NICE National Institute for Health and Care Excellence

Slides for public observers

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

Lead team presentation

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ERG: Kleijnen Systematic Reviews

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Company: Vifor Pharma

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Avacopan (Tavneos, Vifor Pharma)

Appraisal population narrower than NICE scope, but in line with European MA and ADVOCATE trial

Marketing authorisation (EMA approved, 11/01/2022)	Avacopan, 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)
Mechanism of action	Highly selective C5aR1 antagonist
Dosage & administration	3 x 10 mg capsules taken orally twice per day with food
Price	List price: [redacted] capsule of avacopan ([redacted] capsule pack) PAS price: [redacted] capsule of avacopan ([redacted] capsule pack)

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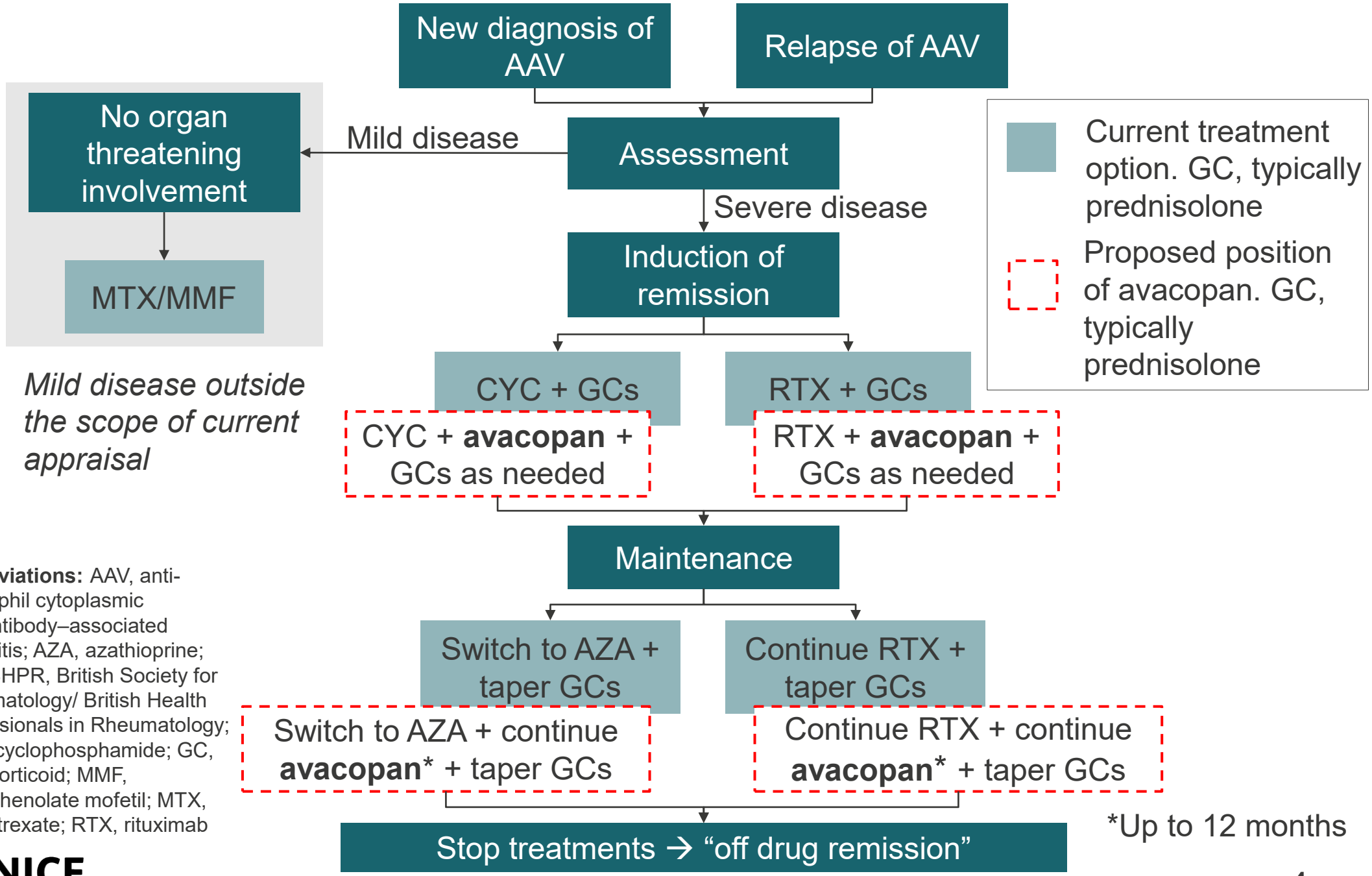
C5aR1, C5a receptor 1; EMA, European Medicines Agency; MA, marketing authorisation; mg, milligram

Disease background

- Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) is group of rare autoimmune conditions characterised by blood vessel inflammation
  - Autoantibodies attach to neutrophils and target small blood vessels causing inflammation
  - Can affect kidneys, lungs, sinuses, eyes, ears, nerves and skin. When kidneys are involved, people can develop end-stage renal disease
  - Typically present with non-specific symptoms so AAV often misdiagnosed
- 3 variants of AAV: GPA, MPA and EGPA
  - **Granulomatosis with polyangiitis (GPA)**: Most common type. Inflammation usually affects upper and lower respiratory tract, and small to medium vessels (e.g., capillaries, venules, arterioles, arteries, and veins)
    - Estimated prevalence of GPA: 2.3 to 146 cases per 1 million persons[1]
  - **Microscopic polyangiitis (MPA)**: Inflammation mostly affecting small vessels. Kidney involvement (glomerulonephritis) is common, but can also involve lungs and skin. Glomerulonephritis impairs kidney filtration and can cause permanent damage to kidneys
    - Estimated prevalence of MPA: 9 to 94 cases per 1 million persons[1]
  - **Eosinophilic granulomatosis with polyangiitis (EGPA)** is not a proposed indication

