeks for 1 month, then every 4 weeks—*primary intervention*	**Demographics** ▪ ITT analysis: 39 patients **Disease status** ▪ Newly diagnosed: 100% **Diagnosis** ▪ GPA: Not reported ▪ MPA: AZA 70%, CYC 63% **ANCA type** ▪ PR3: Not reported ▪ MPO: Not reported **Renal function (serum creatinine)** ▪ AZA: 77 µmol/L ▪ CYC: 85 µmol/L **Disease activity (BVAS)** ▪ AZA: 9 ▪ CYC: 8.7 **Vasculitis damage** ▪ Not reported	To treat patients with PAN or MPA who have no poor-prognosis factors with corticosteroids alone as first-line therapy and to identify the subgroup of patients requiring additional immune suppression	**Primary** ▪ Major or minor relapse ▪ Treatment failure or death ▪ Adverse events	▪ Ribi et al. (2010) ▪ Guillevin et al. (2003) ▪ Samson et al. (2017)
NCT00103792	**Oral CYC** 2 mg/kg/d (remission maintenance 1.5 mg/kg oral AZA)—*primary intervention* *Per-protocol steroids* ▪ Prednisolone **Oral MMF** 1 g (Remission maintenance 1.5 mg/kg oral AZA) twice daily—*primary intervention* *Per-protocol steroids* ▪ Prednisolone	**Demographics** ▪ ITT analysis: 84 patients **Disease status** ▪ Relapsing: 100% **Diagnosis** ▪ GPA: Not reported ▪ MPA: Not reported **ANCA type** ▪ PR3: CYC 88, MMF 90 ▪ MPO: Not reported **Renal function (serum creatinine)** ▪ CYC: 1.1 µmol/L ▪ MMF: 1.3 µmol/L **Disease activity (BVAS)** ▪ CYC: 16	To compare the efficacy and safety of MMF versus CYC for the induction treatment of non–life-threatening relapses of proteinase 3–ANCA- and myeloperoxidase–ANCA-associated vasculitis	**Primary** ▪ Remission at 6 months **Secondary** ▪ Disease-free survival at 2 and 4 years ▪ Time to induction of remission ▪ Cumulative organ damage ▪ ANCA status ▪ Adverse events	Tuin et al. (2019)

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
		▪ MMF: 15 **Vasculitis damage** ▪ CYC: 1.8 ▪ MMF: 1.6			
CYCLOPS (NCT00430105)	**IV CYC** 15 mg/kg every 2-3 weeks. 3 intravenous pulses of cyclophosphamide, The maximum dose per pulse was 1.2 g. 15 mg/kg, given 2 weeks apart, followed by pulses at 3-week intervals (15 mg/kg intravenously or 5 mg/kg orally on 3 consecutive days, at the physician's discretion) until remission, and then for another 3 months—*primary intervention* **Oral CYC** 2 mg/kg initially (until remission), then 1.5 mg/kg/d—*primary intervention*	**Demographics** ▪ ITT analysis: 84 patients **Disease status** ▪ Newly diagnosed: 100% **Diagnosis** ▪ GPA: IV 33, oral 42 ▪ MPA: IV 50, oral 45 **ANCA type** ▪ PR3: IV 39, oral 41 ▪ MPO: IV 50, oral 51 **Renal function (serum creatinine)** ▪ IV: 225 µmol/L ▪ Oral: 222 µmol/L **Disease activity (BVAS)** ▪ IV: 20 ▪ Oral: 21 **Vasculitis damage** ▪ IV: 0 ▪ Oral: 0	To compare pulse CYC with daily oral CYCfor induction of remission	**Primary** ▪ Time to remission **Secondary** ▪ Change in renal function ▪ Adverse events	▪ de Groot et al. (2009) ▪ Harper et al. (2012)
Gottenberg et al. (2007) (trial number not reported)	**Oral CYC** (arm 1) 2 mg/kg/d taken orally for 12 months—*primary intervention* *Per-protocol immunosuppressants* ▪ Prednisone 1 mg/kg/d taken orally **IV CYC** (arm 2) 0.7 g/m^2 every 3 for 12 months—*primary intervention* *Per-protocol immunosuppressants* ▪ Prednisone 1 mg/kg/d taken orally for 6 weeks	**Demographics** ▪ ITT analysis: 37 patients **Disease status** ▪ Newly diagnosed: 100% **Diagnosis** ▪ GPA: 100% **ANCA type** ▪ PR3: Not reported ▪ MPO: not reported **Renal function (serum creatinine):** Not reported **Disease activity (BVAS):** Not reported	To assess the long-term outcome and identify prognostic factors of patients with kidney disease related to WG	**Primary** ▪ Not reported **Secondary** ▪ Not reported	Gottenberg et al. (2007)

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
		Vasculitis damage: Not reported			
Guillevin et al. (1997) (trial number not reported)	**IV CYC** (arm 1) 0.7 g/m^2 every 3 weeks until complete remission, then every 3 weeks for 12 months—*primary intervention* *Per-protocol immunosuppressants* ▪ Prednisone 1 mg/kg/d taken orally for 6 weeks **Oral CYC** (arm 2) 2 mg/kg/d taken orally—*primary intervention* *Per-protocol immunosuppressants* ▪ Prednisone 1mg/kg/d taken orally for 6 weeks	**Demographics** ▪ ITT analysis: 50 patients **Disease status** ▪ Newly diagnosed: 100% **Diagnosis** ▪ GPA: arm 1 85.2%, arm 2 100% ▪ MPA: arm 1 14.8%, arm 2 0% **ANCA type** ▪ Not reported **Renal function (serum creatinine)** ▪ Arm 1: 252.4 µmol ▪ Arm 2: 182.5 µmol **Disease activity (BVAS):** Not reported **Vasculitis damage:** Not reported	To examine whether a pulse CYC regimen could induce and maintain remission in systemic WG, with a lower cumulative dose of CYC and fewer toxic side effects	**Primary** ▪ Number of patients achieving complete or partial remission ▪ Number of patient deaths during study **Secondary** ▪ Number of relapses ▪ Safety (adverse events/side effects)	Guillevin et al. (1997)
Haubitz et al. (1998) (trial number not reported)	**IV CYC** (arm 1) 0.75 g/m^2 every 4 weeks for 12 months—*primary intervention* *Per-protocol immunosuppressants* ▪ Prednisone 1 mg/kg/d on days 4-14, then treated according to tapering regimen **Oral CYC** (arm 2) 2 mg/kg/d taken orally—*primary intervention* *Per-protocol immunosuppressants* ▪ Prednisone 1 mg/kg/d on days 4-14, then treated according to tapering regimen	**Demographics** ▪ ITT analysis: 47 patients **Disease status** ▪ Newly diagnosed: 100% **Diagnosis** ▪ GPA: Arm 1 50%, arm 2 44% ▪ MPA: Arm 1 50%, arm 2 56% **ANCA-type** ▪ Not reported **Renal function (serum creatinine)** ▪ Arm 1: 252.4 µmol ▪ Arm 2: 182.5 µmol **Disease activity (BVAS):** Not reported **Vasculitis damage:** Not reported	To compare the efficacy and toxicity of IV pulse and oral CYC treatments in patients with WG or MPA, with renal involvement.	**Primary** ▪ Disease progression, remission after 12 months of treatment and relapse during or up to 1 year after the end of CYC therapy after a complete remission had been achieved. **Secondary** ▪ Safety (adverse events/side effects)	Haubitz et al. (1998)
WGET/VCRC-LS (NCT00315393)	NA	**Demographics** **Disease status** ▪ Not reported **Diagnosis**	To assess a generic measure of HRQOL as an outcome measure in GPA	**Primary** ▪ Discover biomarkers in GPA/MPA capable of measuring disease activity and	Tomasson et al. (2012)

Study (trial number)	Intervention/comparator(s)	Baseline population description	Objective	Endpoint(s)	Primary study reference(s)
		▪ GPA: WGET trial 100%, VCRC-LS trial 100% ▪ MPA: Not reported **ANCA-type** ▪ PR3: Not reported ▪ MPO: Not reported **Renal function:** Not reported **Disease activity (BVAS)** ▪ WGET trial: 6 ▪ VCRC-LS trial: 0 **Vasculitis damage** ▪ WGET trial: 1.8 ▪ VCRC-LS trial: 2.2		response to treatment **Secondary** ▪ Measure the predictive value of biomarkers for clinical outcome in GPA/MPA	

Abbreviations: AAV, antineutrophil cytoplasmic antibody–associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; AZA, azathioprine; BID, twice daily; BVAS, Birmingham Vasculitis Scale; BVAS1, Birmingham Vasculitis Scale for new or worse symptoms; BVAS2, BVAS, Birmingham Vasculitis Scale for persistent symptoms; BVAS/WG, Birmingham Vasculitis Scale for Wegener's granulomatosis; c-ANCA, cytoplasmic ANCA; CRP, C-reactive protein; CSR, clinical study report; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; EudraCT, European Union Drug Regilating Authorities Clinical Trials Database; GC, glucocorticoid; FS, fixed schedule; GFR, glomerular filtration rate; GPA, granulomatosis with polyangiitis; IFX, infliximab; ITD, individually tailored dose; ITT, intent to treat; IV, intravenous; IVIg, intravenous immunoglobulin; mITT, modified intent to treat; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MPO, myeloperoxidase; MTX, methotrexate; PLEX, plasma exchange; PR3, proteinase 3; PRO, patient-reported outcome; RTX, rituximab; SAE, serious adverse event; SC, subcutaneous; SF-36, 36-Item Short Form Health Survey; VDI, Vasculitis Damage Index; UACR, urine albumin-to-creatinine ratio; WG, Wegner's granulomatosis

Table 9 Other studies of interest

Trial name/study group (trial number)	Study title	Study arms	Authors (year)
BREVAS (NCT01663623)	Efficacy and safety of belimumab and azathioprine for maintenance of remission in antineutrophil cytoplasmic antibody-associated vasculitis: A randomized controlled study	AZA + IV belimumab vs AZA + IV placebo	(Jayne et al. 2019)
	Belimumab in combination with azathioprine for remission maintenance in granulomatosis with polyangiitis and microscopic polyangiitis: Effect on biomarkers	AZA + IV belimumab vs AZA + IV placebo	(Jayne et al. 2018)
Metzler (2007) (trial number not reported)	Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis	Oral MTX vs oral leflunomide	(Metzler et al. 2007)
de Groot (1996) (trial number not reported)	Remission-preserving therapy in generalised Wegener granulomatosis: Methotrexate (MTX) versus trimethoprim/sulfamethoxazole (T/S)	IV MTX vs oral trimethoprim/sulfamethoxazole	(de Groot et al. 1996)
Abbreviations: AZA, azathioprine; IV, intravenous; MTX, methotrexate			

Quality assessment

Quality assessment of clinical trials was carried out according to criteria adapted from the assessment of risk of bias recommended by NICE (2012), the Centre for Reviews and Dissemination (2009), and the Cochrane Collaboration (2011). The quality assessment process required the analyst to answer specific questions for each study regarding selection, performance, attrition, and detection bias. A summary of the overall risk of bias is shown in table 10.The full quality assessment tables are available in Report Clinical systematic literature review Avacopan for

the treatment of ANCA-associated vasculitis Summery report of 2018 review and update in 2020 and 2021. Ver. 1. 16. July 2021.

Table 10 Overall risk of bias assessment

Trial	Related publications	Overall risk of bias (high, moderate, low, unclear/unknown)
ADVOCATE	Jayne et al. (2021)	Low risk
AZA-ANCA	Sanders et al. (2016)	Low risk
CHUSPAN	Guillevin et al. (2003); Samson et al. (2017); Ribi et al. (2010)	High risk (high performance bias, high detection bias)
CLEAR	Jayne et al. (2017)	Low risk
CLASSIC	Merkel et al. (2020)	Low risk
CYCAZAREM	Walsh et al. (2014)	High risk (high selection bias, high performance bias)
CYCLOPS	Harper et al. (2012); de Groot et al. (2009)	High risk (high performance bias, high detection bias)
IMPROVE	Hiemstra et al. (2010)	Low risk
LoVAS	Furuta et al. (2021)	Low risk
MEPEX	de Lind van Wijngaarden et al. (2006); Jayne et al. (2007); Walsh et al. (2013)	Unclear/unknown (selection and performance bias could not be assessed)
MYCYC	Jones et al. (2019)	High risk (high selection bias, high performance bias)
MAINRITSAN	Montante et al. (2019); Pugnet et al. (2016); Terrier et al. (2018); Guillevin et al. (2014)	Low risk
MAINRITSAN 2	Charles et al. (2018)	High risk (high performance bias, high detection bias)
MAINRITSAN 3	Charles et al. (2020)	Low risk
NORAM	de Groot et al. (2005); Faurschou et al. (2012)	Unclear/unknown (selection and performance bias could not be assessed)
PEXIVAS	Walsh et al. (2020)	Low risk
RAVE	Berti et al. (2019); Geetha et al. (2015); Specks et al. (2013); Unizony et al. (2016); Stone et al. (2010); Miloslavsky et al. (2015); Miloslavsky et al. (2014); Miloslavsky et al. (2013); Wallace et al. (2019)	Low risk
RITUXVAS	Jones et al. (2010); Jones et al. (2015)	High risk (high selection bias, high performance bias)
VCRC-LS	Tomasson et al. (2012)	Unclear/unknown (selection and performance bias could not be assessed)
WEGENT	Pagnoux et al. (2008); Puéchal et al. (2016); Seror et al. (2010)	Low risk

Trial	Related publications	Overall risk of bias (high, moderate, low, unclear/unknown)
WGET	Silva et al. (2011); Tomasson et al. (2012); WGET Group (2005); Stone et al. (2006)	Low risk
de Menthon et al. (2011)	de Menthon et al. (2011)	High risk (high selection bias, high performance bias)
Gottenberg et al. (2007)	Gottenberg et al, (2007)	High risk (high performance bias, high detection bias)
Guillevin et al. (1997)	Guillevin et al. (1997)	High risk (high performance bias, high detection bias)
Han et al. (2011)	Han et al. (2011)	Unclear/unknown (selection and performance bias could not be assessed)
Haubitz et al. (1998)	Haubitz et al. (1998)	Unclear/unknown (selection and performance bias could not be assessed)
Hu et al. (2008)	Hu et al. (2008)	Moderate risk (high selection bias, unknown performance bias)
Jayne et al. (2000)	Jayne et al. (2000)	Low risk
Jayne et al. (2003)	Jayne et al. (2003)	Low risk
Maritati et al. (2017)	Maritati et al. (2017)	Moderate risk (low selection bias, high performance bias)
Ribi et al. (2010)	Ribi et al. (2010)	Moderate risk (low selection bias, high performance bias)
Szpirt et al. (2010)	Szpirt et al. (2010)	Moderate risk (unknown selection bias, high performance bias)
Tuin et al. (2019)	Tuin et al. (2019)	Low risk
[a]Tomasson et al. (2012) reported data from both WGET and VCRC-LS trials		

APPENDIX B MAIN CHARACTERISTICS OF INCLUDED STUDIES

Trial name: ADVOCATE **NCT number: NCT02994927**

Objective:
Formålet med studiet er at bestemme andelen af patienter, som opnår remission i uge 26 og som har vedvarende remission i uge 52, defineret ved Birmingham Vasculitis Activity Score (BVAS) = 0 og ingen indtagelse af glukokortikoid indenfor de seneste 4 uger før uge 26 og uge 52 [153].

Det sekundære formål inkluderer vurdering af effekten af behandling med avacopan versus konventionel behandling (prednison) på sikkerhed, glukokortikoid-relateret toksicitet, hurtigt respons, ændring i HRQoL, ændring i nyresygdom, og kumulativt organ skade (Vaskulitis Damage Index) [153,155]

Publications – title, author, journal, year
Avacopan for the Treatment of ANCA-Associated Vasculitis. David R. W. Jayne, M.D., Peter A. Merkel, M.D., M.P.H., Thomas J Schall, Ph.D., and Pirow Bekker, M.D., Ph.D., for the ADVOCATE Study Group. N Engl J Med 2021; 384: 599-609. DOI:10.1056/NEJMoa2023386 [155]

Supplementary Appendix to Jayne DRW, Merkel PA, Schall TJ, Bakker P. Avacopan for the treatment of ANCA-associated vasculitis. N Engl J med 2021; 384: 599-609. DOI:10.1056/NEJMoa2023386 [155]

Editorials Avacopan – Time to Replace Glucocorticoids? Kenneth J Warrington. N Engl J Med 2021; 384: 664-665 [218].

Merkel PA, Jayne DR et al. Protocol Evaluation of the Safety and Efficacy of Avacopan, a C5a Receptor Inhibitor, in Patients With Antineutrophil Cytoplasmic Antibody-Associated Vasculitis Treatment Concomitantly With Rituximab or Cyclophosphamide/ Azathioprine: Protocol for a Randomized, Double-Blind, Active-Controlled, Phase 3 trial [153]

Study type and design
Studiet er et multicenter, randomiseret, dobbeltblindet (deltager; pårørende/hjælper; investigator og resultat bedømmer), dobbelt dummy, aktivt kontrolleret (prednison), to-armet fase 3 intervention-studie.

Studiet belyser effekt og sikkerhed bland 331 patienter med ANCA-associeret vaskulitis ved behandling med oral avacopan sammenlignet med oral prednison, med gradvis aftrapning. Alle patienter i begge behandlingsgrupper modtog immunsuppresiv behandling med enten cyclofosfamid (efterfulgt af azathioprin) eller rituximab.