1. Kitching et al. 2020

Treatment pathway and proposed position



Mild disease outside the scope of current appraisal

Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; AZA, azathioprine; BSR/BHPR, British Society for Rheumatology/ British Health Professionals in Rheumatology; CYC, cyclophosphamide; GC, glucocorticoid; MMF, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab

*Up to 12 months

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Adapted from BSR/BHPR guideline for the management of adults with ANCA-associated vasculitis

Patient and carer perspectives

- ANCA-associated vasculitis (AAV) comes in different forms according to type, degree of disease aggression, organs affected and delay to diagnosis
- When not diagnosed and treated promptly, it can progress rapidly to multiple organ failure and death
- Symptoms include: rash, fatigue, night sweats
- Treatment involves high dose glucocorticoids, cyclophosphamide or rituximab and increased prednisolone during flares
- There are many side effects of glucocorticoids:
  - increased appetite and weight gain, common complaint of “moon face”
  - risk of diabetes
  - cataracts
  - osteoporosis
- Many patients want an alternative to glucocorticoids → avacopan may reduce need for prednisolone

> “Vasculitis affected my sinuses, lungs, abdomen, skin and joints. I couldn’t move at all; the pain was unbearable”

> “My treatment started with 60mg prednisolone daily… My weight increased, my face got round, and I didn’t recognise myself. I started having bad mood swings and my rheumatologist and GP agreed these were side effects of the steroids.”

Clinical expert perspectives

Current care

- Care pathway well defined but variation depending on presenting organ features and specialty leading management
  - Variation in access to specialised multidisciplinary teams
- Managed in 2 phases:
  1. Induction therapy to control inflammation, induce disease remission and reduce damage from disease
  2. Maintenance therapy to prevent disease relapsing
- Clinicians are trying to reduce exposure to rituximab because of risks of reduced response to vaccination (e.g. COVID-19)
- Infection and CVD are commonest causes of death in people with AAV both are associated with corticosteroid usage (Wu et al. 2019 and Pujades-Rodriguez et al. 2020)

Avacopan and implementation

- Avacopan may reduce glucocorticoid use and associated toxicity → likely beneficial for life expectancy
- Implementation: would it be given at or in discussion with a specialised centre?
  - Patients could present acutely for induction treatment to any NHS Trust
  - Most important aspect of care is rapid initiation of treatment, so appropriate not to limit initiation by requiring involvement of specialised centre
  - If recommended, it should be available in Rheumatology and Renal specialist centres and for shared care with primary care

AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; COVID-19, coronavirus 2019 pandemic; CVD, cardiovascular disease; e.g., for example

Summary

Comparators	Standard of care • Induction: CYC + GCs or RTX + GCs • Maintenance: AZA
Clinical trial – ADVOCATE (N=331)	RCT comparing: • Avacopan + CYC then AZA or RTX • Prednisone + CYC then AZA or RTX
Key result - ADVOCATE	At week 52, 65.7% of people in the avacopan group vs 54.9% in prednisone group had sustained remission
Model	Markov model. 9 health states relating to remission, relapse, ESRD and death
Company deterministic ICER	£19,441/QALY
ERG deterministic ICER	£40,516/QALY

AZA, azathioprine; CYC, cyclophosphamide; ESRD, end-stage renal disease; GC, glucocorticoids; ICER, incremental cost-effectiveness ratio; N, number; QALY, quality-adjusted life year; RCT, randomised controlled trial; RTX, rituximab

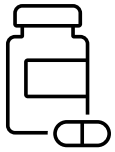
ADVOCATE trial summary

Randomised, double-blind, active-controlled phase 3 trial

Population | **Treatment** | **Endpoint**

- Adults with GPA or MPA
- Anti-PR3 or anti-MPO antibody positive
- At least 1 major item, 3 minor items, or 2 renal items of proteinuria and hematuria in BVAS†
- eGFR ≥ 15 mL/minute/1.73 m^2

A



Prednisone + CYC then AZA or RTX n=165

1:1

B

Avacopan + CYC then AZA or RTX n=166

Primary: Proportion with disease remission at weeks 26 & 52

- BVAS = 0
- No glucocorticoids in 4 weeks before assessment
- No BVAS > 0 in 4 weeks before week 26
- No relapse from week 26 to 52

Secondary:

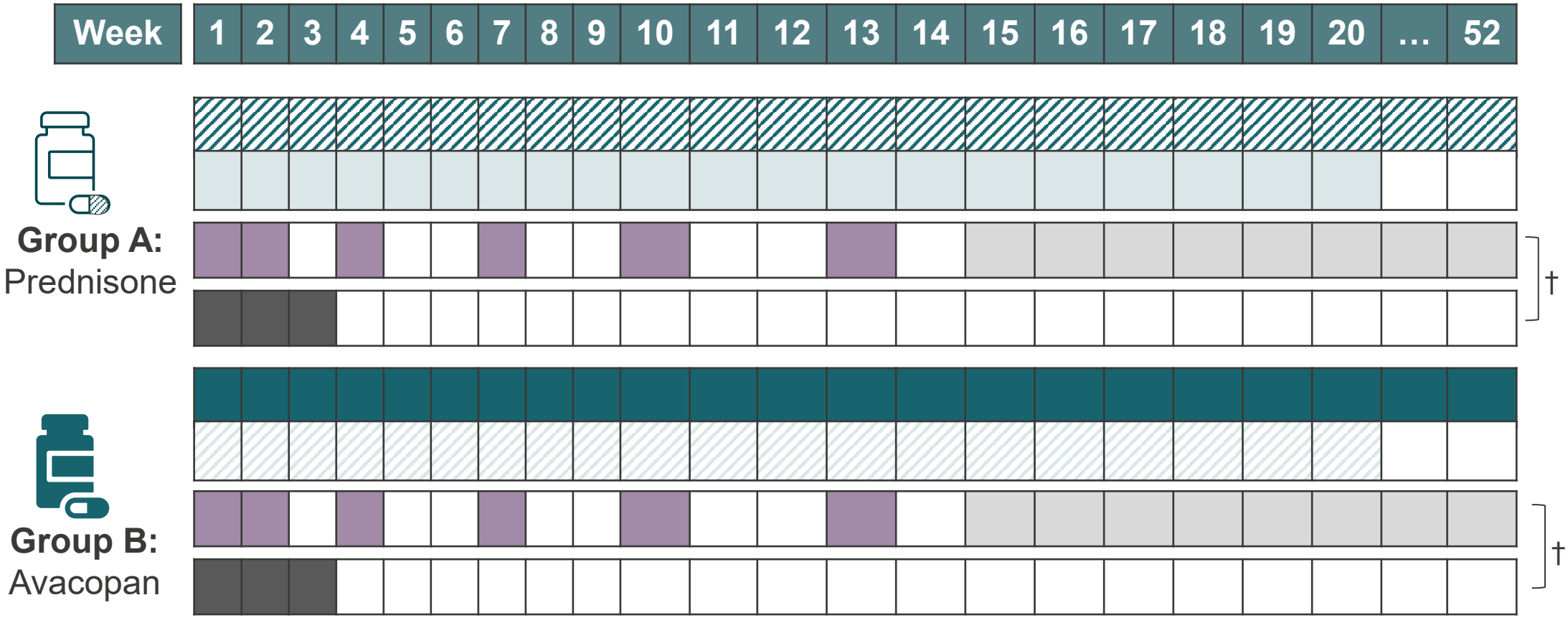
- Glucocorticoid-induced toxicity
- BVAS = 0 at week 4
- Change in HRQoL
- Proportion with relapse
- Change in VDI
- In people with renal disease
  - Change in eGFR
  - Change in UACR
  - Change in urinary MCP-1 creatine ratio

†Birmingham Vasculitis Activity Score

57 clinical features across: general, cutaneous, mucous membranes/eyes, ENT, chest, cardiovascular, abdominal, renal, nervous system, "other"

AZA, azathioprine; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; ENT, ear, nose & throat; GPA, Granulomatosis with polyangiitis; HRQoL, health-related quality of life; m^2, square metre, MCP, monocyte chemoattractant protein-1; MPA, Microscopic polyangiitis; MPO, Myeloperoxidase; mL, millilitre; PR3, Proteinase 3; RTX, rituximab; UACR, urinary albumin to creatine ratio; VDI, Vasculitis Damage Index

ADVOCATE trial, study treatments



†Cyclophosphamide then azathioprine OR rituximab and no pre-specified maintenance

Avacopan matching placebo | Prednisone (tapering) | IV Cyclophosphamide*

Azathioprine | Rituximab | Prednisone matching placebo | Avacopan

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People in both groups could have non-study supplied GCs as needed

*oral cyclophosphamide as alternative, given daily from day 1 to day before week 15

GC, glucocorticoid; IV, intravenous

ADVOCATE results (1/2)

Outcome	Treatment group	% (n/N) or LSM ± SEM	Estimated common difference (95% CI, p-value) or p-value
Remission at 26 weeks*	Avacopan group	72.3% (120/166)	3.4% (-6.0 to 12.8, p<0.001 for non-inferiority and p=0.24 for superiority)
	Prednisone group	70.1% (115/164)	
Sustained remission at 52 weeks	Avacopan group	65.7% (109/166)	12.5% (2.6 to 22.3, p<0.001 for non-inferiority and p=0.007 for superiority)
	Prednisone group	54.9% (90/164)	
Glucocorticoid-induced toxicity (GTI) cumulative worsening score at 26 weeks	Avacopan group	39.7±3.43	p=0.0002
	Prednisone group	56.6±3.45	

*Defined as BVAS of 0 at week 26; no GCs for AAV in 4 weeks before week 26; no BVAS >0 in 4 weeks before week 26

Clinical experts

BVAS = 0 implies no evidence of disease activity, clinically significant response

ERG

- GCs are a confounder
- Large proportion in avacopan arm had non-study GCs so comparison appears to be 'avacopan + non-study supplied GCs' vs 'study GCs + non-study supplied GCs'→ concerned about meaningfulness of comparison (slides 16 to 17)

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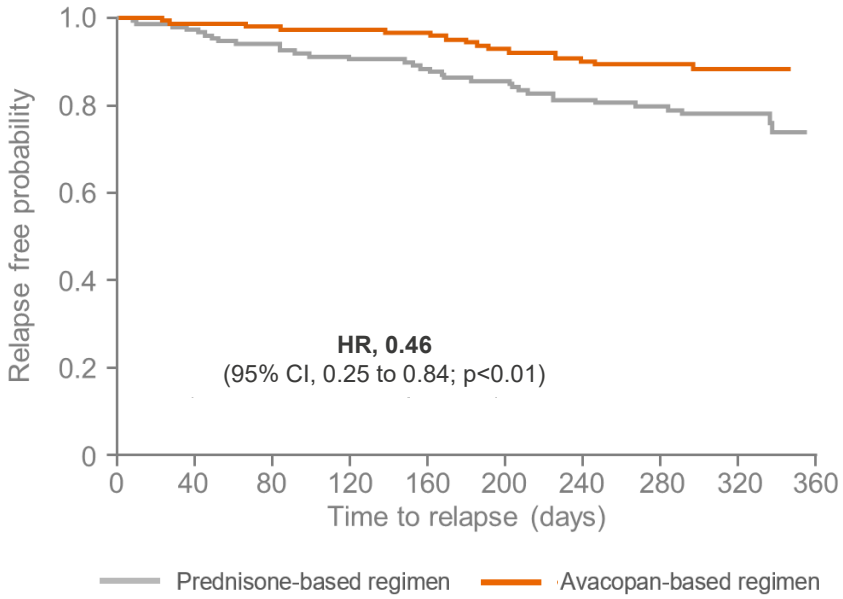
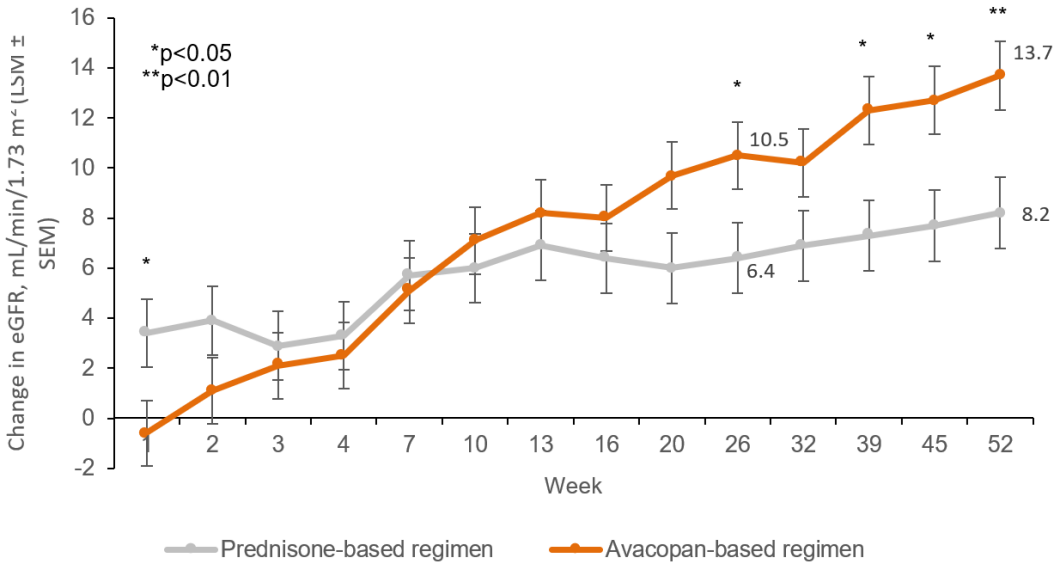
AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; BVAS, Birmingham Vasculitis Activity Score; CI, confidence interval; GC, glucocorticoid; LSM, least squares mean; n, number of participants; SEM, standard error of measurement

ADVOCATE results (2/2)

Relapse-free probability following remission



Change from baseline in eGFR in people with renal disease at baseline (based on BVAS) and baseline eGFR <30 mL/min/1.73 m^2



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BVAS, Birmingham Vasculitis Activity Score; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LSM, least squares mean; m^2 , square metre; mL/min, millilitre per min; SEM, standard error of measurement

Subgroup results - remission

Subgroup	Time	Avacopan: % (n/N)	Prednisone: % (n/N)
Patients receiving RTX	Week 26	77.6% (83/107)	75.7% (81/107)
	Week 52	71.0% (76/107)	56.1% (60/107)
Patients receiving CYC	Week 26	62.7% (37/59)	59.6% (34/57)
	Week 52	55.9% (33/59)	52.6% (30/57)
Anti-PR3+ patients	Week 26	70.8% (51/72)	71.4% (50/70)
	Week 52	59.7% (43/72)	57.1% (40/70)
Anti-MPO+ patients	Week 26	73.4% (69/94)	69.1% (65/94)
	Week 52	70.2% (66/94)	53.2% (50/94)
Newly diagnosed disease	Week 26	66.1% (76/115)	66.7% (76/114)
	Week 52	60.9% (70/115)	57.9% (66/114)
Relapsed disease	Week 26	86.3% (44/51)	78.0% (39/50)
	Week 52	76.5% (39/51)	48.0% (24/50)
Patients with GPA	Week 26	71.4% (65/91)	72.2% (65/90)
	Week 52	61.5% (56/91)	57.8% (52/90)
Patients with MPA	Week 26	73.3% (55/75)	67.6% (50/74)
	Week 52	70.7% (53/75)	51.4% (38/74)