Sample size (n)
331 patienter blev randomiseret til behandling med avacopan (n=166) eller prednison (n=165)

Main inclusion and exclusion criteria:

Væsentlige inklusionskriterier [153]:
- alder ≥ 12 år

- ny diagnosticeret eller relaps antineutrofil cytoplasmisk antistof (ANCA)-associeret vaskulitis (AAV) med granulomatose med polyangiitis (GPA) (tidligere Wegener) eller mikroskopisk polyangiit (MPA)
- Positiv for antiproteinase 3 eller antimyeloperoxidase ANCA
- Aktiv sygdom, vurderet ved ≥ 1 major item og ≥ 3 nonmajor items, eller ≥ 2 nyre items på Birmingham Vaskulitis Activity Score [19,20]
- Estimated glomerular filtration rate ≥ 15 ml/min/1.73 m²

Væsentlige eksklusionskriterier [153]:
- enhver af følgende tilstande: alveolær blødning, der kræver invasiv pulmonal ventilationsstøtte, andre multiorgan autoimmune sygdomme (inklusiv eosinofil granulomatose med polyangiitis, lupus, IgA vaskulitis (Henoch-Schönlein), Rheumatoid vaskulitis, Sjögren's syndrom, anti glomerulær basalmembran sygdom eller kryoglobulinæmi vaskulitis)
- behov for dialyse eller plasmaferese indenfor 12 uger før screening
- anamnese med nyretransplantation
- Immunsuppressiv behandling: modtaget behandling med cyclophosphamid ≤ 12 uger før screening
- I behandling med azathioprin, methotrexat, mycophenolatmofetil ved screening og ikke ønsker at ophøre med behandlingen og skifte til cyclophosphamid eller rituximab på dag 1
- modtager intravenøs glukokortikoider, > 3000 mg methylprednisolon ækvivalent, indenfor 4 uger før screening eller oral glukokortikoid > 10 mg prednison-ækvivalent kontinuerligt indenfor 6 uger før screening
- modtaget behandling med rituximab eller andre B-celle antistoffer ≤ 52 uger før screening eller ≤ 26 uger før screening, forudsat at der er fundet B-celle-rekonstitution sted, dvs. CD19-tal >0,01 x 109/L
- modtaget behandling med TNF-hæmmer < 12 uger før screening
- patienter planlagt til at modtage behandling med cyclophosphamid: obstruktiv urin retention, aktive infektioner, eller blodplade tælling < 50.000/µL før start dosering
- tidligere behandling med avacopan
- anamnese med cancer indenfor de sidste 5 år, med undtagelse af basalcelle- eller plade epitelkarcinom i huden, eller Karcinom in situ som livmoderhals- eller brystkræft in situ, som er blevet fuldstændig fjernet ved udskæring eller resektion og er uden tegn på lokalrecidiv eller metastaser
- bevis på leversygdom (transaminase, basisk fosfatase > 3 gange øvre grænse af normalområdet)
- kendt aktiv infektion med tuberkulose, hepatitis B eller C virus, eller human immundefektvirus
- leukocyt tælling < 3500/µL, eller neutrofil tælling < 1500/ µL, eller lymfocyt tælling < 500/µL ved baseline

Intervention
Intervention: 30 mg avacopan oralt to gange daglig og placebo, der matcher prednison

Alle patienter i begge arme modtog immunsuppressiv behandling med en af investigator valgt behandling (konventionel behandling) Regime.

- Intravenøs rituximab 375 mg/m² ugentlig x 4 infusioner

- Intravenøs cyclophosphatemid: 15 mg/kg op til 1,2 g hver 2 til 3 uge i 13 uger, og derefter starte behandling i uge 15 med oral azathioprin 1 mg/kg dagligt med titrering op til 2 mg/kg daglig (mycophenolat mofetil 2 g daglig er tilladt i stedet for azathioprin
- Oral cyclophosphamid: 2 mg/kg daglig i 14 uger efterfulgt af oral azathioprin eller mycophenolat mofetil med start i uge 15 (samme dosering regime som intravenøst cyclophospamid)

Anvendelse af glukokortikoid udover studiemedicinen skulle i udgangspunktet undgås under studiet. Undtagelserne var:
- binyrebarkinsufficiens
- patienter i vedvarende behandling med glukokortikoid skulle ved inklusionen kunne leve op til følgende inklusionskriterier:

- Før og gennem screeningen besøg, brug af intravenøs glukokortikoid må ikke overstige en kumulativ dosis ækvivalent med 3 g methylprednisolon i 4 uger før screening eller brug af orale glukokortikoider ikke overstiger 10 mg oral prednison 1 gang daglig i op til 6 uger før screening. Igennem screeningsperioden (≤ 14 dage), er orale glukokortikoider tilladt (nedtrappet til ≤ 20 mg daglig prednison ækvivalent ved dag 1). Såfremt en patient i behandling med orale glukokortikoider blev inkluderet i studiet, skal dosis nedtrappes til 0 ved udgangen af uge 4.
- Patienter, som i løbet af studiet oplever forværring af sygdommen i form af en major item (BVAS) kan behandles med intravenøs glukokortikoid (typisk 0,5-1 g methylprednisolon/ dag i 3 dage) eller orale glukokortikoider nedtrappet i overensstemmelse med patientens tilstand, eller begge. Forværring, som ikke involverer en major item (BVAS) kan behandles med et kort bust (≤2 uger) med orale glukokortikoider, med en maksimum daglig dosis på 20 mg prednison ekvivalent. Brug af anden medicin, såsom yderligere rituximab eller cyclophosphamid, er drøftet med den medicinske monitor før implementeringen. Anvendelse af plasmaferese er ikke tilladt.
- Patienter, som oplever et relaps eller en forværring af sygdommen kan fortsætte med studie medicinen og kan fortsætte i studiet. For patienter, som oplever et relaps, vil studie medicinen prednison/matching placebo midlertidigt blive standset i løbet af behandlingen med glukokortikoid. Hvis patientens tilstand stabiliseres, kan studiemedicinen prednison/matchende placebo genstartes i overensstemmelse med protokollens besøgsplan. Efter investigators skøn kan avacopan/matchende placebo fortsættes under og efter behandlingen for relaps [153,155]

Comparator
Komparator: Oral prednison behandling med aftrapning af prednison og placebo, der matcher avacopan. Dosis og nedtrapning af Prednison fremgår af nedenstående tabel.

Forud defineret aftrapning af Prednison dosis for intervention og komparator [155]

Studie dag	Intervention	Komparator			
	Avacopan*	Daglig prednison dosis**			
	all	voksne		unge	
		≥55 kg	<55 kg	>37 kg	≤37 kg
1 - 7	0	60 mg	45 mg	45 mg	30 mg
7 - 14	0	45 mg	45 mg	45 mg	30 mg
15 - 21	0	30 mg	30 mg	30 mg	30 mg
22 - 42	0	25 mg	25 mg	25 mg	25 mg
43 - 56	0	20 mg	20 mg	20 mg	20 mg
57 - 70	0	15 mg	15 mg	15 mg	15 mg
71 - 98	0	10 mg	10 mg	10 mg	10 mg
99 - 140	0	5 mg	5 mg	5 mg	5 mg
≥ 141	0	0	0	0	0

* alle patienter, der stadig tog 20 mg prednison (ikke studiemedicin) på dag 1 blev trappet ned til 0 mg ved udgangen af uge 4.

**prednison blev leveret til studiecentrerne som 20 mg og 5 mg tabletter, overtrukket med en hård gelatinekapsel for at holde blindingen. Placebo matchende prednison blev givet en gelatinekapsel til Avacopangruppen. Doseringsinstruktioner for hver periode blev givet til hvert studiecenter.

Follow-up time

Behandlingstiden var 52 uger med en efterfølgende opfølgningstid på 8 uger, dvs. i alt 60 uger. Studiet er afsluttet og resultaterne er publiceret [155]

Is the study used in the health economic model?

Yes

Primary, secondary and exploratory endpoints

- **Endpoint included in this application**

De to primære endepunkter var:

- andelen af patienter, som opnår remission ved uge 26, defineret ved Birmingham Vasculitis Activity Score (BVAS) = 0 og ingen anvendelse af glukokortikoid for antineutrofil cytoplasmisk antistof (ANCA) associeret vaskulitis indenfor fire uger før uge 26
- andelen af patienter, som opnår vedvarende remission ved uge 52, defineret ved remission i uge 26 og 52 og uden relaps i løbet af perioden mellem uge 26 og 52 og ingen anvendelse af glukokortikoid for ANCA-associeret vaskulitis fra fire uger før uge 52 [153]

Relaps var defineret ved tilbagevenden af vaskulitis aktivitet vurderet på basis af mindst en major item (BVAS), mindst tre minor items (BVAS) eller en eller to minor items (BVAS) ved mindst to fortløbende studiebesøg.

De sekundære endepunkter:

- Sikkerhed: bivirkninger, helbredsundersøgelse, vitale parametre (Vital signs som f.eks. temperatur, puls, respirationsrate og blodtryk), serumanalyse, hæmatologi, urinprøver, og elektrokardiogram [155]
- ændring i glukokortikoid induceret toksisk effekt igennem de første 26 uger vurderet ved Glucocorticoid Toxicity Index (GTI), version 2.0 (bestemt ved både Cumulative Worsening Score (GTI-CWS), med interval fra 0 – 410, og Aggregate Improvement Score (GTI-AIS), med interval fra -

317 til 410. På begge skalaer indikerer højere score større sværhedsgrad af toksisk effekt) [155,219].
- En BVAS på 0 i uge 4, ændring fra baseline i health-related quality of Life, vurderet med en 36-Item Short Form Health Survey (SF-36), version 2, og EuroQoL Group 5-dimentioner, 5 niveauer spørgeskema (EQ-5D-5L). For begge skalaer er intervallet fra 0-100 og en højere score indikerer bedre livskvalitet [155,158,220].
- Relaps (vurderet i en tid til hændelse-analyse) [11]
- ændring fra baseline i e-GFR [155]
- urin albumin: kreatinin ratio [155]
- urin monocyte chemoattractant protein 1: kreatinin ratio [155]
- ændring i Vasculitis Damage Index (interval fra 0 til 64, og højere score indikerer mere skade [138,155].

Method of analysis
All efficacy analysis was intention to treat analysis.

Subgroup analysis
De to randomiserede grupper var stratificeret i forhold til:
- status af vaskular sygdom (ny diagnosticerede patienter eller patienter med sygdomsrelaps)
- ANCA type (antiproteinase-3 positiv (PR3-ANCA) eller antimyeloperoxidase positiv (MPO-ANCA)
- baggrundsbehandling med immunsuppressiv behandling (cyclophosphamid eller rituximab, tildelt hver patient efter investigatorernes skøn ved starten af studiet og fortsatte igennem hele studiet).

Subgruppeanalyserne (remission ved uge 26 og 52) var ikke præspecificerede før studie start. Analyserne blev udført på nedenstående subgrupper, studiet var ikke tilrettelagt til at drage konklusioner fra subgruppeanalyserne og der har derfor heller ikke kunnet beregnes signifikans [155]

- Sygdoms status: ny diagnosticerede patienter eller patienter med sygdomsrelaps
- ANCA type: antiproteinase-3 positiv (PR3-ANCA) eller antimyeloperoxidase positiv (MPO-ANCA)
- Baggrundsbehandling med immunsuppressiv: cyclophosphamid eller rituximab, tildelt hver patient efter investigators skøn ved starten af studiet og fortsatte igennem hele studiet
- Type af ANCA-associeret vaskulitis: granulomatose med polyangiitis eller mikroskopisk polyangiit

Other relevant information:
Det kan oplyses, at 6 hospitaler fordelt på regionerne i Danmark deltog i ADVOCATE studiet og der blev i Danmark inkluderet 12 patienter.

Trial name: CLASSIC **NCT number: NCT02222155**

Objective:
Formålet med studiet er vurdere sikkerhed af avacopan i to forskellige styrker til behandling af antineutrofil cytoplasmisk antistof (ANCA)-associeret vaskulitis i tillæg til standard-of-Care med glukokortikoider og med cyclophosphamid eller rituximab [152].

Publications – title, author, journal, year
Adjunctive Treatment With Avacopan, an Oral C5a Receptor Inhibitor in patients With Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Merkel PA, Niles J, Jimenez R, Spiera RF et al. ACR Open Rheumatology vol 2. no.11 November 2020, pp 662-671 [152]

Study type and design
CLASSIC-studiet var et randomiseret, dobbeltblindet, placebo-kontrolleret fase II studie med tre arme (to doser af avacopan i kombination med konventionel behandling og en arm med konventionel behandling alene) til behandling af patienter med ANCA-associeret vaskulitis i 12 uger.
Studiet belyser sikkerhed og effekt blandt 42 patienter med nydiagnosticeret ANCA-associeret vaskulitis (diagnosticeret indenfor de seneste 4 uger før randomisering) eller med relaps hvor den behandlende læge vurderede konventionel behandling relevant. Patienterne blev randomiseret 1:1;1 til behandling med:

1. Placebo + konventionel behandling (n=13)
2. 10 mg avacopan oralt 2 gange dagligt + konventionel behandling (n=13), Avacopan blev kun administreret i 84 dage (12 uger).
3. 30 mg avacopan oralt 2 gange dagligt + konventionel behandling (n=16), Avacopan blev kun administreret i 84 dage (12 uger).

Konventionel behandling består af intravenøs (IV) Cyclophosphamid 15 mg/kg på dag 1, 15, 29, 57 og 85 eller IV rituximab 375 mg/m² på dag 1, 8, 15 og 22. Alle patienter blev behandlet med oral prednison 60 mg/dag aftrappet til 10 mg/dag i uge 11 og til 0 mg/dag i uge 20 [152].

Sample size (n)
42 patienter bliver randomiseret 1:1:1
- Placebo + konventionel behandling* (SOC only) (n=13)
- 10 mg avacopan oralt 2 gange dagligt + konventionel behandling* (avacopan-10) (n=13),
- 30 mg avacopan oralt 2 gange dagligt + konventionel behandling* avacopan 30) (n=16),

Main inclusion and exclusion criteria
Væsentlige inklusionskriterier [152]
- kvinder og mænd alder ≥ 18 år, med ny-diagnosticeret eller relaps ANCA associeret vaskulitis (AAV), hvor behandling med cyclophosphamid eller rituximab er indiceret
- Klinisk diagnose granulomatose med polyangiitis (GPA), mikroskopisk polyangiit (MPA) ifølge Chapel Hill Concensus Conference definition 2012 [3]
- Nuværende eller historisk positiv test for anti-myeloperoxidase (MPO) eller antiproteinase-3 (PR3)-ANCA
- Estimeret glomerular filtraktion rate (e-GFR) ≥ 20 ml/min/1,73 m²

- ≥ 1 major item eller ≥ 3 non-major items eller ≥ 2 nyre items på Birmingham Vasculitis Activity Score (BVAS) Version 3 [185,221]

Væsentlige eksklusionskriterier [152]
- hurtig progredierende glomerulonephritis med forventet behov for nyretransplantation terapi indenfor 7 dage eller alveolar blødning, som leder til grad 3 eller højere hypoxia (faldende iltmætning i hvile (f.eks. pulsoximeter på mindre end 88 % eller partielt tryk af arteriel oxygen på 55 mmHg eller mindre).

Intervention
- 1 arm med 10 mg avacopan oralt to gange dagligt + konventionel behandling* (avacopan-10) (n=13), Avacopan blev kun administreret i 84 dage (12 uger).
- 1 arm med 30 mg avacopan oralt 2 gange dagligt + konventionel behandling* avacopan 30) (n=16), Avacopan blev kun administreret i 84 dage (12 uger).

*Konventionel behandling består af intravenøs (IV) Cyclophosphamid 15 mg/kg på dag 1, 15, 29, 57 og 85 eller IV rituximab 375 mg/m² på dag 1, 8, 15 og 22. Alle patienter blev behandlet med oral prednison 60 mg/dag aftrappet til 10 mg/dag i uge 11 og til 0 mg/dag i uge 20 [152]
Glukokortikoid udover studiemedicin blev anvendt ved behov til patienter med forværring af sygdommen.
Alle patienter medtog behandling for at forebygge Pneumocystis jirovecil pneumonia.
Profylaktisk behandling for osteoporose, gastroprotection og behandling-relateret kvalme blev anvendt i overensstemmelse med lokal praksis.

Comparator (s)
Placebo + konventionel behandling* (SOC only) (n=13)
*Konventionel behandling består af intravenøs (IV) Cyclophosphamid 15 mg/kg på dag 1, 15, 29, 57 og 85 eller IV rituximab 375 mg/m² på dag 1, 8, 15 og 22. Alle patienter blev behandlet med oral prednison 60 mg/dag aftrappet til 10 mg/dag i uge 11 og til 0 mg/dag i uge 20 [152].
Glukokortikoid udover studiemedicin blev anvendt ved behov til patienter med forværring af sygdommen.
Alle patienter medtog behandling for at forebygge Pneumocystis jirovecil pneumonia.
Profylaktisk behandling for osteoporose, gastroprotection og behandling-relateret kvalme blev anvendt i overensstemmelse med lokal praksis.

Follow-up time
12 ugers behandling efterfulgt af 84 dages opfølgning

Is the study used in the health economic model?
No

Primary, secondary and exploratory endpoints
- **Endpoint included in this application**
- **Other endpoint**

Fordi dette studie primært var et sikkerhedsstudie, er effektresultaterne deskriptive. Studiet er ikke statistik power efter hverken sikkerhed- eller effektendepunkterne.

Det primære endepunkt var incidensen af bivirkninger.

Det store effektendepunkt var andelen af patienter, som opnåede sygdomsrespons på dag 85, som var defineret som ≥ 50 % reduktion i BVAS (version 3) fra baseline med ingen forværring i noget organsystem.

Hastighed i at opnå en BVAS på 0 blev også målt, som tidlig opnåelse af en BVAS = 0 på dag 29 og som vedvarer frem til dag 85, begge tidspunkter var præspecificeret i protokollen.

På dag 29 blev BVAS kun vurderet på sygdomsaktivitet, som var til stede indenfor 7 dage før dag 29. For alle andre studiebesøg blev BVAS sygdomsaktiviteten vurderet som sygdomsaktiviteten indenfor 28 dage før studiebesøget.

Andre endepunkter inkluderer [152]:
- incidens af infektioner
- laboratorieværdier
- vital signs
- VDI mål
- e-GFR,
- nyre respons
- hæmaturi
-albuminuri
- inflammatorisk aktivitet i nyrene
- kreatinin ratio og serum C-reaktivt protein (CPR) niveau
- Health related quality of Life (HRQoL) var målt med den korte form SF-36v2 og EuroQOL-5D-5L (EQ-5D-5L)

Method of analysis

The safety population included all randomized patients who received at least one dose of study medication (avacopan. The modified intent-to-treat (ITT) population consisted of all randomized patients who resived at least one dose of study medication and had at least one postbaseline, on-treatment BVAS assessment. The main efficacy analysis was conducted in the modified ITT population.

Subgroup analysis

Før randomiseringen blev patienterne stratificeret på følgende måde:
- status af vaskular sygdom (nydiagnosticerede eller sygdomsrelaps)
- ANCA status (antiproteinase-3 positiv (PR3-ANCA) eller antimyeloperoxidase positiv (MPO-ANCA)
- immunsuppressiv behandling (cyclophosphamid eller rituximab)

Der blev udført subgruppeanalyser (klinisk respons ved dag 29 og 85) på følgende subgrupper:
- status af vaskular sygdom (nydiagnosticerede eller sygdomsrelaps)
- ANCA-status (antiproteinase-3 positiv (PR3-ANCA) eller antimyeloperoxidase positiv (MPO-ANCA)
- immunsuppressiv behandling (cyclophosphamid eller rituximab)
- med og uden nyre påvirkning ved baseline

Subgruppeanalyserne var ikke præspecificerede før studie start og studiet var ikke tilrettelagt til at drage konklusioner fra subgruppeanalyserne og der har derfor heller ikke kunnet beregnes signifikans [152]:

Other relevant information

Trial name: CLEAR **NCT number:NCT01363388**

Objective:

Studiets formål er at optimere behandlingen til at inducere remission blandt patienter med ikke livstruende Antineutrofil cytoplasmisk antistof vaskulitis (AAV). Hensigten er at reducere toksiciteten ved induktions behandling ved at nedsætte hele udsættelsen for – eller fuldstændig eliminerer brugen af systemiske kortikosteroid i induktionsperioden med avacopan (inhibitor af komplement C5a receptoren) plus cyclophosphamid eller rituximab.

Det primære sikkerhedsmål for studiet er at vurdere sikkerhed og toleabilitet af CCX 168 hos patienter med AAV og i behandling med cyclophosphamid eller rituximab.

Det primære effektmål er at vurdere effekten af CCX 168 baseret på Birmingham Vasculitis Activity Score (BVAS) version 3.

De sekundære mål for studiet omfatter vurdering af gennemførligheden af at reducere eller eliminere brugen af kortikosteroider i behandlingen af patienter med ANCA-associeret vaskulitis uden behov for kortikosteroid behandling ud over studiemedicinen og effekten af CCX168 på flere sygdomsparametre.

Publications – title, author, journal, year

Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis. Jayne DRW, Bruchfeld AN, Harper L, Schaier M, et al. J Am Soc Nephrol 28: 2756-2767, 2017, doi: httpt://doi.org/10,1681/2016111179 [149].

Study type and design

CLEAR-studiet var et randomiseret, dobbelt-blindet, placebo-kontrolleret fase-II studie med tre arme. 87 voksne patienter med nydiagnosticeret vaskulitis eller med relaps blev screenet og 67 patienter blev randomiseret til tre arme i forholdet 1:1:1 til behandling med:

1. Placebo + 60 mg prednison (n=23). Placebo blev administreret i 84 dage.
2. Avacopan 30 mg 2 gange daglig + en reduceret dosis af 20 mg prednison (n=22). Avacopan blev administreret i 84 dage.
3. Avacopan 30 mg 2 gange daglig uden prednison (n=22). Avacopan blev administreret i 84 dage.

Alle patienter blev behandlet med cyclophosphamid eller rituximab.

formålet med studiet var at reducere eller eliminere glykokortikoid behandling med avacopan uden at kompromittere effekten af behandlingen. Da studiet blev planlagt, var der ingen tilgængelige data om avacopans evne til sikkert at erstatte glukokortikoid. Derfor blev studiet planlagt ud fra et forsigtighedsprincip med en trinvis metode med tre sekventielle trin.

<u>Trin 1.</u>

I trin 1 blev det testet om avacopan tillod en reduktion i oral prednison dosis. Såfremt der ikke var uventede bivirkninger eller et øget forbrug af glukokortikoid udover studiemedicinen, blev trin 2 sat i gang.

<u>Trin 2.</u>

I trin 2 blev det testet om avacopan kan erstatte oral prednison fuldstændigt, såfremt det lykkedes fulgte trin 3.

<u>Trin 3.</u>

Trin 3 var en udvidelse af antal patienter i studiet.

Efter succesfuld afslutning af trin 1 og 2, blev et effekt-endepunkt, på basis af behandlingsrespons, tilføjet. 12 ugers behandling med avacopan blev efterfulgt af 12 uger uden behandling med studiemedicin.

Sample size (n)

67 patienter blev randomiseret til tre arme i forholdet 1:1:1

1. Placebo + 60 mg prednison (n=23).
2. Avacopan 30 mg 2 gange daglig + en reduceret dosis af 20 mg prednison (n=22).
3. Avacopan 30 mg 2 gange daglig uden prednison (n=22).

Main inclusion and exclusion criteria

Væsentlige inklusionskriterier [149]

-Patienter ≥ 18 år, med ny-diagnosticeret eller relaps granulomatose med polyangiitis (Wegener) eller mikroskopisk polyangiit
ifølge Chapel Hill Concensus Conference definition 2012 [222]
-behandling med cyclophosphamid (trin 1 og 2) og behandling med cyclophosphamid eller rituximab (trin 3) er indiceret
-PR3 eller MPO-ANCA positiv eller ANCA positiv med indirekte immunofluocens
-e-GFR ≥ 20 ml/min/1,73 m²
-har biopsi dokumenteret nyre-vaskulitis eller hæmaturi og albumin i urinen (for trin 1 og 2) eller har ≥ 1 major item eller ≥ 3
Non-major items eller ≥ 2 nyre items på BVAS, version 3 for trin 3 [20,23].

Væsentlige eksklusionskriterier [149]

- svær sygdom (inklusiv hurtig progressiv glomerulonephritis, alveolær blødning, som leder til grad 3 hypoxia, hurtig indsættende mononeuritis multikompleks, eller involvering af det centrale nervesystem),
-enhver anden autoimmun sygdom, koagulopati eller blødningsforstyrrelser
-er blevet behandlet med cyclophosphamid indenfor 12 uger, rituximab indenfor 12 måneder før screening (eller 6 måneder med B-cell rekonstitution, CD19 tælling > $0{,}01 \times 10^9$/L)
-kummulative doser af IV glukokortikoider > 3 g indenfor 12 uger, eller oral glukokortikoider af > 10 mg Prednison ækvivalenter/dag i mere end 6 uger før screening

Intervention

Intervention 30 mg avacopan oralt 2 gange dagligt plus 20 mg (15 mg for patienter < 55 kg legemesvægt) prednison (n=22) med gradvis aftrapning of prednison. Dosis og nedtrapning af Prednison fremgår af nedenstående tabel.
Intervention 30 mg avacopan oralt 2 gange dagligt uden prednison (n=22). Placebo prednison blev givet, som gelatine kapsler, som matchede prednison

Præ-defineret aftrapning af prednison dosis for intervention og komparator

Study Week	Placebo plus 60 mg prednisone* control	Avacopan plus 20 mg prednisone	Avacopan without prednisone
1	60 mg (or 45 mg for <55 kg subjects)	20 mg (or 15 mg for <55 kg subjects)	0†
2	45 mg	15 mg	0
3	30 mg	10 mg	0
4-6	25 mg	10 mg	0
7-8	20 mg	5 mg	0
9-10	15 mg	5 mg	0
11-14	10 mg	5 mg	0
15-20	5 mg	0	0
≥21	0	0	0

*Prednison blev leveret til studiecentrene i 20 mg og 5 mg tabletter, indkapslet med hård gelatine kapsler.
† Placebo prednison blev leveret i tilsvarende hårde gelatine kapsler

Comparator (s)
Komparator: behandling med oralt prednison 60 mg dagligt (eller 45 mg for patienter <55 kg legemesvægt) (n=23) og med aftrapning af prednison. Dosis og nedtrapning af Prednison fremgår af ovenstående tabel.

Follow-up time
Behandlingstiden med avacopan eller placebo var 84 dage (12 uger) efterfulgt af yderligere 12 ugers opfølgning. Studiet er afsluttet og resultaterne fra de første 12 ugers behandling er publiceret [149].

Is the study used in the health economic model?
No

Primary, secondary and exploratory endpoints

- **Endpoint included in this application**
- **Other endpoint**

Det primære effekt-endepunkt var andelen af patienter, som opnåede ≥ 50 % reduktion i BVAS i uge 12 fra baseline og ingen forværring i nogen organpåvirkning. Patienter, som modtog glukokortikoid efter behov blev betragtet, som ikke respondenter.

De sekundære endepunkter:
-andelen af patienter med et renalt respons, defineret ved en forbedring i e-GFR beregnet ved brug af Modified Diet in Renal Disease ligningen, hæmaturi og albuminuri i uge 12
-andelen af patienter med sygdomsremission (BVAS 0)
-ændring fra Baseline i BVAS; e-GFR; UACR (mg/g kreatinin); tælling af røde blodlegemer i urin (cells per high-power field),
Inflammationsmarkør: urin MCP-1/kreatinin (pg/mg); Vaskulitis damageindex; Health-related quality-of-Life: SF-36 version 2, EQ-5D-5L visual analog skala samt anvendelse af glukokortikoid efter behov.

Method of analysis
Effekt analysen blev gennemført på intention to treat populationen, defineret som alle patienter med mindst 1 postbaseline on-treatment BVAS assessment.

The safety population included all randomized patients who received at least one dose of study drug.

Subgroup analysis

Der blev udført subgruppeanalyser (behandlingsrespons er defineret som et fald fra baseline til uge 12 i BVAS på $\geq$ 50 % og ingen organpåvirkning) på følgende subgrupper:

- status af vaskular sygdom: nydiagnosticerede eller sygdomsrelaps
- type af ANCA-associeret vaskulitis (AAV): granulomatose med polyangiitis (GPA) eller mikroskopisk polyangiit (MPA)
- ANCA-status: antiproteinase-3 positiv (PR3-ANCA) eller antimyeloperoxidase positiv (MPO-ANCA)
- immunsuppressiv behandling: cyclophosphamid eller rituximab
- Sygdomslokation: nyre +/- andre sygdomme eller kun ikke nyresygdom

Analyserne var ikke præspecificerede før studie start og studiet var ikke tilrettelagt til at drage konklusioner fra subgruppeanalyserne og der har derfor heller ikke kunnet beregnes signifikans [149].

APPENDIX C BASELINE CHARACTERISTICS OF PATIENTS IN STUDIES USED FOR THE COMPARATIVE ANALYSIS OF EFFICACY AND SAFETY

The table below provide a description of the comparability of the baseline characteristics of the modified ITT population.

The modification of the ITT population consists of: 1 patient out of the 165 randomized patients allocated to the comparator arm did not receive study medication, this patient was therefore excluded from the ITT population. The comparator arm was decreased from 165 randomized patient to 164 patients going into analysis [155,184].

ADVOCATE study: Demographics and Clinical Characteristics of the Patients baseline* [184]

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

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

Comparability of patients across studies.

N/A

Comparability of the study populations with the Danish patients eligible for treatment

The Danish patient population is similar to ADVOCATE ITT-population at age, gender and proportion of ANCA-positive patients. It has not been possible to find data to discriminate between specific diagnosis (GPA/MPA) and serology (PR3, MPO), but both DRS and DNS reports 90 to > 95 % of the patients are ANCA positive and 100 % of the patients in the ADVOCATE study are ANCA-positive (one of the inclusion criterions).

Key Demographics and Clinical Characteristics of the Patients baseline ADVOCATE ITT compared to Danish Patient Population

	ADVOCATE ITT		Danish Patient population
	Prednisone	Avacopan	
	164	166	
Age (years) at screening, mean ± SD	60,5 ± 14,50	61,2 ± 14,56	60,2 ± 16,7 [155]
Gender n (%)			
Male	88 (53,7%)	98 (59%)	52% [155]
Female	76 (46,3%)	68 (41%)	48% [155]
ANCA positivity, %	100%	100%	ca. 90% GPA [188] >95% [189]
Proteinase 3 positive, n (%)	70 (42,7)	72 (43,4)	
Myeloperoxidase positive, n (%)	94 (57,3)	94 (56,6)	
Type of ANCA-associated vasculitis, n (%)			
Granulomatosis with polyangiitis	90 (54,9)	91 (54,8)	Incident 88%, Prevalence 81% [DNPR 2021]
Microscopic polyangiitis	74 (45,1)	75 (45,2)	Incident 12 %, Prevalence 16 % [DNPR 2021]

The frequency of GPA is higher in the Danish patient population than in the Advocate population. The Danish frequency of GPA is implemented in the Danish patient population. The Danish Patient Population is the base case population in the health economic analysis.

APPENDIX D EFFICACY AND SAFETY RESULTS PER STUDY

Definition, validity and clinical relevance of included outcome measures

The efficacy, safety and tolerability, and pharmacokinetic (PK) measurements used in the ADVOCATE trial are widely used and generally recognised to be reliable, accurate, and relevant for the study design. The pharmacodynamic (PD) measures were exploratory. Brief descriptions of the measures used in the study can be found in table 1, [153, 155].

Table 1 Measures and assessments used in the ADVOCATE trial [1, 153, 155]

Measure/assessment	Description
Efficacy measures	
Disease activity	
Birmingham Vasculitis Activity Score (BVAS)	BVAS is a robust and validated clinical tool for the assessment of systemic vasculitis. It is used as a checklist of parameters to examine in daily practice, to assess disease activity (identify remission major and minor relapses) and to assess response to treatment. It is calculated from a checklist of 56 items/descriptors of vasculitis manifestation across 9 organ-based systems, cf. table 2 below. Each item is weighted and each organ-system has a maximum score to reflect major or minor vasculitis disease activity, BVAS 0 = no disease and BVAS ≥1= active disease. Remission is defined as: Proportion of patients in remission at week 26; defined as Birmingham Vasculitis Activity Score (BVAS) = 0 and not taking glucocorticoid for antineutrophil at week 26. Sustained, steroid free remission is defined as: Proportion of patients achieving sustained remission at week 52; defined as remission at week 26 and week 52, without relapse through week 52, and not taking glucocorticoids for ANCA-associated vasculitis within 4 weeks before week 52. Relapse is defined as > 1 major item in BVAS, > 3 minor items in BVAS, or 1 or 2 minor items in BVAS at 2 consecutive visits.
Renal function	
Albuminuria	Albuminuria refers to the presence of albumin protein in the urine. This was assessed using urinalysis of midstream urine samples used to measure quantitative albumin concentrations.
Urinary monocyte chemoattractant protein-1 (MCP-1): creatinine ratio	Urinary monocyte chemoattractant protein-1 is a chemokine and a potent chemoattractant for monocytes and macrophages. Increased levels of MCP-1 can be seen in vasculitis patients. In this study, quantitative urinary MCP-1 concentrations were determined using a specific ELIZA assay.
Urine albumin: creatinine ratio (UACR)	The UACR is used as a measure of kidney function. In UK clinical practice, proteinuria is defined as a UACR >30 mg/mmol. In this study, uranalysis of midstream urine samples was used to measure quantitative albumin and creatinine concentrations and was expressed as mg albumin/g creatinine.
Estimated Glomerular Filtration Rate (eGFR)	The eGFR is a key indicator of renal function which is derived from the patient's serum creatinine concentration, age, gender, and ethnicity. In this study, eGFR was calculated using the creatinine measures for all applicable study visits using the MDRD equation of adults (including a unique equation for Japanese adults) and the modified Schwartz equation for adolescents.
Disease damage	
Vasculitis Damage Index (VDI)	The VDI is used to measure organ damage occurring since the onset of vasculitis. The VDI comprises 64 items of damage grouped into 11 organ systems. Damage is defined as the presence of non-healing scars present within the previous 3 months. Each item of damage is assigned 1 point and the points from all 11 categories are totalled to provide a VDI total score. New patients usually have a VDI score of 0.

Measure/assessment	Description
GC AEs and complications	
Glucocorticoid AEs and complications 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). Increases in both the CWS and AIS indicate increased GC AEs and complications.
HRQoL	
SF-36 v2	The SF-36v2 is a multi-purpose HRQoL short form survey with 36 questions. It comprises 8 scales assessing functional health and wellbeing, psychometrically based physical and mental measures and a preference-based health utility index. Higher scores represent a better functional status.
EQ-5D	EQ-5D is a standardised measure of health outcomes including five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a EuroQoL visual analogue scale (VAS).
Safety and tolerability assessments	
GC use	Exposure by study period, duration of exposure, total dose, average daily dose, and overall percent compliance, and non-study supplied GC use, was summarised by treatment group
Adverse events	Analysis of TEAEs, SAEs, TEAEs leading to study drug discontinuation, events related to study medication, GC use, IV CYC, oral CYC, RTX, AZA, or MYO, and TEAEs by maximum severity
TEAEs related to GC use	Incidence of TEAEs attributed to GC use following assessment using EULAR-recommended event terms
Pharmacokinetic and pharmacodynamic assessments	
Pharmacokinetic (PK) assessment	Plasma concentrations of Avacopan (and metabolites) were determined from blood samples collected at baseline and on weeks 1, 2, 4,7, 13, 26, 39 and 52.
Pharmacodynamic (PD) assessment	Pharmacodynamic markers were collected throughout the study using plasma, blood, urine and saliva samples.

ANCA-AV, ANCA-associated vasculitis; **AEs;** Adverse Events; **AZA**, azathioprine; **BVAS**, Birmingham Vasculitis Activity Score; **CYC**, cyclophosphamide; **eGFR**, estimated glomerular filtration rate; **EQ-5D VAS,** EQ-5D Visual Analogue Scale; **GC**, Glucocorticoids; **GTI**, Glucocorticoid induced AEs and complications; **HRQoL,** Health related quality of life; **MYC**, mycophenolate; **PD**; Pharmacodynamic; **PK**, Pharmacokinetic; **RTX**, rituximab; **SAEs**, Serious Adverse Events; **SF-36,** 36 item Short Form Survey; **TESAEs**, Treatment Emergent Serious Adverse Events; **UACR**, Urine Albumin to creatinine ratio; **VDI,** vasculitis damage index

Table 2 Use of Birmingham Vasculitis Activity Score in the ADVOCATE-study [155].

The two primary efficacy end points were clinical remission at week 26, defined as a BVAS of 0 and no receipt of glucocorticoids for 4 weeks before week 26, and sustained remission, defined as remission at week 26 and at week 52 and no receipt of glucocorticoids for 4 weeks before week 52. Patients were not considered to be in sustained remission if they had remission at week 26 but a relapse thereafter; 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.

The BVAS was completed during screening, and at weeks 4, 10, 16, 26, 39, 52, and 60. The BVAS organ systems are shown below. Major items are indicated in bold italics. For study eligibility, a patient had to have at least one major item, at least 3 minor items, or at least the two renal items of hematuria and proteinuria. For the week 4 BVAS assessment, disease activity within 7 days prior to the week 4 visit was assessed. This was done because the typical 28 days

would potentially include the baseline assessment. For all other visits, disease activity within 28 days prior to the visit was assessed. Relapses were assessed at all study visits after week 4.