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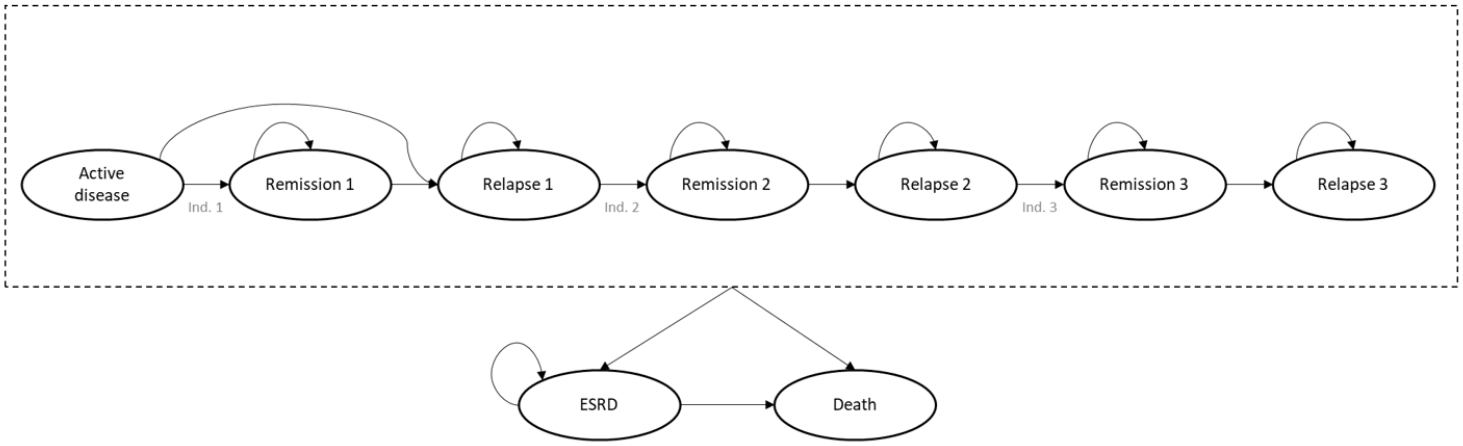
CYC, cyclophosphamide; GPA, Granulomatosis with polyangiitis; MPA, Microscopic polyangiitis; MPO, Myeloperoxidase; PR3, Proteinase 3; RTX, rituximab

Company's Markov model



Population	People with newly diagnosed or relapsed GPA or MPA, cohort starting age = 60 years	
Intervention	**Induction**	**Maintenance**
	avacopan + CYC	avacopan + AZA (7 cycles) then AZA (19 cycles)
	avacopan + RTX	avacopan + AZA (7 cycles) then AZA (19 cycles)
Comparators	CYC + GCs	AZA (26 cycles)
	RTX + GCs	AZA* (26 cycles)
Outcomes	Mortality; organ damage; remission rate and duration; GC toxicity and related AEs; sustained GC-free remission; change in renal function; immunosuppressants and GCs use; adverse effects of treatment; risk of infection; HRQoL	

Company

- 40 year horizon
- 28-day cycle with half-cycle corrections
- Relapse 1 & 2 each have tunnel states for 6 cycles of induction therapy
- Transitions through model based on disease remission or relapse until ESRD, 3rd relapse or death
- *AZA as maintenance after RTX is a deviation from ADVOCATE, based on assumption from TA308
- RTX maintenance therapy is a key issue (slide 18)

AE, adverse event; AZA, azathioprine; BSR/BHPR, British Society for Rheumatology/ British Health Professionals in Rheumatology; CYC, cyclophosphamide; ESRD, end-stage renal disease; GC, glucocorticoid; GPA, Granulomatosis with polyangiitis; HRQoL, health-related quality of life; MPA, Microscopic polyangiitis; RTX, rituximab

Key issues

Model driver Unknown impact Small impact

	Issue description	Questions	Impact
2	Glucocorticoids in avacopan group may have biased effect estimates	Does the inclusion of glucocorticoids in the intervention group bias the effect estimates?	
4	Rituximab maintenance therapy	Should rituximab maintenance treatment be included in the cost-effectiveness estimates?	
5	ESRD hazard ratio	Is the single study estimate or pooled HR for ESRD most appropriate?	
7	Hospitalisation costs	Is the company or ERG approach to hospitalisation costs most appropriate?	
8	Representativeness of healthcare costs	Do the modelled healthcare costs reflect those in the NHS?	

Partially resolved/for brief discussion Unresolved, for discussion

NICE

ESRD, end-stage renal disease; GC, glucocorticoid; HR, hazard ratio

Resolved issues

Model driver | Unknown impact | Small impact

Issue	Technical engagement description	Impact
Narrower population than scope	Appraisal population narrower than scope (excludes EGPA) but reflects clinical trial and EMA MA population: adults with GPA or MPA	
Comparator treatments	ERG noted company's comparators differed from those in NICE scope but reflect clinical practice in the NHS	
ESRD transition probability	Different approaches to estimate ESRD transition probability. Company calibrated model estimates with published evidence. ERG happy with company's approach	
Transition probabilities from active disease and remission into relapse	Company updated transition probabilities and ERG is happy with new approach	

Resolved

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EGPA, eosinophilic granulomatosis with polyangiitis EMA, European Medicines Agency; ESRD, end-stage renal disease; GPA, Granulomatosis with polyangiitis; MPA, Microscopic polyangiitis