Body Systems:

1. General
- Myalgia
- Arthralgia / arthritis
- Fever ≥38 ° C
- Weight loss ≥2 kg

2. Cutaneous
- Infarct
- Purpura
- Ulcer
- ***Gangrene***
- Other skin vasculitis

3. Mucous membranes / eyes
- Mouth ulcers
- Genital ulcers
- Adnexal inflammation
- Significant proptosis
- ***Scleritis / Episcleritis***
- Conjunctivitis / Blepharitis / Keratitis
- Blurred vision
- Sudden visual loss
- Uveitis
- ***Retinal changes (vasculitis / thrombosis / exudate / haemorrhage)***

4. Ear Nose & Throat
- Bloody nasal discharge / crusts / ulcers / granulomata
- Paranasal sinus involvement
- Subglottic stenosis
- Conductive hearing loss
- ***Sensorineural hearing loss***

5. Chest
- Wheeze
- Nodules or cavities
- Pleural effusion / pleurisy
- Infiltrate
- Endobronchial involvement
- ***Massive hemoptysis / alveolar hemorrhage***
- ***Respiratory failure***

6. Cardiovascular
• Loss of pulses
• Valvular heart disease
• Pericarditis
• Ischemic cardiac pain
• Cardiomyopathy
• Congestive cardiac failure

7. Abdominal
• Peritonitis
• Bloody diarrhea
• ***Ischemic abdominal pain***

8. Renal
• Hypertension
• Proteinuria >1+ or >0.2 g/g creatinine
• Hematuria ≥10 RBCs/hpf
• Serum creatinine 125-249 μ mol/L
• Serum creatinine 250-499 μ mol/L
• Serum creatinine ≥500 μ mol/L
• ***Rise in serum creatinine >30% or fall in creatinine clearance >25%***

9. Nervous system
• Headache
• ***Meningitis***
• Seizures (not hypertensive)
• ***Cerebrovascular accident***
• Organic confusion
• ***Spinal cord lesion***
• ***Cranial nerve palsy***
• ***Sensory peripheral neuropathy***
• ***Mononeuritis multiplex***

10. Other
• ***RBC casts and/or glomerulonephritis***

Appendix D Efficacy and safety results per study cont.
Results of ADVOCATE (NCT02994927)

Phase 3 study: Summery of Primary Efficacy Results – Primary Endpoints (Intent-to-Treat Population)

Outcome	Study arm	N	n	Result %	95 % CI*b	Estimated commen Difference in %	Two-sided 95% CI for commen difference	P-value for difference between groups *a, (non-inferiority)	P-value for difference between groups *a, (Superiority)
Primary end point (Intention-to-Treat Population)									
Remission*c at wk 26 no.(%)	Avacopan	166	120	72,3	64,8. 78,9	3,4	(-6,0, 12,8)	<0,0001	0,2387
	Prednisolone	164	115	70,1	62,5, 77,0				
Sustained remission*d at wk 52 no.(%)	Avacopan	166	109	65,7	57,9 72,8	12,5	(2,6 to 22,3)	<0,0001	0,0066
	Prednisolone	164	90	54,9	46,9,62,6				

*a One-side P values

*b Clopper and perason exact CI

*c remission was defined as: the proporsion of patients in remission at week 26; defined as Birmingham Vasculitis Activity Score (BVAS) = 0 and not taking glucocortioid for antineutrophil at week 26.

*d Sustained remission was defined as: Proportion of patients achieving sustained remission at week 52; defined as remmision at week 26 and week 52, without relapse through week 52, and not taking glucocorticoids for ANCA-assocoated vasculitis within 4 weeks before week 52. Relapse is defined as > 1 major item in BVAS, > 3 minor items in BVAS, or 1 or 2 minor items in BVAS at 2 consecutive visits.

Glucocorticoid Toxicity Index

Secondary end points were glucocorticoidinduced toxic effects according to the Glucocorticoid Toxicity Index (GTI) during the first 26 weeks (measured by both the Cumulative Worsening Score [GTI-CWS], which ranges from 0 to 410, and the Aggregate Improvement Score [GTI-AIS], which ranges from –317 to 410; on both scales, higher scores indicate greater severity of toxi effects) (Table S3) [153, 219, 241].

Glucocorticoid toxicity was analyzed using the Glucocorticoid Toxicity Index (GTI) version 2.0, [241] an instrument upgrade from the original GTI version 1.0.[219] Data for completion of the GTI were collected on day 1 (pre-dosing) and at weeks 13 and 26. The GTI 2.0 instrument provides two GTI scores: the Cumulative Worsening Score (CWS) and the Aggregate Improvement Score (AIS).
The GTI-CWS captures cumulative glucocorticoid 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 glucocorticoid 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 glucocorticoid toxicity.
The GTI components and scoring are provided in Table 3 [155a]. Definitions of individual items are provided in the original publication [129].

Table 3 Glucocorticoid Toxicity Index Version 2.0 Item with Scoring [155, 155a]

Feature/Body System	**Item Weight**
Body Mass Index (BMI)	
Decrease of ≥5 BMI units	-36
Decrease of >2 but <5 BMI units	-21
No significant change in BMI (±2 BMI units)	0
Increase of >2 to <5 BMI units	21
Increase of 5 or more BMI units	36
Glucose tolerance	
Improvement in HbA1c AND decrease in medication	-44
Improvement in HbA1c OR decrease in medication	-32
No significant change	0
Increase in HbA1c OR increase in medication	32
Increase in HbA1c AND increase in medication	44

Blood pressure	
Improvement in BP AND decrease in medication	-44
Improvement in BP OR decrease in medication	-19
No significant change in blood pressure	0
Increase in BP OR increase in medication	19
Increase in BP AND increase in medication	44
Lipids	
Decrease in LDL AND decrease in medication	-30
Decrease in LDL OR decrease in medication	-10
No significant change in lipids	0
Increase in LDL OR increase in medication	10
Increase in LDL AND increase in medication	30
Steroid myopathy	
Moderate weakness to none	-63
Moderate to Mild weakness	-54
Mild weakness to none	-9
No significant change	0
None to mild weakness	9
Mild to moderate weakness	54
None to Moderate weakness	63

Skin toxicity	
Decrease in Skin Toxicity - Moderate to None	-26
Decrease in Skin Toxicity - Moderate to Mild	-18
Decrease in Skin Toxicity - Mild to None	-8
No significant change	0
Increase in Skin Toxicity - None to Mild	8
Increase in Skin Toxicity - Mild to Moderate	18
Increase in Skin Toxicity - None to Moderate	26
Neuropsychiatric (NP) toxicity	
Decrease in NP Toxicity - Moderate to None	-74
Decrease in NP Toxicity - Moderate to Mild	-63
Decrease in NP Toxicity - Mild to None	-11
No significant change	0
Increase in NP Toxicity - None to Mild	11
Increase in NP Toxicity – Mild to Moderate	63
Increase in NP Toxicity - None to Moderate	74
Infection	
No significant infection	0
Oral/vaginal candidiasis or uncomplicated zoster	19
Grade 3, 4 or 5 infection	93

BMI = body mass index; BP = blood pressure; HbA1c = hemoglobin A1c; LDL = low density lipoprotein; NP = neuropsychiatric

Phase 3 study: Summery of Efficacy Results – secondary end points Glucocorticoid Toxicity Index (Intent-to-Treat Population) [155,184]

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

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

Quality of Life assessment

Phase 3 study: Secondary End Points: Health-Related Quality of LIfe – Short Form-36 Version 2 (SF-36) Analysis (ITT- Population) [155,184)

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

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

Phase 3 study: Secondary End Points: Health-Related Quality of LIfe – EQ-5D-5L Index Analyses (ITT Population) [155,184]

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

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

Phase 3 study: Secondary End Point – Change in Estimated Glomerular Filtration Rate (ITT Population) [155,184]

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

[a] *Two-sided P-values*

APPENDIX E SAFETY DATA FOR INTERVENTION AND COMPARATOR(S)

The safety data presented in section 7.1.2 is in accordance with the EMA Assessment Report presented in the tables below [184].

Overview of Treatment-Emergent Adverse Events in the phase 3 Study ADVOCATE (Safety Population) [184]

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

Overview of Treatment-Emergent Adverse Events in the phase 2 Studies CLEAR and CLASSIC in ANCA-Associated Vasculitis (Pooled Safety Population) [184]

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

Treatment-Emergent Adverse Events by system Organ Class in the Phase 3 study ADVOCATE (Safety population) [184]

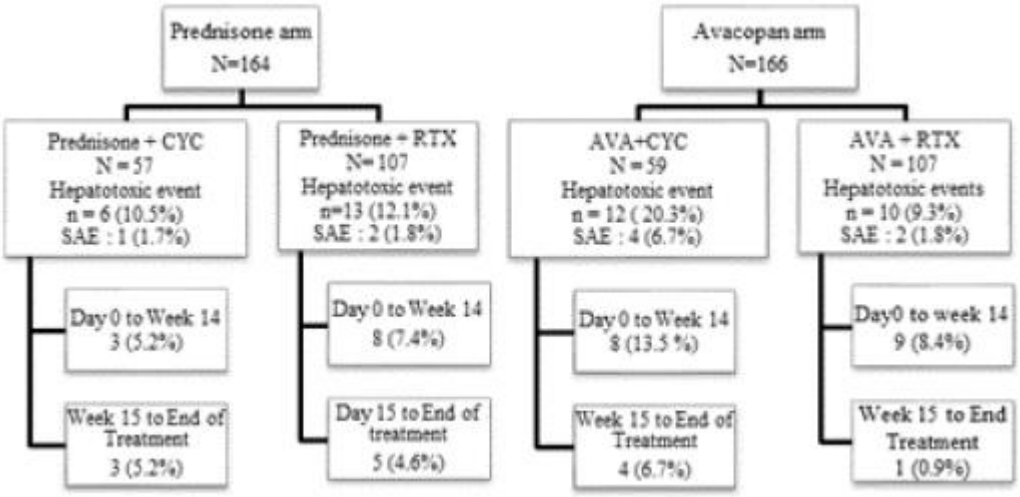
System Organ Class	Prednisone (N=164) n (%)	Avacopan (N=166) n (%)
Infections and Infestations	124 (75.6)	113 (68.1)
Gastrointestinal Disorders	83 (50.6)	101 (60.8)
Musculoskeletal and Connective Tissue disorders	93 (56.7)	92 (55.4)
General Disorders and Administrative Site Conditions	87 (53.0)	76 (45.8)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

Incidence of Treatment-Emergency Adverse Events Associated with Elevated Hepatic Fuction Tests by System Organ Class and Preferred Terms in the Phase 3 study ADVOCATE (Safety Population)

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

Reported term: azathioprine induced liver toxicity

Number of Subjects Experiencing Hepatic Disorder in different stratum [184]



Notes: Ava Avacopan; AZA azathioprime; CYC Cyclophosphamid;e; RTX Rituximab; N Number of subjects per treatment group; n Number of subjects with observation; SAE Serious adverse events .

Treatment-Emergent Adverse Events of Increased Blood Creatine Phosphokinase in ADVOCATE study (Safety Population) [184]

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

Incidence of Treatment-Emergent Infection in the Phase 3 Study ADVOCATE (Safety Population) [184]

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

Serious Treatment-Emergent Adverse Events by Preferred Term Occurring in ≥ 1% of subjects in Either Treatment Group in ADVOCATE study (Safety Population) [184].

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

APPENDIX F COMPARATIV ANALYSIS OF EFFECACY AND SAFETY

N/A for meta-analyser.

APPENDIX G EXTRAPOLATION

APPENDIX H – LITERATURE SEARCH FOR HR-QoL DATA

A literature review with a systematic methodology was undertaken to identify and summarise the best available HR-QoL evidence available for avacopan and relevant comparator therapies for the treatment of AAV. The highest quality and most relevant evidence identified by the literature review.

The key objective was to identify utility values associated with AAV and related treatments.

Literature searches strategy

The search strategies broadly had 2 sets of terms:

- Terms to search for the health condition of interest
- Terms to search the subject area of interest

Search terms included a number of indexing and free-text terms to ensure that the highest proportion of relevant articles were captured.

The key characteristics for the searches were the following:

- Language: English
- Scope countries: No limit
- Publication type/status: No limit
- Time frame:
    - **Original**: 1998-present (20 years)
    - **Update**: 2018-2020 (2 years)
    - **Update**: 2020-2021 (1 year)

Electronic databases

The search plan included both electronic and hand searches. Databases that were searched for this literature review include the following:

- Embase (OvidSP)
- MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE<1946 to Present>, MEDLINE In-Process Citations & Daily Update (OvidSP)
- NHSEED (Wiley): http://www.thecochranelibrary.com
- NICE health technology appraisals: https://www.nice.org.uk

The search strategies can be found in Appendix A Search strings for HR-QoL reviews and were translated as necessary for each of the resources searched. The search strategies and searches were designed and run by an experienced information specialist.

Hand-searching and validation of the search strategies

Relevant systematic literature reviews and key articles were cross-checked to confirm that the search strategy identified the most relevant records. Additionally, the electronic search was supplemented by hand-searching the reference lists of key included articles.

Internal validation was performed using a variety of methods, including the following:

- The PRESS evidence-based checklist was used to quality assess all searches used in the literature review [A]
- Relevant SLRs previously performed in this area were used to compare the search strategies and studies included in this review

- Several relevant studies that were expected to be identified by the search strategy were identified by hand-searching and the search strategy was checked to ensure that it included them

As well as predetermined, specific hand searches, general hand searches were also performed to identify further studies of interest. This included searching review articles, the reference lists of included full-text publications, and free text.

Selection of relevant studies

A single reviewer performed title and abstract screening. Any indecisions were reviewed by a second analyst to reach a consensus. Every citation retrieved in the searches was marked as either *include* or *exclude* after review of the study title and abstract, after which the full-text articles were obtained for citations that were considered most relevant. Each full-text article was evaluated by a reviewer and marked as either *include* or *exclude*. If a study was excluded based on the full-text assessment, a reason was documented. The eligibility criteria for utility studies are listed in table A.

Table A. Eligibility criteria for utility studies NICE appraisal checklist: cost-effectiveness studies (NICE, 2015)

Criteria	Inclusion	Exclusion
Patient population	▪ Adult patients (≥18 years) with GPA (Wegener's) or MPA	▪ Patients <18 years ▪ Patients without GPA or MPA
Intervention(s)	No limit	
Comparator(s)	No limit	
Outcome(s)	▪ 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
Study type	▪ 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
Language	English	▪ Publications with non-English language title and abstracts ▪ Publications with non-English language at full text
Publication time frame	1998-present	Publications <1998
Countries	No limit	
Abbreviations: aTNFs, anti-tumour necrosis factors; AZA, azathioprine; GPA, granulomatosis with polyangiitis; HRQoL, health-related quality of life; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; RCT, randomised controlled trials		

Identified studies

Original review (1998-2018): The literature was reviewed to identify studies reporting health-related utility evidence for AAV patients. The literature review searches were conducted in electronic databases on 9 July 2018 and retrieved a total of 250 citations with potentially with useful content. An additional 2 citations were retrieved through hand searches. Duplicates were removed, and 191 papers were carried forward for screening against the eligibility criteria for utility studies. During title and abstract screening, 171 papers were excluded when an evaluation of their title and abstract deemed them to be irrelevant to the research question. Full-text screening was conducted on the remaining papers, of which 18 were excluded because of lack of relevant outcome data (Appendix B:

Reasons for study exclusion at full text) Two articles remained for data extraction. The flow diagram detailing the different stages of the utility studies is shown in Figure B (a).

Updated review (2018-2020): Literature searches were also conducted on 16 June 2020 to gather any additional evidence published since June 2018. The searches retrieved a total of 388 citations with potentially useful content. Following removal of duplicates and cross-checks against the 2018 searches, 61 citations were carried forward. Three citations were included during title and abstract screening. These were all excluded during full-text screening because they did not contain any outcomes of interest. No further studies from the original 2018 searches were added. Details are presented in Figure B (b).

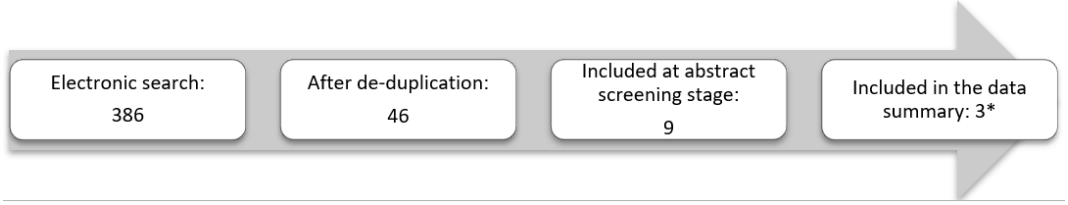
Updated review (2020-2021): Literature searches were also conducted on 17 June 2021 to gather any additional evidence published since June 2020. The searches retrieved a total of 386 citations with potentially useful content. Forty six citations were carried forward. Nine citations were included during title and abstract screening. Seven of these were excluded during full-text screening because they were in the wrong population (N=5) or did not report outcomes of interest (N=2). An additional study was identified through hand searching; thus 3 further studies were added. Details are presented in Figure B (c).

Figure B Flow diagram: (a) original utilities literature review (1998-2018); (b) review update searches (2018-2020); and (c) review update searches (2020-2021)

a original utilities literature review (1998-2018)

b review update searches (2018-2020)

c review update searches (2020-2021)



* One study identified by hand searching

Summary of identified studies providing utility values for health states

Two studies were included in the literature review of utility studies. These consisted of 2 HTAs of RTX in combination with GCs for treating AAV (National Institute for Health and care Excellence (NICE) 2014 and Scottish Medicines Consortium (SMC) 2013) [B,C]; . A summary of these studies can be found in Table C.

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 36-Item Short Form Health Survey (SF-36) data collected at baseline and at 6 months in the RAVE trial using a previously published mapping algorithm (Ara and Brazier 2008; Stone JH 2010) [D,E]. 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.

However, there was a lack of clarity regarding exactly which data from the RAVE trial were used to inform estimates. Although the same method was applied for both the NICE and SMC submissions, final average utility scores differed for the *uncontrolled disease* health state (i.e., disease not controlled by RTX with GCs). Because no published data exist to inform the quality-of-life data for patients in the uncontrolled disease health state, the corresponding utility value could only be calculated as an assumption. However, AAV is rarely left untreated; therefore, it is likely that, in the uncontrolled disease state, patients would be treated with alternative available therapies such as mycophenolate mofetil, leflunomide, AZA, and methotrexate, as advised by clinical specialists, meaning this health state would have a higher utility score than that assumed by the manufacturer. A new utility value was therefore assumed, which was worse than non-remission by the same absolute amount that non-remission was worse than complete remission. The utility value for uncontrolled disease was amended from 0.671 to 0.710 to reflect this (National Institute for Health and care Excellence (NICE) 2014) [D]. There was no amendment of the utility value in the SMC submission, so 0.671 was the published value (Scottish Medicines Consortium (SMC) 2013) [E].

As reported by NICE (2014), the manufacturer's review used for submission failed to identify relevant studies with respect to utility data. Of the 21 studies excluded during the full-text screening stage for the purposes of this review, all were excluded on the grounds that they contained no useable utility values. Three studies, however, reported total physical component summary and mental component summary scores derived from SF-36 dimensions as a representation of physical and emotional well-being (Faurschou et al. 2010; Srouijl et al.2006; Tomasson et al 2012). Five studies also assessed HRQoL within patient populations with GPA, MPA, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), immunoglobulin A vasculitis, or renal-limited vasculitis. However, specific results for GPA and MPA patients were not reported separately from the whole population, meaning applicable data could not be obtained (Brezinova et al. 2013; Carpenter et al. 2009; Hinojosa-Azaola et al. 2018; Pugnet et al.2016; Walsh et al.2011) [I,J,K,L,M]

Table C. Characteristics of utility studies included in the review

Study (year)	Country	Patient populations	Intervention/comparator	Disease state for utility: average utility score
NICE, 2014 [TA308]	United Kingdom	Adult patients with severe, active GPA and MPA.	RTX (in combination with GCs) CYC (in combination with GCs)	Uncontrolled disease: 0.71 Remission: 0.84 Non-remission: 0.754
SMC, 2013 [SMC ID 894/13]	United Kingdom	Adult patients with severe, active GPA and MPA.	RTX (in combination with GCs) CYC (in combination with GCs)	Uncontrolled disease: 0.671 Remission: 0.837 Non-remission: 0.754

Abbreviations: 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.

Summary of identified HRQoL studies

Two studies were included in the literature review of HRQoL. These consisted of a single-centre cross-sectional study to evaluate the impact of sinonasal morbidity on global QoL, and a phase 2 placebo-controlled RCT conducted primarily to evaluate the safety of avacopan in addition to standard of care (SOC).

The population in both studies were patients with GPA and MPA. Cazzador et al. (2020) conducted a cross-sectional case-control study at the University of Padua, in which patients with an established diagnosis of GPA or MPA with a minimum disease duration of 6 months and patients with chronic rhinosinusitis, matched by age and sex were enrolled (Cazzador et al 2020) [N]. Three validated questionnaires were administered to each patient, which were the Sino-Nasal Outcomes Test-22 (SNOT-22), Nasal Obstruction Symptom Evaluation (NOSE) and SF-36. An AAV-specific, modified sinonasal outcome test score (SNOT-25) was also reported; this included 3 sinonasal symptoms in addition to those in the SNOT-22. Responses were scored for their perceived current disease activity. Twenty GPA patients (45.5%) presented with ear, nose and throat (ENT) involvement, whereas 24 patients (54.5%) without ENT symptoms. Patients with ENT-AAV had significantly higher SNOT-22, SNOT-25 and NOSE scores compared with non-ENT-AAV patients. Considering SF-36 score, patients with ENT-AAV demonstrated significant impairment in physical functioning, role limitations, energy/fatigue and social functioning compared with non-ENT-AAV patients. The authors concluded that QoL is significantly reduced in GPA/MPA patients, especially in the presence of ENT involvement. Generic HRQoL data (SF-36) from the Cazzador study is reported in Table 9.

Merkel et al. (2020) reported the results of CLASSIC, a phase 2, randomised, double-blind, placebo-controlled, three-arm study evaluating two doses of avacopan plus SOC (CYC/RTX + standard oral glucocorticoids) versus SOC only (Merkel et al. 2020) [O]. From 2015 to 2016 at 15 sites in the US and Canada, patients ≥18 years of age with newly diagnosed (within 4 weeks of screening) or relapsing GPA/MPA were randomised using a 1:1:1 protocol to 12 weeks of treatment with placebo plus SOC, avacopan 10 mg orally twice daily plus SOC or avacopan 30 mg orally twice daily plus SOC. All patients also received oral prednisone. HRQoL was measured by SF-36v2 and EQ-5D-5L and assessed at baseline, day 29 and day 85. At baseline, before treatment was initiated, the mean SF-36 physical component summary was 37.5±3.0 and the mean SF-36 mental component summary was 40.8±3.0 in the placebo arm. The EQ-5D utility was reported as a mean of 0.77, with a VAS score of mean 60.5. There were no significant differences reported in these value reported between treatment arms at baseline.

The ADVOCATE study was published in 2021 (Jayne et al.2021) [P]. This was a phase 3 double blind RCT that randomised patients with AAV to receive oral avacopan at a dose of 30 mg twice daily or oral prednisone on a tapering schedule (In combination with CYC or RTX). The study reported generic HRQoL outcomes in the form of SF-36 and EQ-5D VAS. The authors reported the baseline SF-36 physical component score was 39.2±0.8 (SD) in the intervention arm and 40.1±0.8 in the comparator arm. Baseline EQ-5D VAS scores were 65.8±1.5 and 63.4±1.8 in intervention and comparator arms, respectively.

The ADVOCATE and CLASSIC studies are key RCTs demonstrating the safety and efficacy of avacopan and changes to HRQoL associated with the intervention are fully described in the clinical SLR.

Table D. Generic HRQoL (SF-36) results reported by Cazzador et al. (2020).

Population description	Other population characteristics	Measure	Time point	Score
AAV with ear, nose and throat involvement	Median BVAS v3 score: 0 (0–10) BVAS v3 score > 0, n=7 (35.0%) Median VDI score: 3 (2–4) Sample size: 20 Male, n=9 (45.0%); female, n=11 (55.0%) Median age: 53 (26.7-61.0)	SF-36 physical functioning	NA	75 median, 66.3-90.0
		SF-36 role limitations because of physical health	NA	50 median, 0-93.8
		SF-36 role limitations because of emotional problems	NA	50 median, 0-100
		SF-36 energy/fatigue	NA	42.5 median, 20.0-67.5
		SF-36 emotional well-being	NA	52 median, 37.0-77.0
		SF-36 social functioning	NA	50 median, 40.6-87.5
		SF-36 pain	NA	65 median, 45.0-100
		SF-36 general health	NA	42.5 median, 20.0-58.8
		SF-36 health change	NA	50 median, 50.0-75.0
		SNOT-22 total	NA	33.5 median, 24.0-60.3
		SNOT-25 total	NA	43.5 median, 27.8-63.8
		NOSE total	NA	30 median, 25-51
AAV without ear, nose and throat involvement	Median BVAS v3 score: 0 (0–7) BVAS v3 score > 0, n=2 (8.3%) Median VDI score: 3 (2–4) Sample size: 24 Male, n=11 (45.8%); female, n=13 (54.2%) Median age 63.5 (52.2-71.0)	SF-36 physical functioning	NA	90 median, 90.0-95.0
		SF-36 role limitations because of physical health	NA	75 median, 6.3-100
		SF-36 role limitations because of emotional problems	NA	100 median, 100-100
		SF-36 energy/fatigue	NA	60 median, 50.0-68.7
		SF-36 emotional well-being	NA	68 median, 53.0-72
		SF-36 social functioning	NA	100 median, 65.6-100
		SF-36 pain	NA	90 median, 57.5-100
		SF-36 general health	NA	45 median, 36.3-63.8
		SF-36 health change	NA	50 median, 50.0-75.0
		SNOT-22 total	NA	14.5 median, 4.0-26.8
		SNOT-25 total	NA	14.5 median, 4.0-26.8
		NOSE total	NA	5 median, 0-15

Quality assessment and generalizability of estimates

The methodological quality of the sources assessed is shown in Table E. Because both citations were HTA submissions, rather than primary empirical data, the quality could not be assessed in full. Despite the robustness applied during HTA submissions, given that there is some uncertainty about how the utility values were derived, the quality of the utility data has been judged as moderate for both HTA submissions. The quality of the 2 RCTs reporting HRQoL data (CLASSIC and ADVOCATE) was assessed utilising Version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB2), reported in the clinical SL report.

Table E Quality assessment criteria for health-related quality of Life studies

Key criteria	Description	NICE (2014)	SMC (2013)	Cazzador (2020)
Sample size	This is not an exclusion criterion, but the precision of the estimate should be reflected in the variance around any estimate used in the decision model	Not reported	Not reported	44
Respondent selection and recruitment	Does this result in a population comparable to that being modelled?	Not reported	Not reported	Yes
Inclusion/exclusion criteria	Do these exclude any individuals? (e.g., the very elderly >80 years old are often excluded)	Not reported	Not reported	Patients with AAV at disease onset or with relapsing disease
Response rates to the measure used	Are response rates reported and, if so, are the rates likely to be a threat to validity?	Not reported	Not reported	Yes, no
Loss to follow-up	How large is the loss to follow-up (e.g., 1 year after fracture) and are reasons given? Are these likely to threaten the validity of the estimates?	Not reported	Not reported	Not applicable; cross-sectional study
	Are these likely to threaten the validity of the estimates?	Not applicable	Not applicable	Not applicable
Missing data	What is the extent of missing data and how are they handled?	Gaps in providing rationale for applying various utility scores (for remission disease state score)	No rationale given for scores (ERG in NICE submission criticised this)	No missing data
	Are missing data likely to threaten the validity of the estimates?	No	No	Not applicable
Any other problems with the study	Example: the relevance of location (e.g., country from which patients were recruited)	No	No	Relatively small number of patients; lack of information on their work/employment condition. Study design does not allow performing a risk factor analysis.
Appropriateness of measure	Is the measure used valid in the group of patients?	Yes, given limited data availability	Yes, given limited availability	Yes

Was a standardised measure used? If not, was the method used to describe the health states reported clearly? *Only applicable to direct elicitation*	Example: If vignettes were used, the method used to develop and validate them must be robust	Yes	Yes	Not applicable
Were the methods of valuation clear? *Only applicable to direct elicitation*	Were descriptions of anchors provided? Was the time horizon for the health states stated? Was the iteration procedure described?	Not reported	Not reported	Not applicable
Were the statistical properties fully described? *Only applicable to mapping study*	Yes/no. If no, is there uncertainty about the methods used?	Not available	Not available	Not applicable
Methodological quality	Reviewer judgement based on the above criteria (high, moderate, low)	Moderate (limited data availability)	Moderate (limited data availability)	Moderate
Abbreviations: ERG, evidence review group; NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicines Consortium				

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

C Scottish Medicines Consortium (SMC) (2013) 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). https://www.scottishmedicines.org.uk/medicines-advice/rituximab-mabthera-fullsubmission-89413/.

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E Stone JH MP, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Turkiewicz A, Tchao NK, Webber L, Ding L, Sejismundo LP, Mieras K, Weitzenkamp D, Ikle D, Seyfert-Margolis V, Mueller M, Brunetta P, Allen NB, Fervenza FC, Geetha D, Keogh KA, Kissin EY, Monach PA, Peikert T, Stegeman C, Ytterberg SR, Specks U; RAVE-ITN Research Group (2010) Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 363 (3):221-232. doi:10.1056/NEJMoa0909905

F Faurschou M, Sigaard L, Bjorner JB, Baslund B (2010) Impaired health-related quality of life in patients treated for Wegener's granulomatosis. J Rheumatol 37 (10):2081-2085. doi:10.3899/jrheum.100167

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I Brezinova P, Englbrecht M, Lovric S, Samann A, Strauss B, Wolf G, Schett G, Haubitz M, Neumann T, Zwerina J (2013) Coping strategies and depressiveness in primary systemic vasculitis--what is their impact on health-related quality of life? Rheumatology (Oxford) 52 (10):1856-1864. doi:10.1093/rheumatology/ket237

J Carpenter DM, Thorpe CT, Lewis M, Devellis RF, Hogan SL (2009) Health-related quality of life for patients with vasculitis and their spouses. Arthritis Rheum 61 (2):259-265. doi:10.1002/art.24235

K Hinojosa-Azaola A, Jiménez-González A, Alcocer-Castillejos N (2018) Patient and physician perspectives on the impact of health-related quality of life in Mexican patients with ANCA-associated vasculitis. Rheumatol Int 38 (4):631-640. doi:10.1007/s00296-017-3904-1

L Pugnet G, Pagnoux C, Terrier B, Perrodeau E, Puechal X, Karras A, Khouatra C, Aumaitre O, Cohen P, Maurier F, Decaux O, Ninet J, Gobert P, Quemeneur T, Blanchard-Delaunay C, Godmer P, Carron PL, Hatron PY, Limal N, Hamidou M, Ducret M, Daugas E, Papo T, Bonnotte B, Mahr A, Ravaud P,

Mouthon L, Guillevin L, French Vasculitis Study G (2016) Rituximab versus azathioprine for ANCA-associated vasculitis maintenance therapy: impact on global disability and health-related quality of life. Clin Exp Rheumatol 34 (3 Suppl 97):S54-59

M Walsh M, Mukhtyar C, Mahr A, Herlyn K, Luqmani R, Merkel PA, Jayne DR (2011) Health-related quality of life in patients with newly diagnosed antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Care Res (Hoboken) 63 (7):1055-1061. doi:10.1002/acr.20471

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P Jayne DRW, Merkel PA, Schall TJ, Bekker P, Group AS (2021) Avacopan for the Treatment of ANCA-Associated Vasculitis. N Engl J Med 384 (7):599-609. doi:10.1056/NEJMoa2023386

Summery

In summary, the primary sources of cost-effectiveness and health related utility data identified by the literature reviews were the NICE and SMC submissions for RTX in patients with severe, active GPA and MPA. These submissions are now between 7 and 8 years old. As a result, the availability and quality of the identified literature is limited, which suggests that further evidence generation is required to support future HTA submissions.

The quality of the cost-effectiveness data provided by the included conference abstracts could not be assessed in full; therefore, the quality of data from the studies was assessed as low by the reviewer (Harland 2014; Montante et al. 2017b; Ndir et al. 2011a). Although the publications published by NICE (2014) and SMC (2013) were deemed to only have minor limitations by the reviewer, the paucity of information available on ICER data across all sources was noted. No studies reporting new cost-effectiveness data were identified in the 2 most recent literature search updates.

There was a lack of studies reporting utility values associated with AAV. Despite the robustness applied during HTA submission processes, limited information was provided to support the rationale for applying the utility values that were identified in the report, particularly within the SMC analysis (National Institute for Health and Care Excellence (NICE) 2014; Scottish Medicines Consortium (SMC) 2013). Five studies that were excluded during the full-text screening stage published HRQoL data for AAV populations with disease subgroups that were not relevant to this review, which therefore limited the data analyses. Although few data were available for a high-quality assessment, it was reasonable to assess the quality of the 2 included sources as moderate, given the nature of the publications. The negative impact of AAV was confirmed in a recent study, particularly in individuals with ENT involvement (Cazzador et al. 2020).

The variation in cost and HCRU data with respect to publication year, geographical location, and interventions resulted in difficulties comparing data sets. This was also true of the studies identified by the updated literature searches. Overall, the data highlight a substantial burden on the healthcare system in terms of both costs and use of resources.

References used in the application/excel model

Refernce	Reference nr	Model use
National Institute for Health and Care Excellence (NICE) (2014) Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis. https://www.nice.org.uk/guidance/ta308.	117	**Pkt. 8.1** A state transition or Markov model was previously developed in Microsoft Excel. The structure was based on a previous model used for the cost-effectiveness analysis of rituximab (RTX) in the NICE evaluation of RTX (TA308) in combination with glucocorticoids (GCs) for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [117].
Stone JH MP, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Turkiewicz A, Tchao NK, Webber L, Ding L, Sejismundo LP, Mieras K, Weitzenkamp D, Ikle D, Seyfert-Margolis V, Mueller M, Brunetta P, Allen NB, Fervenza FC, Geetha D, Keogh KA, Kissin EY, Monach PA, Peikert T, Stegeman C, Ytterberg SR, Specks U; RAVE-ITN Research Group (2010) Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 363 (3):221-232. doi:10.1056/NEJMoa0909905	109	**Pkt 8.3.3.1** 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 [155]. 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 [109].
Jayne DRW, Merkel PA, Schall TJ, Bekker P, Group AS (2021) Avacopan for the Treatment of ANCA-Associated Vasculitis. N Engl J Med 384 (7):599-609. doi:10.1056/NEJMoa2023386	155	**Pkt. 8.3.3.1** 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 [155]. Table 38 Recovery of eGFR points at induction observed in ADVOCATE The risk of ESRD in relapse is assumed to be the same for Tavneos® and SoC, based on the rates in Robson et al. [44] and adjusted using the change in eGFR points observed in ADVOCATE. The data for EQ-5D-5L were collected at baseline, week 26 and 52 from ADVOCATE study [155]. Health-state utility values used in the base case analysis, Mean number og hospitalisation, length of stay.
Flossmann O, Berden A, de Groot K, Hagen C, Harper L, Heijl C, Höglund P, Jayne D, Luqmani R, Mahr A, Mukhtyar C, Pusey C, Rasmussen N, Stegeman C, Walsh M, Westman K (2011) Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis 70 (3):488-494. doi:10.1136/ard.2010.137778	3	Treatment with immunosuppressants in ANCA-associated vasculitis is associated with a significantly increased risk of infections [105,128]. Around half of all deaths in the first year following an ANCA-associated vasculitis diagnosis are caused by infections [3,64].
Tomasson, G., et al., *Assessment of health-related quality of life as an outcome measure in granulomatosis with polyangiitis (Wegener's).* Arthritis care & research, 2012. **64**(2): p. 273-9.	95	7.2.1.1 SF-36-v2 and EQ-5D
Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Höglund P, Jayne D, Mahr A, Westman K, Luqmani R (2015) Damage in the anca-associated vasculitides: long-term data from the European Vasculitis Study group (EUVAS) therapeutic trials. Ann Rheum Dis 74 (1):177-184. doi:10.1136/annrheumdis-2013-203927	44	The risk of ESRD in relapse is assumed to be the same for Tavneos® and SoC, based on the rates in Robson et al. [44] and adjusted using the change in eGFR points observed in ADVOCATE.
Wallace ZS, Lu N, Unizony S, Stone JH, Choi HK (2016) Improved survival in granulomatosis with polyangiitis: a general population-based study. Semin Arthritis Rheum 45 (4):483-489. doi:10.1016/j.semarthrit.2015.07.009	82	Hazard ratios and standard mortality ratios for ANCA-associated vasculitis
Brezinova, P., et al., *Coping strategies and depressiveness in primary systemic vasculitis-what is their impact on health-related quality of life?* Rheumatology (United Kingdom), 2013. **52**(10): p. 1856-1864.	99	Pkt. 5.1.2.3.1 Discussion of Quality of Life
Carpenter, D.M., et al., *Health-related quality of life for patients with vasculitis and their spouses.* Arthritis & Rheumatism, 2009. **61**(2): p. 259-65.	100	Pkt. 5.1.2.3.1 Discussion of Quality of Life
Hinojosa-Azaola, A., A. Jimenez-Gonzalez, and N. Alcocer-Castillejos, *Patient and physician perspectives on the impact of health-related quality of life in Mexican patients with ANCA-associated vasculitis.* Rheumatology International, 2018. **38**(4): p. 631-640.	97	Discussion of Quality of Life and for Burden of SoC for Relapsing ANCA-AV
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.	105	Pkt. 8.3.3.6 Mortality ajustment for Tavneos.