Issue 2: Glucocorticoids in intervention (1/2)

Background

In ADVOCATE trial, people in both avacopan and prednisone-based regimen arms had non-study supplied glucocorticoids
→ ERG think glucocorticoids should be stated as part of intervention and may bias estimates

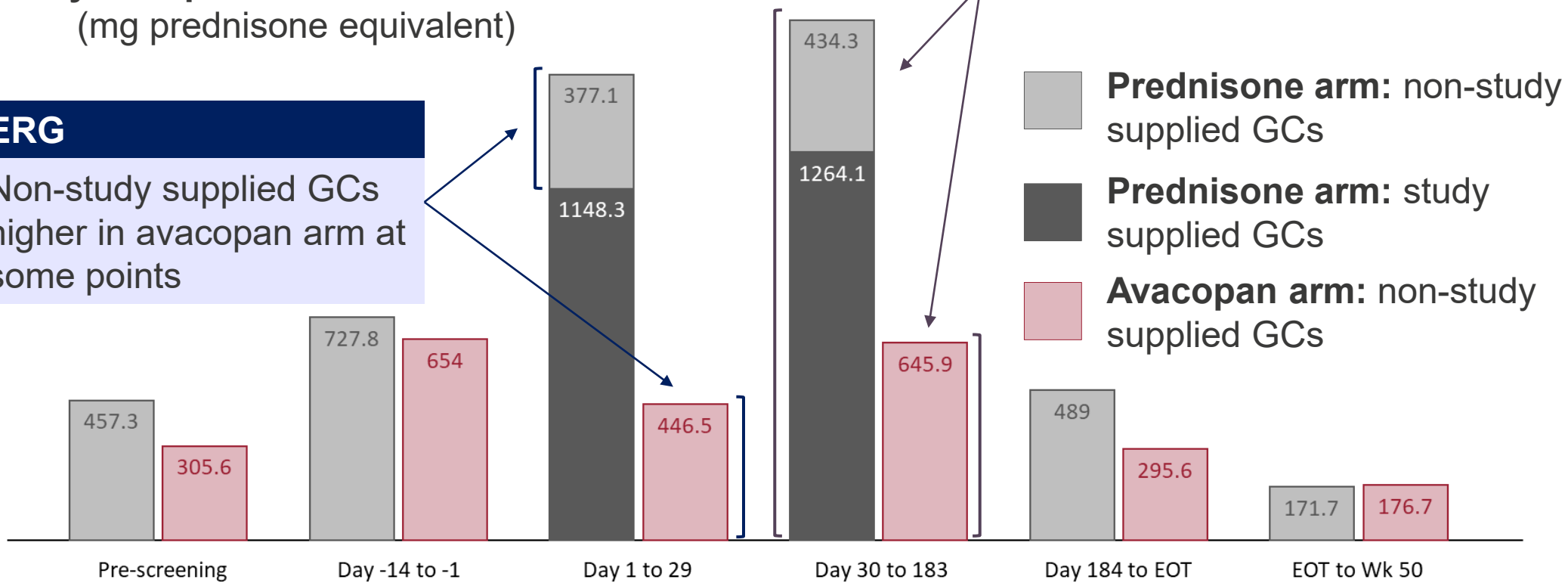
Mean cumulative glucocorticoid dose by time period in ADVOCATE
(mg prednisone equivalent)

Company

Total GC use higher in prednisone arm

ERG

Non-study supplied GCs higher in avacopan arm at some points



EoT, end of treatment; GCs, glucocorticoids; mg, milligram; Wk, week

Issue 2: Glucocorticoids in intervention (2/2)

Company

- ADVOCATE study protocol envisioned some GCs in both groups during screening and prior to randomisation; as co-administration with RTX and to manage adrenal insufficiency
- In trial, extra GCs given for AAV relapse in line with expected use of avacopan in practice
- GC use reasonably balanced between groups so benefits can be ascribed to avacopan
- Cost and adverse events of GCs in model for both intervention and comparator

Clinical experts

- Unlikely to significantly bias outcome if non-study steroid use similar in treatment arms
- Steroids during screening may have reduced effect estimates on toxicity of intervention but less likely to impact effect size at 6 or 12 months
- Steroids with intervention during screening and rescue reflects practice

	Avacopan arm (N = 166)	Prednisone arm (N = 164)
Non-study GC use* , n (%)		
Day 1 to EoT**	145 (87.3)	149 (90.9)
Non-study supplied GCs Day 1 to EoT, mg		
Mean (SD)	1348.9 (2040.29)	1265.3 (1650.64)
Total (study + non-study) GCs Day 1 to EoT, mg		
Mean (SD)	1348.9 (2040.29)	3654.5 (1709.83)

ERG

- Mean non-study supplied GCs higher in avacopan
- Concerns remain due to large proportion in avacopan arm with non-study GCs (87%)

Does the inclusion of glucocorticoids in the intervention group bias the effect estimates?

AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; EoT, end of treatment; IV, intravenous; GC, glucocorticoid; N, number; mg, milligram; RTX, rituximab; SD, standard deviation

Issue 4: Rituximab maintenance treatment

Background

Only AZA modelled as maintenance treatment, but BSR/BHPR guideline states RTX may be used

Company

- RTX maintenance included as option, but not in base case
- Patients with avacopan + RTX induction may continue RTX maintenance but no ITC due to lack of data (explored)
- RTX maintenance effects would 'cancel out' if in both arms

Clinical experts

- SoC maintenance: AZA + low dose corticosteroids
- RTX used in small eligible subset
- RTX inhibits response to some vaccines so AZA may be preferrable

NHS England Clinical Commissioning Policy - rituximab

RTX maintenance therapy only commissioned when:

1. Person is in trial with B cell suppression maintenance; **OR**
2. Relapse requiring re-induction occurred after RTX induced remission; **OR**
3. RTX was required to induce remission in CYC refractory disease and relapse has high organ damage risk

- **AND** treatment decision made with specialised centre **AND** given opportunity for clinical trial **AND** registered with UKIVAS
- Maintenance therapy stopped after 2 years or earlier

ERG

- Company noted RTX comparison was non-adjusted naïve comparison and explorative
- Suggested company explore observational data for RTX maintenance, not provided

Should rituximab maintenance treatment be included in the cost-effectiveness estimates?

AZA, azathioprine; CYC, cyclophosphamide; BSR/BHPR, British Society for Rheumatology/ British Health Professionals in Rheumatology; ITC, indirect treatment comparison; RTX, rituximab; SoC, standard of care; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; UKIVAS, UK and Ireland Vasculitis Rare Disease Group

Key issues

Model driver | Unknown impact | Small impact

	Issue description	Questions	Impact
2	Glucocorticoids in avacopan group may have biased effect estimates	Does the inclusion of glucocorticoids in the intervention group bias the effect estimates?	
4	Rituximab maintenance therapy	Should rituximab maintenance treatment be included in the cost-effectiveness estimates?	
5	ESRD hazard ratio	Is the single study estimate or pooled HR for ESRD most appropriate?	
7	Hospitalisation costs	Is the company or ERG approach to hospitalisation costs most appropriate?	
8	Representativeness of healthcare costs	Do the modelled healthcare costs reflect those in the NHS?	

Partially resolved/for brief discussion | Unresolved, for discussion

ESRD, end-stage renal disease; GC, glucocorticoid; HR, hazard ratio

Issue 5: Hazard ratio for ESRD (1/2)

Background

- AVV is associated with progression to ESRD, impacting survival, QoL and healthcare costs
- Relapse in AAV is associated with worsening renal outcomes and a 9-fold increase in the risk of ESRD
- In the company model, ESRD could occur from worsening kidney function (modelled by changes in eGFR) and relapse associated with decreased eGFR
- As a key cost driver, the model is very sensitive to the risk of developing ESRD

- **Company:** The model includes an adjustment for current and future eGFR to simulate the increasing risk of ESRD with subsequent relapses. Calculated by:
  - The probability of ESRD in active disease or remission is adjusted by the improvement in eGFR in the avacopan and comparator arms of the ADVOCATE trial
  - The hazard rate, and subsequently the probability of ESRD, was adjusted based on a study by Gercik et al → **HR 0.90 (95% CI 0.86 to 0.95)** per mL/min change in eGFR
  - For each subsequent relapse, the hazard rate was adjusted based on a 10-mL/min drop in eGFR and the corresponding hazard ratio estimated from the Gercik et al

- **ERG:** Noted that the company had identified other studies that could inform the HR
  - After technical engagement the ERG preferred to pool 2 studies: Gercik et al and Brix et al = **HR 0.947 (95% CI 0.904 to 0.996)** per unit eGFR

AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; mL/min; millilitre per minute; HR, hazard ratio; QoL, quality of life

Issue 5: Hazard ratio for ESRD (2/2)

Company

- Not appropriate to pool across 2 studies because estimates from Cox proportional hazards regression models are conditional on covariates specific to each model
- Prefer to use Gercik et al because: most recent, large sample size, treatments received align with those in cost-effectiveness model

Clinical experts

- Risk of ESRD is dependent on the population included in the study
- Pooled estimate may be more representative of a broader AVV population

ERG

ERG considered the 4 studies identified in the company's submission: Brix et al (HR=0.96), Ford et al (HR=0.66), Menez et al (HR=0.91) and Gercik et al (HR=0.90)

- Menez not relevant because different population
- Ford not relevant because HR included ESRD or death
- Brix and Gercik considered both plausible and relevant
- ERG understand need for caution, but prefer pooled estimate (HR 0.947)

Is the single study estimate or pooled HR for ESRD most appropriate?

AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio

Issue 7: Hospitalisation costs

Background: Company's original base case applied unit costs from 2019/20 NHS reference costs combined with excess bed days taken from 2017/18 version

	ERG Issue	Company response
1	Not clear that a difference in length of stay should imply additional cost for excess bed days beyond the mean length of stay associated with hospitalisation in the NHS reference costs (2019/20)	Disagree: Mean length of stay observed in the ADVOCATE study was longer than that in the NHS ref costs (2019/20) → adjustment is needed to avoid underestimating overall cost
2	2019/20 reference costs no longer include separate excess bed days → suggests costs calculated differently in different years	Disagree: No evidence that excess bed day costs are incorporated in 2019/20 costs **NHSE:** '19/20 costs include excess bed days
3	Most relevant unit costs decreased in 2019/20 version, suggesting that care maybe given differently to 2017/18. Excess bed day costs therefore might not be applicable	Disagree: Unit costs increased and decreased. Overall, a modest increase was seen in weighted average of costs from 2017/18 to 2019/20
Base case	2019/2020 unit costs with no adjustment for excess bed days beyond the mean length of stay	Revised base case: 2017/18 unit costs and excess bed day costs. Final cost inflated to 2020 prices

Is the company or ERG approach to hospitalisation costs most appropriate?