The references have been endorsed by Nordic clinicians based on their experience from the clinical practice.

Appendix A Search strings for HR-QoL

Part of DMC Appendix H Literature search for HR-QoL

Original searches July 2018

MEDLINE

Searched 09 July 2018 via OvidSP interface.

Limited to English language abstracts and 1998 onward.

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, and Ovid MEDLINE(R) <1946 to Present>

Search strategy:

1 Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/ (1296)

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. (2071)

3 Granulomatosis with Polyangiitis/ (6546)

4 ((wegener$ or polyangiitide$ or polyangiitis) adj2 granulomatos$).ti,ab. (6999)

5 Microscopic Polyangiitis/ (428)
6 microscopic polyangiiti$.ti,ab. (1415)
7 or/1-6 (10992)
8 quality-adjusted life years/ or quality of life/ (171642)
9 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (22517)
10 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (1863)
11 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab. (4770)
12 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab. (695)
13 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab. (380)
14 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab. (464)
15 (short form$ or shortform$).ti,ab. (27795)
16 ("European Organization for Research and Treatment of Cancer Quality of Life Questionnaire" or EORTC-QLQ).ti,ab. (3218)
17 "health related quality of life".ti,ab. (35653)
18 (Quality adjusted life or Quality-adjusted-life).ti,ab. (10410)
19 "assessment of quality of life".ti,ab. (1605)
20 (euroqol or euro qol or euroqual or euro qual or eq5d or eq 5d or eq-5d or eq5-d or eq-sdq or eqsdq).ti,ab. (8337)
21 (qol or hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab. (45912)
22 (hye or hyes).ti,ab. (61)
23 health$ year$ equivalent$.ti,ab. (40)
24 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab. (1269)
25 (quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab. (794)
26 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab. (3139)
27 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab. (11754)
28 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab. (6252)
29 (15D or 15-D or "15 dimension").ti,ab. (4682)
30 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab. (356)
31 illness state$.ti,ab. (120)
32 (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. (29871)
33 (utilities or disutili$).ti,ab. (6257)
34 (Severity Weighted Assessment Tool or SWAT or mSWAT).ti,ab. (606)
35 (patient$ 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. (101588)

36 Patient Reported Outcome Measures/ 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. (15497)
37 or/8-36 (345706)
38 7 and 37 (81)
39 limit 38 to (english language and yr="1998 -Current") (76)
76 results.

Embase
Searched 09 July 2018 via OvidSP interface.
Limited to English language abstracts and 1998 onward.
Database: Embase <1996 to 2018 Week 28>
Search strategy:
1 ANCA associated vasculitis/ (4586)
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$)).ti,ab. (3714)
3 Wegener granulomatosis/ (8856)
4 ((wegener$ or polyangiitide$ or polyangiitis) adj2 granulomatos$).ti,ab. (7147)
5 microscopic polyangiitis/ (2541)
6 microscopic polyangiiti$.ti,ab. (2225)
7 or/1-6 (14855)
8 quality adjusted life year/ or quality of life index/ (23716)
9 Short Form 12/ or Short Form 20/ or Short Form 36/ or Short Form 8/ (27404)
10 "International Classification of Functioning, Disability and Health"/ or "Ferrans and Powers Quality of Life Index"/ (2329)
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. (35574)
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. (1495)
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. (7650)
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. (1262)
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. (336)
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. (748)
17 (short form$ or shortform$).ti,ab. (36407)
18 ("European Organization for Research and Treatment of Cancer Quality of Life Questionnaire" or EORTC-QLQ).ti,ab. (6368)
19 "health related quality of life".ti,ab. (50421)
20 (Quality adjusted life or Quality-adjusted-life).ti,ab. (15384)
21 "assessment of quality of life".ti,ab. (2368)
22 (euroqol or euro qol or euroqual or euro qual or eq5d or eq 5d or eq-5d or eq5-d or eq-sdq or eqsdq).ti,ab. (15415)
23 (qol or hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab. (81470)
24 (hye or hyes).ti,ab. (93)
25 health$ year$ equivalent$.ti,ab. (26)

26 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab. (1775)
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. (925)
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. (3598)
29 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab. (19540)
30 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab. (9103)
31 15d.ti,ab. (2235)
32 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab. (491)
33 illness state$.ti,ab. (148)
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. (42474)
35 (utilities or disutili$).ti,ab. (9331)
36 (Severity Weighted Assessment Tool or SWAT or mSWAT).ti,ab. (802)
37 (patient$ 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. (143713)
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. (27880)
39 or/8-38 (363514)
40 7 and 39 (177)
41 limit 40 to (english language and yr="1998-Current") (174)
174 results.

Update searches June 2020;

MEDLINE
Searched 16 June 20 via OvidSP interface.
Limited to English language abstracts and 1998 onward.
Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to June 15, 2020>
Search strategy:
1 Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/ (1728)
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$)).ti,ab. (2551)
3 Granulomatosis with Polyangiitis/ (6934)
4 ((wegener$ or polyangiitide$ or polyangiitis) adj2 granulomatos$).ti,ab. (7612)
5 Microscopic Polyangiitis/ (516)
6 microscopic polyangiiti$.ti,ab. (1586)
7 or/1-6 (12228)
8 quality-adjusted life years/ or quality of life/ (203053)
9 (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. (25495)

10 (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. (2133)
11 (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. (5780)
12 (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. (845)
13 (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. (404)
14 (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. (584)
15 (short form$ or shortform$).ti,ab. (33285)
16 ("European Organization for Research and Treatment of Cancer Quality of Life Questionnaire" or EORTC-QLQ).ti,ab. (3910)
17 "health related quality of life".ti,ab. (43273)
18 (Quality adjusted life or Quality-adjusted-life).ti,ab. (12828)
19 "assessment of quality of life".ti,ab. (1813)
20 (euroqol or euro qol or euroqual or euro qual or eq5d or eq 5d or eq-5d or eq5-d or eq-sdq or eqsdq).ti,ab. (10997)
21 (qol or hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab. (55911)
22 (hye or hyes).ti,ab. (69)
23 health$ year$ equivalent$.ti,ab. (40)
24 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab. (1512)
25 (quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab. (888)
26 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab. (4020)
27 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab. (14569)
28 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab. (7792)
29 (15D or 15-D or "15 dimension").ti,ab. (5227)
30 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab. (406)
31 illness state$.ti,ab. (131)
32 (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. (35424)
33 (utilities or disutili$).ti,ab. (7379)
34 (Severity Weighted Assessment Tool or SWAT or mSWAT).ti,ab. (836)
35 (patient$ 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. (121926)
36 Patient Reported Outcome Measures/ 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. (23688)
37 or/8-36 (411589)
38 7 and 37 (98)
39 limit 38 to (english language and yr="1998 -Current") (93)
93 results.

Embase

Searched 16 June 2020 via OvidSP interface.

Limited to English language abstracts and 1998 onward.

Database: Embase <1974 to 2020 Week 24>

Search strategy:

1 ANCA associated vasculitis/ (5980)

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. (4901)

3 Wegener granulomatosis/ (12931)

4 ((wegener$ or polyangiitide$ or polyangiitis) adj2 granulomatos$).ti,ab. (10600)

5 microscopic polyangiitis/ (3077)

6 microscopic polyangiiti$.ti,ab. (2707)

7 or/1-6 (20850)

8 quality adjusted life year/ or quality of life index/ (29154)

9 Short Form 12/ or Short Form 20/ or Short Form 36/ or Short Form 8/ (35304)

10 "International Classification of Functioning, Disability and Health"/ or "Ferrans and Powers Quality of Life Index"/ (2871)

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. (41187)

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. (2383)

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. (9357)

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. (1528)

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. (454)

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. (937)

17 (short form$ or shortform$).ti,ab. (45281)

18 ("European Organization for Research and Treatment of Cancer Quality of Life Questionnaire" or EORTC-QLQ).ti,ab. (8142)

19 "health related quality of life".ti,ab. (62658)

20 (Quality adjusted life or Quality-adjusted-life).ti,ab. (19580)

21 "assessment of quality of life".ti,ab. (2884)

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. (20478)

23 (qol or hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab. (101449)

24 (hye or hyes).ti,ab. (133)

25 health$ year$ equivalent$.ti,ab. (41)

26 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab. (2275)

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. (1154)

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. (4824)

29 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab. (25079)

30 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab. (11922)
31 15d.ti,ab. (2563)
32 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab. (612)
33 illness state$.ti,ab. (197)
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. (54868)
35 (utilities or disutili$).ti,ab. (12099)
36 (Severity Weighted Assessment Tool or SWAT or mSWAT).ti,ab. (1136)
37 (patient$ 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. (192078)
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. (44405)
39 or/8-38 (470010)
40 7 and 39 (241)
41 limit 40 to (english language and yr="1998-Current") (234)
234 results.

Update searches June 2021

MEDLINE
Searched 17/06/21 via OvidSP interface.
Limited to English language abstracts and 1998 onwards.
Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to June 16, 2021>
Search Strategy:
1 Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/ (2009)
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$)).ti,ab. (2910)
3 Granulomatosis with Polyangiitis/ (7183)
4 ((wegener$ or polyangiitide$ or polyangiitis) adj2 granulomatos$).ti,ab. (8045)
5 Microscopic Polyangiitis/ (577)
6 microscopic polyangiiti$.ti,ab. (1717)
7 or/1-6 (13063)
8 quality-adjusted life years/ or quality of life/ (223744)
9 (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. (27159)
10 (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. (2273)
11 (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. (6376)
12 (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. (893)

13 (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. (419)
14 (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. (647)
15 (short form$ or shortform$).ti,ab. (36680)
16 ("European Organization for Research and Treatment of Cancer Quality of Life Questionnaire" or EORTC-QLQ).ti,ab. (4406)
17 "health related quality of life".ti,ab. (47879)
18 (Quality adjusted life or Quality-adjusted-life).ti,ab. (14195)
19 "assessment of quality of life".ti,ab. (1935)
20 (euroqol or euro qol or euroqual or euro qual or eq5d or eq 5d or eq-5d or eq5-d or eq-sdq or eqsdq).ti,ab. (12716)
21 (qol or hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab. (62273)
22 (hye or hyes).ti,ab. (75)
23 health$ year$ equivalent$.ti,ab. (40)
24 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab. (1650)
25 (quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab. (986)
26 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab. (4596)
27 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab. (16300)
28 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab. (8784)
29 (15D or 15-D or "15 dimension").ti,ab. (5557)
30 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab. (442)
31 illness state$.ti,ab. (138)
32 (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. (38913)
33 (utilities or disutili$).ti,ab. (8076)
34 (Severity Weighted Assessment Tool or SWAT or mSWAT).ti,ab. (983)
35 (patient$ 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. (135007)
36 Patient Reported Outcome Measures/ 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. (29263)
37 or/8-36 (453737)
38 7 and 37 (114)
39 limit 38 to (english language and yr="1998 -Current") (109)
109 results.

Embase

Database: Embase <1974 to 2021 Week 23>
Search Strategy:
1 ANCA associated vasculitis/ (7080)

2 (("anca associated" or anca-associated or "anti neutrophil cytoplasmic antibody" or "anti-neutrophil cytoplasmic 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)

277 results.

Appendix B Reason for study exclusion at full text

Part of DMC Appendix H Literature Search for HR-QoL

Author, year	Title	Reason for exclusion
Health-related quality of life (utilities)		
Ahn, 2021	Serum chitinase-3-like 1 protein is a useful biomarker to assess disease activity in ANCA-associated vasculitis: an observational study	Wrong population
Basu, 2017	Psychological interventions delivered by allied health professionals (AHPS) can improve quality of life in patients with inactive ANCA associated vasculitis: Results from a pilot randomised trial	No outcome data of interest
Basu, 2012	Determinants of poor quality of life in ANCA associated vasculitis (AAV)	No outcome data of interest
Basu, 2014	The characterisation and determinants of quality of life in ANCA associated vasculitis	No outcome data of interest
Brezinova, 2013	Coping strategies and depressiveness in primary systemic vasculitis—what is their impact on health-related quality of life?	No outcome data of interest
Carpenter, 2009	Health-related quality of life for patients with vasculitis and their spouses	No outcome data of interest
Dahlan, 2014	Patients' quality of life after stopping plasma exchange: A pilot study	No outcome data of interest
Faurschou., 2010	Impaired health-related quality of life in patients treated for Wegener's granulomatosis	No outcome data of interest
Harland, 2014	Mabthera (rituximab) for the treatment of severe granulomatosis with polyangiitis (Gpa) and microscopic polyangiitis (Mpa)—a cost-utility model for the United Kingdom	No outcome data of interest
Hirahara, 2019	Association of work productivity assessed by absenteeism and presenteeism with disease activity,	Wrong population

	damage and health-related quality of life in patients with ANCA-associated vasculitis	
Hinojosa-Azao, 2018	Patient and physician perspectives on the impact of health-related quality of life in Mexican patients with ANCA-associated vasculitis	No outcome data of interest
Hira, 2016	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	No outcome data of interest
Hoffman, 1998	Wegener's granulomatosis: Patient-reported effects of disease on health, function, and income	No outcome data of interest
Montante, 2019	Cost-effectiveness of rituximab versus azathioprine for maintenance treatment in antineutrophil cytoplasmic antibody-associated vasculitis	No outcome data of interest
Naznin, 2020	Outcomes of therapeutic plasma exchange; single tertiary center experience in Bangladesh	No outcome data of interest
Patel, 2018	Rituximab versus cyclophosphamide for vasculitic neuropathy: A patient reported outcomes study	No outcome data of interest
Pugnet, 2014	Rituximab versus azathioprine for ANCA-associated vasculitis maintenance therapy: Impact in health-related quality of life	No outcome data of interest
Pugnet, 2016	Rituximab versus azathioprine for ANCA-associated vasculitis maintenance therapy: impact on global disability and health-related quality of life	No outcome data of interest
Schwartz, 2020	Utility of the brief illness perception questionnaire to monitor patient beliefs in systemic vasculitis	No outcome data of interest
Srouji, 2006	General and rhinosinusitis-related quality of life in patients with Wegener's granulomatosis	No outcome data of interest
Suka, 2012	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	No outcome data of interest
Tomasson, 2011	Measurement of health-related quality of life among patients with ANCA- AAV using the SF-36	No outcome data of interest
Tomasson, 2012	Assessment of health-related quality of life as an outcome measure in granulomatosis with polyangiitis (Wegener's)	No outcome data of interest
Walsh, 2011	Health-related quality of life in patients with newly diagnosed antineutrophil cytoplasmic antibody-associated vasculitis	No outcome data of interest
Yaseen, 2020	Measuring Disease Activity and Functional Status in Patients with Granulomatosis with Polyangiitis (Wegener's) (GPA)	No outcome data of interest
Yoon, 2020	Serum Amyloid A Is a Biomarker of Disease Activity and Health-Related Quality-of-Life in Patients with Antineutrophil Cytoplasmic Antibody-Associated Vasculitis	Wrong population
Yoon, 2020	Serum vitamin D level correlates with disease activity and health-related quality of life in antineutrophil cytoplasmic antibody-associated vasculitis	Wrong population

Yoon, 2021	Association between follistatin-related protein 1 and the functional status of patients with anti-neutrophil cytoplasmic antibody-associated vasculitis	Wrong population

APPENDIX I MAPPING OF HRQoL DATA

Summary of identified studies providing utility values for health states

Two studies were included in the literature review of utility studies. These consisted of 2 HTAs of RTX in combination with GCs for treating AAV (National Institute for Health and care Exellence (NICE) 2014 and Scottish Medicines Consortium (SMC) 2013) [B,C]; . A summary of these studies can be found in Table C.

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 36-Item Short Form Health Survey (SF-36) data collected at baseline and at 6 months in the RAVE trial using a previously published mapping algorithm (Ara and Brazier 2008; Stone JH 2010) [D,E]. 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.

However, there was a lack of clarity regarding exactly which data from the RAVE trial were used to inform estimates. Although the same method was applied for both the NICE and SMC submissions, final average utility scores differed for the *uncontrolled disease* health state (i.e., disease not controlled by RTX with GCs). Because no published data exist to inform the quality-of-life data for patients in the uncontrolled disease health state, the corresponding utility value could only be calculated as an assumption. However, AAV is rarely left untreated; therefore, it is likely that, in the uncontrolled disease state, patients would be treated with alternative available therapies such as mycophenolate mofetil, leflunomide, AZA, and methotrexate, as advised by clinical specialists, meaning this health state would have a higher utility score than that assumed by the manufacturer. A new utility value was therefore assumed, which was worse than non-remission by the same absolute amount that non-remission was worse than complete remission. The utility value for uncontrolled disease was amended from 0.671 to 0.710 to reflect this (National Institute for Health and care Exellence (NICE) 2014) [D]. There was no amendment of the utility value in the SMC submission, so 0.671 was the published value (Scottish Medicines Consortium (SMC) 2013) [E].

As reported by NICE (2014), the manufacturer's review used for submission failed to identify relevant studies with respect to utility data. Of the 21 studies excluded during the full-text screening stage for the purposes of this review, all were excluded on the grounds that they contained no useable utility values. Three studies, however, reported total physical component summary and mental component summary scores derived from SF-36 dimensions as a representation of physical and emotional well-being (Faurschou et al. 2010; Srouijl et al.2006; Tomasson et al 2012). Five studies also assessed HRQoL within patient populations with GPA, MPA, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), immunoglobulin A vasculitis, or renal-limited vasculitis. However, specific results for GPA and MPA patients were not reported separately from the whole population, meaning applicable data could not be obtained (Brezinova et al. 2013; Carpenter et al. 2009; Hinojosa-Azaola et al. 2018; Pugnet et al.2016; Walsh et al.2011) [I,J,K,L,M)

Table C. Characteristics of utility studies included in the review

Study (year)	Country	Patient populations	Intervention/comparator	Disease state for utility: average utility score
NICE, 2014 [TA308]	United Kingdom	Adult patients with severe, active GPA and MPA.	RTX (in combination with GCs) CYC (in combination with GCs)	Uncontrolled disease: 0.71 Remission: 0.84 Non-remission: 0.754
SMC, 2013 [SMC ID 894/13]	United Kingdom	Adult patients with severe, active GPA and MPA.	RTX (in combination with GCs) CYC (in combination with GCs)	Uncontrolled disease: 0.671 Remission: 0.837 Non-remission: 0.754

Abbreviations: 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.

Summary of identified HRQoL studies

Two studies were included in the literature review of HRQoL. These consisted of a single-centre cross-sectional study to evaluate the impact of sinonasal morbidity on global QoL, and a phase 2 placebo-controlled RCT conducted primarily to evaluate the safety of avacopan in addition to standard of care (SOC).

The population in both studies were patients with GPA and MPA. Cazzador et al. (2020) conducted a cross-sectional case-control study at the University of Padua, in which patients with an established diagnosis of GPA or MPA with a minimum disease duration of 6 months and patients with chronic rhinosinusitis, matched by age and sex were enrolled (Cazzador et al 2020) [N]. Three validated questionnaires were administered to each patient, which were the Sino-Nasal Outcomes Test-22 (SNOT-22), Nasal Obstruction Symptom Evaluation (NOSE) and SF-36. An AAV-specific, modified sinonasal outcome test score (SNOT-25) was also reported; this included 3 sinonasal symptoms in addition to those in the SNOT-22. Responses were scored for their perceived current disease activity. Twenty GPA patients (45.5%) presented with ear, nose and throat (ENT) involvement, whereas 24 patients (54.5%) without ENT symptoms. Patients with ENT-AAV had significantly higher SNOT-22, SNOT-25 and NOSE scores compared with non-ENT-AAV patients. Considering SF-36 score, patients with ENT-AAV demonstrated significant impairment in physical functioning, role limitations, energy/fatigue and social functioning compared with non-ENT-AAV patients. The authors concluded that QoL is significantly reduced in GPA/MPA patients, especially in the presence of ENT involvement. Generic HRQoL data (SF-36) from the Cazzador study is reported in Table D.

Table D. Generic HRQoL (SF-36) results reported by Cazzador et al. (2020).

Population description	Other population characteristics	Measure	Timepoint	Score
AAV with ear, nose and throat involvement	Median BVAS v3 score: 0 (0–10) BVAS v3 score > 0, n=7 (35.0%) Median VDI score: 3 (2–4) Sample size: 20 Male, n=9 (45.0%); female, n=11 (55.0%) Median age: 53 (26.7-61.0)	SF-36 physical functioning	NA	75 median, 66.3-90.0
		SF-36 role limitations because of physical health	NA	50 median, 0-93.8
		SF-36 role limitations because of emotional problems	NA	50 median, 0-100
		SF-36 energy/fatigue	NA	42.5 median, 20.0-67.5
		SF-36 emotional well-being	NA	52 median, 37.0-77.0
		SF-36 social functioning	NA	50 median, 40.6-87.5
		SF-36 pain	NA	65 median, 45.0-100
		SF-36 general health	NA	42.5 median, 20.0-58.8
		SF-36 health change	NA	50 median, 50.0-75.0
		SNOT-22 total	NA	33.5 median, 24.0-60.3
		SNOT-25 total	NA	43.5 median, 27.8-63.8
		NOSE total	NA	30 median, 25-51

AAV without ear, nose and throat involvement	Median BVAS v3 score: 0 (0–7) BVAS v3 score > 0, n=2 (8.3%) Median VDI score: 3 (2–4) Sample size: 24 Male, n=11 (45.8%); female, n=13 (54.2%) Median age 63.5 (52.2-71.0)	SF-36 physical functioning	NA	90 median, 90.0-95.0
		SF-36 role limitations because of physical health	NA	75 median, 6.3-100
		SF-36 role limitations because of emotional problems	NA	100 median, 100-100
		SF-36 energy/fatigue	NA	60 median, 50.0-68.7
		SF-36 emotional well-being	NA	68 median, 53.0-72
		SF-36 social functioning	NA	100 median, 65.6-100
		SF-36 pain	NA	90 median, 57.5-100
		SF-36 general health	NA	45 median, 36.3-63.8
		SF-36 health change	NA	50 median, 50.0-75.0
		SNOT-22 total	NA	14.5 median, 4.0-26.8
		SNOT-25 total	NA	14.5 median, 4.0-26.8
		NOSE total	NA	5 median, 0-15

Merkel et al. (2020) reported the results of CLASSIC, a phase 2, randomised, double-blind, placebo-controlled, three-arm study evaluating two doses of avacopan plus SOC (CYC/RTX + standard oral glucocorticoids) versus SOC only (Merkel et al. 2020) [O]. From 2015 to 2016 at 15 sites in the US and Canada, patients ≥18 years of age with newly diagnosed (within 4 weeks of screening) or relapsing GPA/MPA were randomised using a 1:1:1 protocol to 12 weeks of treatment with placebo plus SOC, avacopan 10 mg orally twice daily plus SOC or avacopan 30 mg orally twice daily plus SOC. All patients also received oral prednisone. HRQoL was measured by SF-36v2 and EQ-5D-5L and assessed at baseline, day 29 and day 85. At baseline, before treatment was initiated, the mean SF-36 physical component summary was 37.5±3.0 and the mean SF-36 mental component summary was 40.8±3.0 in the placebo arm. The EQ-5D utility was reported as a mean of 0.77, with a VAS score of mean 60.5. There were no significant differences reported in these value reported between treatment arms at baseline.

The ADVOCATE study was published in 2021 (Jayne et al.2021) [P]. This was a phase 3 double blind RCT that randomised patients with AAV to receive oral avacopan at a dose of 30 mg twice daily or oral prednisone on a tapering schedule (In combination with CYC or RTX). The study reported generic HRQoL outcomes in the form of SF-36 and EQ-5D VAS. The authors reported the baseline SF-36 physical component score was 39.2±0.8 (SD) in the intervention arm and 40.1±0.8 in the comparator arm. Baseline EQ-5D VAS scores were 65.8±1.5 and 63.4±1.8 in intervention and comparator arms, respectively.

The ADVOCATE and CLASSIC studies are key RCTs demonstrating the safety and efficacy of avacopan and changes to HRQoL associated with the intervention are described in Section 7.2 Improved Quality of Life with Tavneos (avacopan).

APPENDIX J PROBABILISTIC SENSITIVITY ANALYSES

N/A

APPENDIX K Documentation for a data extract on incidence and prevalence of ANCA- incidence and prevalence of ANCA-associated vasculitis in Denmark

May 2022

DLIMI has conducted a data extract on incidence and prevalence of ANCA-associated vasculitis in Denmark.

The study is sponsored by the pharmaceutical company, Vifor Pharma Nordiska and performed by DLI MI.

DLIMI is the Data controller and Data processor.

Data access, anonymity, ethics and legal considerations
The extract has been conducted on pseudo-anonymized data and DLIMI have defined specific instructions for assessing and processing data to insure compliance with the General Data Protection Regulation (EU) 2016/679 of 27/04/2016 and the Danish Act of Processing of Personal Data Act no. 502 of 23/05/2018.

Only specialized staff with an appropriate training have access to the to the pseudo-anonymized data on the authority's secure server system – research machine at the National Data Health Authority (NDHA) and Statistics Denmark (DST). Instructions for access and processing will be accurately followed.

All analyses will be performed on pseudo-anonymized data on the authority's secure server system – research machine at The National Data Health Authority.

Data from the different registries at the protected server are linked by means of an encrypted personal identifier. Only data at the aggregated level can be exported from the server to a local PC in DLIMI.

The discretion limit is between 3-5, depending on which databases the data has been extracted from. When several databases are gathered or small populations are extracted, DST estimates a discretion limit and in this study it is small populations, so the discretion limit of 5 have been applied.

The Act of Processing of Personal Data from the Danish Registries require permission from the national Danish Health Data Authority.

Documentation

Registers applied
Danish National Patient Registry (LPR3) 2019 - 2021.

Patient population

DLIMI has extracted data relation to four patient populations with the diagnosis-codes:

DM313 Wegeners granulomatose (GPA)
DM313A Neurotiserende respiratorisk granulomatose
DM317 Mikroskopisk polyangiitis (MPA)
DM313 GPA and/or DM317 MPA

Prevalent patients are limited to individuals who have the diagnosis the 1. January in each of the years 2019, 2020 and 2021.

Incident patients are limited to individuals who received the first diagnosis during 1. January – 31. December in each of the years 2019, 2020 and 2021.

Dead patients are limited to individuals who was registered dead during 1. January – 31. December in each of the years 2019, 2020 and 2021.

Data extract

Table 1. Data Extract from LPR3

	2019	2020	2021
DM313 Wegeners granulomatose (GPA)			
Incidens (1/1 - 31/12)		168	136
Dead (1/1 -31/12)	30	38	44
Prevalens (1/1)	992	1130	1228
DM313A Nekrotiserende respiratorisk granulomatose			
Incidens (1/1 - 31/12)	<5	<5	5
Dead (1/1 -31/12)	0	0	0
Prevalens (1/1)	<5	5	10
DM317 Mikroskopisk polyangiitis (MPA)			
Incidens (1/1 - 31/12)		28	26
Dead (1/1 -31/12)	<5	<5	<5
Prevalens (1/1)	116	140	162
DM313 GPA, DM313A and/or DM317 MPA			
Incidens (1/1 - 31/12)		200	167
Dead (1/1 -31/12)			
Prevalens (1/1)	1109	1275	1400

SDS Researcher Service draws attention to the fact that there are challenges about data completeness and the data quality of reports in LPR3 at the beginning of 2019. Data in the beginning of 2019 will be a mixture of old and new reporting, that there is a data breaks due to change in the reporting structure. The data break is only a matter for 2019. The data completeness and the data quality for 2020 and 21 is again in order.

It isn't possible to extract incident patients for 2019, as LPR3 has no history from LPR2 included. with, ie. from the year before 2018. It means all patients is registered as incidens in 2019, even though they are prevalent the 1. January 2019, because they have already been diagnosed the years before 2019.

Confidential - DMC internal use only – Appendix L is attached in a separate file

APPENDIX M SUPPLERENDE ANALYSIS OF SUBGROUPS MPA AND GPA

GPA and MPA, the two main forms of AAV, have a highly overlapping pathology, both being characterised by the production of circulating autoantibodies against neutrophil-expressed antigens. ANCA are thought to be pathogenic, initiating a final common pathway of excessive neutrophil activation and subsequent tissue damage. This similarity provides a biologic basis for the efficacy of other immune-targeted approaches in patients with GPA or MPA. It also provides a rational basis for the practice of recruiting a mixed population of GPA and MPA patients to clinical studies, which are then powered only to show an overall effect across both conditions. This is important because this approach has made appropriately powered interventional clinical trials feasible in these rare diseases. The results of these trials have nonetheless been instrumental in shaping treatment guidelines for both GPA and MPA [71].

The shared biology of complement GPA and MPA suggests that targeting C5aR1 with avacopan should be efficacious in both conditions. Activation of the alternative complement pathway in an AAV context generates C5a, which acts to amplify neutrophil influx and activation, culminating in the severe necrotizing small vessel inflammation characteristic of both GPA and MPA. Thus, there was a strong rationale for avacopan continuing the historic practice of evaluating the efficacy and safety of a therapy in MPA and GPA within the same clinical programme.

The primary endpoints from ADVOCATE study by GPA or MPA classification is summarized in the table 1 and table 2 but proposes that the most relevant analysis to the demonstration of significant benefit in GPA and MPA is the combined analysis, for two reasons: the ADVOCATE study was not statistically powered to demonstrate efficacy in subgroups and these data has not been adjusted for established predictors of disease outcome, which are likely to be distributed differently between GPA and MPA patients.

For example, renal involvement in ADVOCATE study was more advanced in the MPA subgroup than in GPA (e.g., baseline eGFR was 32.1 ml/min/1.73 m2 versus 57.6 ml/min/1.73 m2 in MPA and GPA respectively for participants receiving avacopan) and renal involvement is well described as a strong predictor of outcome [235]. The apparent difference in sustained remission at Week 52 (Table 3) between GPA and MPA is unadjusted for key confounders including baseline eGFR and may therefore not reflect a true underlying difference by AAV subtype but instead confounding differences in clinical/immunological phenotype.

There are other baseline differences in the ADVOCATE study by GPA or MPA classification including in new versus relapsing disease: in the avacopan arm, there were 22.7%relapsed subjects in the MPA subgroup compared with 37.4% relapsed subjects in the GPA subgroup, which might also be anticipated to influence outcomes.

Table 1 Proportion of Subjects with Disease Remission at Week 26 per Disease Phenotype in Study CL010_168 (ITT)

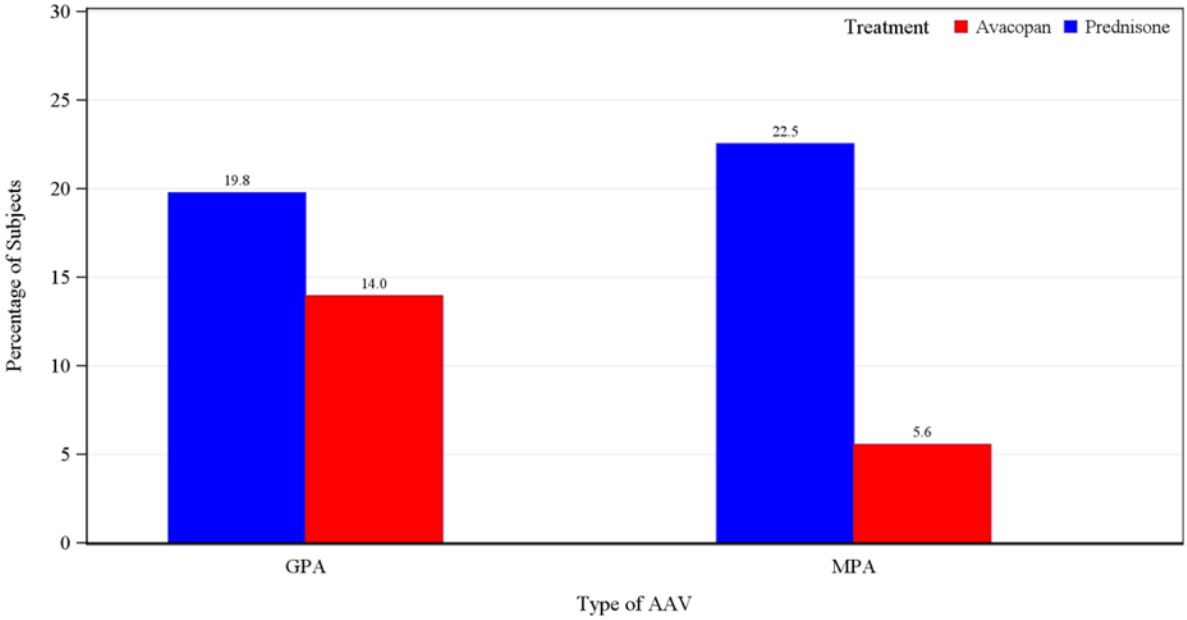
Stratification Factor	N	N(%)	95% CI	Difference in Percentages	Two-sided 95% CI for Difference
Subjects with Granulomatosis with Polyangiitis					
Prednisone	90	65 (72.2)	(61.8, 81.1)		
Avacopan	91	65 (71.4)	(61.0, 80.4)	-0.8	(-13.9, 12.3)
Subjects with Microscopic Polyangiitis					
Prednisone	74	50 (67.6)	(55.7, 78.0)		
Avacopan	75	55 (73.3)	(61.9, 82.9)	5.8	(-8.9, 20.4)

Table 2 **Proportion of Subjects with Sustained Disease Remission at Week 52 per Disease Phenotype in Study CL010_168 (ITT)**

Stratification Factor	N	N(%)	95% CI	Difference in Percentages	Two-sided 95% CI for Difference
Subjects with Granulomatosis with Polyangiitis					
Prednisone	90	52 (57.8)	(46.9, 68.1)		
Avacopan	91	56 (61.5)	(50.8, 71.6)	3.8	(-10.5, 18.0)
Subjects with Microscopic Polyangiitis					
Prednisone	74	38 (51.4)	(39.4, 63.1)		
Avacopan	75	53 (70.7)	(59.0, 80.6)	19.3	(4.0, 34.7)

Despite the potential for confounding, in general terms the direction of effect is in the same direction in analyses stratified by subgroup and any difference is in the magnitude of effect, not in its clinical relevance, with fewer relapses in both MPA and GPA avacopan subgroups compared to their respective prednisone controls. (see, for example, Figure 1 which presents relapse rates stratified by AAV subtype).

Figure 1 Proportion of Subjects Who Relapsed After Achieving BVAS=0 at Any Time in the GPA and MPA Strata in Phase 3 Study CL010_168 (ITT)



A second form of evidence supports the benefit of avacopan in GPA and MPA. Detailed glucocorticoid exposure and glucocorticoid toxicity data was collected during the study ADVOCATE study, and this is much less susceptible to confounding by differences between the GPA and MPA subgroups.

The findings of the GTI analyses are summarised in Table 3 for both GPA and MPA subgroups. Table 3 shows a benefit of avacopan in reducing glucocorticoid toxicity in both MPA and GPA patients, demonstrated by substantially lower CWS and AIS GTI scores at both Weeks 13 and 26. This is consistent with the lower glucocorticoid exposure in the study for avacopan treated patients and represents an additional important benefit to patients.