Issue 8: Modelled healthcare costs vs CPRD

Background

- ERG noted that annual healthcare costs estimated in the model for SoC were lower than costs in the CPRD study

CYC/RTX+GC model	£13,400
CPRD approx.	[redacted]

Company

- Acknowledge substantial difference in total cost in the model compared to CPRD
- CPRD is not suitable for modelling because there is no information about change in resource use with avacopan & cannot be stratified by health state
- CPRD includes aggregate cost of all healthcare episodes, including treatment for unrelated comorbidities and model did not account for hidden costs of AAV
- Cost for specific episodes likely related to AVV are similar between the model and CPRD
- Given that a larger cost associated with worsening AAV (relapse and ESRD) would favour avacopan, it is likely the cost assumptions in the model are conservative

Clinical experts

CPRD may not adequately detect remission and relapse because of the inability to detect secondary prescribed medication for remission induction

ERG

Company response doesn't explain why the ICER goes up, if CPRD is used to estimate cost of AEs

Do the modelled healthcare costs reflect those in the NHS?

AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; AE – adverse event; CPRD, Clinical Practise Research Datalink; CYC, cyclophosphamide; ESRD, end stage renal disease; GC, glucocorticoids; ICER, incremental cost-effectiveness ratio; RTX, rituximab; SoC, standard of care

Other considerations

Innovation

Clinical experts: avacopan is innovative because it addresses unmet need and will significantly change the management of AAV. There are also potential benefits not captured in QALY:

- The ability to reduce risk of relapse and avoid retreatment with rituximab may, in context of COVID-19 or another pandemic, have additional benefits – B cell depletion risks a poor response to vaccination, increasing the risk of infection and mortality
- Reduced tablet burden and reduced complexity of dose tapering associated with corticosteroids
- Patients report salient emotional, physical, and social effects of corticosteroids, including depression, anxiety, irritation, weight gain and change in appearance, and effects on family and work, that impact their quality of life (Robson 2018)

Equality issues

- In TA308 (rituximab), committee noted cyclophosphamide reduces fertility in men and women. But peak onset for AAV in England is between 60 and 70 years. The committee concluded that the number of people with AAV who have not completed their family is likely to be small

AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; COVID-19, coronavirus 2019 pandemic; QALY, quality-adjusted life year

Summary of base case assumptions & inputs – post technical engagement

	Company	ERG
Hospitalisation costs	2017/18 unit costs + excess bed days, inflated to 2020 prices	2019/20 unit costs, no adjustment for excess bed days
HR for ESRD per unit change in eGFR	Single study (Gercik), HR of 0.90	Pooled estimate (Gercik and Brix), HR of 0.95
Probability of ESRD	Calibrated model estimate using published literature	Calibrated model estimate using published literature
Health state utility values	Treatment independent	Treatment independent
Relative risk of mortality for people with ESRD	6.6 from 23rd UK Renal Registry Annual Report	6.6 from 23rd UK Renal Registry Annual Report

NICE

eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio

Deterministic cost-effectiveness results

	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case*	[redacted]	[redacted]	**£19,441**
Company base case + ERG hospitalisation costs (2019/20 with no excess bed day costs)	[redacted]	[redacted]	£26,297
Company base case + ERG estimate for ESRD (pooled)	[redacted]	[redacted]	£30,888
ERG base case**	[redacted]	[redacted]	**£40,516**
Scenarios			
RTX maintenance after RTX induction + company's assumptions	[redacted]	[redacted]	£43,554
RTX maintenance after RTX induction + ERG's assumptions	[redacted]	[redacted]	£69,364

*Probabilistic: £20,635 per QALY, **£42,541 per QALY

ESRD, end-stage renal disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RTX, rituximab

Deterministic cost-effectiveness results, subgroups

Subgroup	Company ICER* (£/QALY)	ERG ICER (£/QALY)
ADVOCATE ITT population	£19,441	£40,516
Newly diagnosed AAV	£44,387	£80,652
Relapsed AAV	£17,019	£27,696
GPA	£64,198	£87,583
MPA	Dominant	£16,586
Rituximab background	£17,867	£34,666
Cyclophosphamide background	£40,414	£77,225
MPO positive	£13,085	£25,455
PR3 positive	£76,102	£102,444

*Scenarios run by the ERG using the company's preferred assumptions

Incremental costs and QALYs on slides 35 and 36

NICE

AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; GPA, granulomatosis with polyangiitis; ICER, incremental cost-effectiveness ratio; ITT, intention to treat; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase; QALY, quality-adjusted life year

Key issues

Model driver | Unknown impact | Small impact

	Issue description	Questions	Impact
2	Glucocorticoids in avacopan group may have biased effect estimates	Does the inclusion of glucocorticoids in the intervention group bias the effect estimates?	
4	Rituximab maintenance therapy	Should rituximab maintenance treatment be included in the cost-effectiveness estimates?	
5	ESRD hazard ratio	Is the single study estimate or pooled HR for ESRD most appropriate?	
7	Hospitalisation costs	Is the company or ERG approach to hospitalisation costs most appropriate?	
8	Representativeness of healthcare costs	Do the modelled healthcare costs reflect those in the NHS?	

Partially resolved/for brief discussion | Unresolved, for discussion

ESRD, end-stage renal disease; GC, glucocorticoid; HR, hazard ratio