Table 3 Summary of Glucocorticoid Toxicity Index Through Week 26 in Subjects with GPA and MPA (ITT)

	Prednisone	Avacopan
Subjects with Granulomatosis with Polyangiitis		
	N=90	**N=91**
Cumulative Worsening Score		
Week 13, Mean (SD) (n)	31.3 (29.09) (88)	23.1 (27.85) (87)
Week 26, Mean (SD) (n)	46.7 (41.48) (87)	32.6 (30.00) (85)
Aggregate Improvement Score		
Week 13, Mean (SD) (n)	18.8 (35.49) (88)	9.5 (33.19) (87)
Week 26, Mean (SD) (n)	21.6 (42.85) (87)	7.6 (26.34) (85)
Subjects with Microscopic Polyangiitis		
	N=74	**N=75**
Cumulative Worsening Score		
Week 13, Mean (SD) (n)	45.2 (40.81) (73)	31.0 (35.05) (73)
Week 26, Mean (SD) (n)	70.0 (62.65) (66)	48.7 (46.10) (69)
Aggregate Improvement Score		
Week 13, Mean (SD) (n)	31.4 (45.94) (73)	12.8 (41.55) (73)
Week 26, Mean (SD) (n)	27.4 (48.31) (66)	17.1 (49.24) (69)

Note: SD=Standard deviation.
Source: CSR CL010_168, Tables 14.2.4.6.9; 14.2.4.6.10 ; 14.2.4.6.25, 14.2.4.6.26

71 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 Nov 6;371(19):1771-80.

235 Kronbichler A, Shin JI, Lee KH, Nakagomi D, Quintana LF, Busch M, et al. Clinical associations of renal involvement in ANCA-associated vasculitis. Autoimmun Rev. 2020;19:102495. p. 1-7. Epub 2020 Feb 15.

APPENDIX N: CSR CL010 168 table 14.3.1.3.3. Summary of treatment-Emergency Serious Adverse Events by System Organ Class and Preferred term by Background Therapy with Rituximab or Cyclophosphamide (Safety Population

Confidential - DMC internal use only - the Appendix N is attached in a separate file

APPENDIX O CSR CL010 168 table 14.3.1.2.1.1 Summery of Treatment-Emergency Adverse Events by Systemic Organ Class and Preferred Term by Background Therapy with Rituximab or Cyclophosphamide (safety population)

Confidential - DMC internal use only – the appendix O is attached in a separate file.

APPENDIX P CSR CL010 168 table 3 Summery and Analysis (ANOVA) of SF-16 v2.0 Change from Baseline during the Study Period (Intention to Treat Population)

Confidential - DMC internal use only – Appendix P is attached in a separate file

APPENDIX Q - LITERATURE SEARCH FOR Sundhedsrelateret QoL for End-Stage Renal Disease

Søgeprotocol

Søgespecialist	Kirsten Birkefoss, StepChange ApS
Senest opdateret	26.10.2022

Søgetermer	Der er brugt termer fra MESH (Medline) og EMTREE (Embase) samt fritekstsøgeord for at finde de referencer, der endnu ikke har fået MESH/EMTREE termer. Ellers henvises til søgestrategien side 2-5.
Inklusions- og eksklusionskriterier	**Sprog:** Ingen begrænsning **År:** 2006-2022 samt juni 2021-okt 2022 **Population:** Alle **Publikationstyper:** Systematiske reviews, metaanalyser, randomiserede studier, observationelle studier, kvalitative studier

Informationskilder

DATABASER	INTERFACE	FUND	DATO FOR SØGNING
Medline	OVID	652	24.10.2022
Embase	OVID	567	24.10.2022
Medline (6/2021-10/2022)	OVID	128	26.10.2022
Embase (6/2021-10/2022)	OVID	111	26.10.2022

Note

- Søgetermer og inklusions- og eksklusionskriterier er tilpasset de enkelte databaser.
- Dubletter er så vidt muligt frasorteret ved hjælp af RefWorks. De fundne referencer er overført til Microsoft Word fil.

SØGESTRATEGI

Medline

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions** 1946 to October 21, 2022
Search Strategy:

#	Searches	Results
1	exp Renal Insufficiency, Chronic/	130574
2	(End-Stage Kidney Disease or End Stage Kidney Disease or End-Stage Renal Disease or End Stage Renal Disease or Renal Failure or kidney failure or ESRD).ti,bt,ab,kf.	145693
3	or/1-2	223030
4	exp Dialysis/	24048
5	(dialys* or hemodialys* or hemo-dialys* or haemodialys* or haemo-dialys*).ti,bt,ab,kf.	176372
6	or/4-5	192360
7	3 and 6	76670
8	(((health-related or health related) adj1 ("quality of life" or QoL)) or HRQoL or HRQL or life quality or HUSV or Health-State Utility Value*).ti,bt,ab,kf.	67078
9	7 and 8	847
10	exp Systematic Reviews/ or exp meta analysis/ or exp meta-analysis/	178073
11	(((systematic* or method* or rapid or integrative or umbrella) adj2 (review* or overview* or study or studies or search* or approach* or analysis or evaluation)) or meta analy* or meta-analy* or metaanaly*).ti,bt,ab,kf.	963205
12	(pool* adj1 (data or analys* or studies)).ti,ab.	28078
13	Cochrane.jw.	16115
14	exp randomized controlled trial/ or exp "randomized controlled trials as topic"/ or exp controlled clinical trial/	824668
15	exp Random allocation/	106889
16	(((random* or cluster-random* or quasi-random* or control?ed or crossover or cross-over or blind* or mask*) adj3 (trial*1 or study or studies or analy*)) or rct).ti,bt,ab,kf.	803871
17	(randomization or placebo* or comparison).ti,bt,ab,kf.	1416551
18	((single-blind* or double-blind* or triple-blind*) adj2 (method or studies)).ti,bt,ab,kf.	4433
19	((single or double or triple) adj2 (blind*3 or mask*3) adj2 (method or studies)).ti,bt,ab,kf.	4517
20	((patient* or person* or participant* or population* or allocat* or assign*) adj3 random*).ti,bt,ab,kf.	292075
21	("research support, american recovery and reinvestment act" or research support, nih, extramural or research support, nih, intramural or research support, non us gov't or research support, us gov't, non phs or research support, us gov't, phs).pt.	10011760
22	exp comparative study/ or exp evaluation studies/ or exp multicenter study/ or exp observational study/ or exp twin study/ or exp validation studies/	2569798
23	Epidemiologic studies/	9190

24	exp Case-Control Studies/ or exp Cohort Studies/ or Controlled Before-After Studies/ or Cross-Sectional Studies/	2999370
25	((Epidemiologic or cohort* or perspective or prospective or longitud* or follow-up or follow up or followup or retro-spective or retrospective or case-control* or case control* or observational or cross-section* or cross section* or multi-cent* or multicent* or evaluation or comparative or intervention or provocat* or validation or qualitative) adj3 (study or studies or trial*1 or analys*)).ti,bt,ab,kf.	2297745
26	exp Qualitative Research/	77541
27	exp "Surveys and Questionnaires"/	1186975
28	exp Interviews as Topic/	66803
29	exp Focus Groups/	34833
30	Empirical research/	3889
31	Narration/	9842
32	((qualitative or empirical or action or ethnographic or ethnological or ethnonursing or ethnomedicine or phenomenological or narrative or narration) adj3 (research or study or study or method* or design or synthes* or analy*)).ti,bt,ab,kf.	232469
33	(metasynthes* or meta-synthes* or meta synthes* or metaethnograph* or meta-ethnograph* or meta ethnograph*).ti,bt,ab,kf.	2436
34	(interview* or questionnaire* or survey*).ti,bt,ab,kf.	1580976
35	(focus group* or focus-group* or focusgroup*).ti,bt,ab,kf.	59701
36	(field work or fieldwork or field-work or key informant* or ground work or groundwork or narration or narrative*).ti,bt,ab,kf.	88563
37	(evidence synthes* or realist synthes*).ti,bt,ab,kf.	7140
38	(Grounded theory or naturalistic inquiry).ti,bt,ab,kf.	14398
39	or/10-38	15667342
40	9 and 39	768
41	40 not (letter or newspaper article or comment or conference).pt.	766
42	exp Animals/ not (humans/ and exp animals/)	5057996
43	41 not 42	766
44	limit 43 to yr="2006-2022"	652
45	43 and ("202106*" or "202107*" or "202108*" or "202109*" or "202110*" or "202111*" or "202112*" or "2022*").dt,ez,ed.	128

Embase

Database(s): **Embase** 1974 to 2022 October 24
Search Strategy:

#	Searches	Results
1	exp chronic kidney failure/	133231

2	(End-Stage Kidney Disease or End Stage Kidney Disease or End-Stage Renal Disease or End Stage Renal Disease or Renal Failure or kidney failure or ESRD).ti,bt,ab,kf.	220545
3	or/1-2	310243
4	dialysis/ or hemodialysis/ or peritoneal dialysis/	197326
5	(dialys* or hemodialys* or hemo-dialys* or haemodialys* or haemo-dialys*).ti,bt,ab,kf.	251934
6	or/4-5	293591
7	3 and 6	103259
8	(((health-related or health related) adj1 ("quality of life" or QoL)) or HRQoL or HRQL or life quality or HUSV or Health-State Utility Value*).ti,bt,ab,kf.	102710
9	7 and 8	1115
10	exp Systematic Review/ or exp meta analysis/	494836
11	(((systematic* or method* or rapid or integrative or umbrella) adj2 (review* or overview* or study or studies or search* or approach* or analysis or evaluation)) or meta analy* or meta-analy* or metaanaly*).ti,bt,ab,kf.	1143178
12	(pool* adj1 (data or analys* or studies)).ti,ab.	42479
13	Cochrane.jx.	23810
14	exp randomized controlled trial/	735061
15	(((random* or cluster-random* or quasi-random* or control?ed or crossover or cross-over or blind* or mask*) adj3 (trial*1 or study or studies or analy*)) or rct).ti,bt,ab,kf.	1112825
16	(randomization or placebo* or comparison).ti,bt,ab,kf.	1885896
17	((single-blind* or double-blind* or triple-blind*) adj2 (method or studies)).ti,bt,ab,kf.	6735
18	((single or double or triple) adj2 (blind*3 or mask*3) adj2 (method or studies)).ti,bt,ab,kf.	6859
19	((patient* or person* or participant* or population* or allocat* or assign*) adj3 random*).ti,bt,ab,kf.	407263
20	Observational study/ or Multicenter study/ or Evaluation study/ or exp comparative study/ or exp case control study/ or intervention study/ or exp longitudinal study/ or prospective study/ or retrospective study/ or Follow up/ or validation study/ or cohort analysis/ or cross-sectional study/ or crossover procedure/ or double blind procedure/ or single blind procedure/	6306358
21	((Epidemiologic or cohort* or perspective or prospective or longitud* or follow-up or follow up or followup or retro-spective or retrospective or case-control* or case control* or observational or cross-section* or cross section* or multi-cent* or multicent* or evaluation or comparative or intervention or provoca* or validation or qualitative) adj3 (study or studies or trial*1 or analys*)).ti,bt,ab,kf.	3287273
22	exp Qualitative Research/	106501
23	exp Questionnaire/	861774
24	exp Interview/	343365
25	Empirical research/	6932
26	Narrative/	19291

27	((qualitative or empirical or action or ethnographic or ethnological or ethnonursing or ethnomedicine or phenomenological or narrative or narration) adj3 (research or study or study or method* or design or synthes* or analy*)).ti,bt,ab,kf.	278268
28	(metasynthes* or meta-synthes* or meta synthes* or metaethnograph* or meta-ethnograph* or meta ethnograph*).ti,bt,ab,kf.	2709
29	(interview* or questionnaire* or survey*).ti,bt,ab,kf.	2084026
30	(focus group* or focus-group* or focusgroup*).ti,bt,ab,kf.	74451
31	(field work or fieldwork or field-work or key informant* or ground work or groundwork or narration or narrative*).ti,bt,ab,kf.	98698
32	(evidence synthes* or realist synthes*).ti,bt,ab,kf.	7838
33	(Grounded theory or naturalistic inquiry).ti,bt,ab,kf.	17904
34	or/10-33	10723134
35	9 and 34	945
36	35 not (letter or note or conference abstract or editorial).pt.	677
37	limit 36 to yr="2006-2022"	567
38	36 and ("202106*" or "202107*" or "202108*" or "202109*" or "202110*" or "202111*" or "202112*" or "2022*").dc,dd.	113
39	limit 38 to human	111

Der blev identificeret 163 referencer.

Efter gennemgang af de 163 abstracts blev 21 referencer identificeret, som mulig relevante med fokus på primært europæiske populationer, ESRD, dialyse og nyretransplanterede, antal af patienter samt QoL effektmål.

Efter fuldtekst gennemgang af de 21 artikler blev artiklen Fletcher BR, Damery S, Aiyegbusi OL, Anderson N et al. Symptom burden and health-related quality of life in chronic kidney disease: A global systematic review and meta-analysis. PLoS Med 2022 19(4), e1003954. http://doi.org/10 1371/journal.pmed. 1003934 [236]

APPENDIX R - Table 14.3.1.1.1 Summery of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

Confidential – DMC internal use only – Appendix R is attached in a separate file

APPENDIX S – Table 14.3.1.6.2 Summary of Treatment – Emergent Serious Adverse Events Possibly Related to Study Treatment (Prednisone/Placebo) by System Organ Class and Preferred Term (Safety Population)

Confidential – DMC internal use only – Appendix S is attached in a separate file

APPENDIX T – CSR CL010-168 Table 14.2.4.1 Summary and Analysis (MMRM) of Glucocorticoid Toxicity Index Cummulative Worsening Score (GTI-CWS) Through week 26 (Intention to Treat Population)

Confidential – DMC internal use only – Appendix T is attached in a separate file

APPENDIX U – CSR CL010-168 Table 14.2.4. Summary of Glucocorticoid Toxicity Index Cummulative Worsening Score (GTI-CWS) Individuel Components Through week 26 (Intention to Treat Population)

Confidential – DMC internal use only – Appendix U is attached in a separate file

APPENDIX V – CSR CL010-168 Table 14.2.4.3 Summary and Analysis (MMRM) of Glucocorticoid Toxicity Index Aggregate Improvement Score (GTI-AIS) Through week 26 (Intention to Treat Population)

Confidential – DMC internal use only – Appendix V is attached in a separate file

APPENDIX W – CSR CL010-168 Table 14.2.4.5 Summary of Glucocorticoid Toxicity Index Specific List Items by visit (Intention to Treat Population)

Confidential – DMC internal use only – Appendix W is attached in a separate file

APPENDIX AA – CSR CL010-168 Table MHRA9 Number of Subjects Censored at Each Time Point for Time to Relapse (Intention to Treat Population)

Confidential – DMC internal use only – Appendix AA is attached in a separate file

APPENDIX AB – CSR CL010-168 THTA1 Summary of Baseline Composite Glucocorticoid Toxicity Index (GTI) (Intention to Treat Population)

Confidential – DMC internal use only – Appendix AB is attached in a separate file

APPENDIX AC – CSR CL010-168 Table THTA2 Summary of Glucocorticoid Toxicity Index Aggregate Improvement Score. Individual Components Categories Through Week 26 (Intention to Treat Population)

Confidential – DMC internal use only – Appendix AC is attached in a separate file

APPENDIX AD – CSR CL010-168 Table THTA3 Summary of Glucocorticoid Toxicity Index Cummulative Worsening Score. Individual Components Categories Through Week 26 (Intention to Treat Population)

Confidential – DMC internal use only – Appendix AD is attached in a separate file

APPENDIX AE – Summary of EQ-5D-5L Health Scale Dimensions Values during the Study Period (Intent-To-Treat Population - CONFIDENTIAL

Confidential – DMC internal use only – Appendix AE is attached in a separate file

APPENDIX AF – Explorative Analysis of Time to Relapse from the First Time Point when BVAS of 0 was Achieved as Assessed by the Adjudication Committee up to Week 26 (Intent-To-Treat Population - CONFIDENTIAL

Confidential – DMC internal use only – Appendix AF is attached in a separate file

APPENDIX AG – Summary of Treatment Changes (Intent-To-Treat Population) - CONFIDENTIAL

Confidential – DMC internal use only – Appendix AG is attached in a separate file

APPENDIX AH – Kaplan-Meier Plot of Time to Relapse as Assessed by the Adjudication Committee (Intent-To-Treat Population) - CONFIDENTIAL

Confidential – DMC internal use only – Appendix AH is attached in a separate file

APPENDIX AI – Computer EQ-5D-5L crosswalk index values with STADA using the United Kingdom (UK) EQ-5D-5L Dolan value Set – CONFIDENTIAL

Confidential – DMC internal use only – Appendix AI is attached in a separate file

APPENDIX AJ – Mean (SD) Index Score based on EQ-5D-5L. Values by Adjudicator Assessed Remission/Relapse (England: Intent-To-Treat Population) - CONFIDENTIAL

Confidential – DMC internal use only – Appendix AJ is attached in a separate file

APPENDIX AK – Summary of Study Supplied and Non-Study Supplied Glucocorticoid Use up to Week 26 (Intent-to-Treat Population) - CONFIDENTIAL

Confidential – DMC internal use only – Appendix AK is attached in a separate file

APPENDIX AL – Summary of Total Glucocorticoid Dose (Intent-to-Treat Population) - CONFIDENTIAL

Confidential – DMC internal use only – Appendix AL is attached in a separate file

APPENDIX AM – Summary of Total Glucocortocoid Dose All Subjects receiving IV Rituximab Background Therapy (Intent-to-treat Population) - CONFIDENTIAL

Confidential – DMC internal use only – Appendix AM is attached in a separate file

APPENDIX AN – Summary of Total Glucocortocoid Dose All Subjects receiving IV or oral cyclophosphamide Background Therapy (Intent-to-treat Population) - CONFIDENTIAL

Confidential – DMC internal use only – Appendix AN is attached in a separate file

APPENDIX AO – Proportion of Subjects with Total Glucocorticoid Daily Dose ≥ 7,5 mg/day and ≥ 15 mg/day of Prednisone equivalent (Intent-to-treat) - CONFIDENTIAL

Confidential – DMC internal use only – Appendix AO is attached in a separate file

APPENDIX AQ - Proportion of Subjects with Total Glucocorticoid Daily Dose ≥ 7,5 mg/day and ≥ 15 mg/day of Prednisone equivalent. All Subjects receiving IV or Oral Cyclophosphamide Background Therapy (Intent-to-treat) - CONFIDENTIAL

Confidential – DMC internal use only – Appendix AQ is attached in a separate file