Avacopan in ANCA-Associated Vasculitis

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Presenter Disclosure

I have no conflicts of interest to declare.

Abbreviations

AAV	ANCA-associated vasculitis
ACR	albumin-to-creatinine ratio
AIS	Aggregate Improvement Score
ANCA	antineutrophil cytoplasmic antibody
AZA	azathioprine
BVAS	Birmingham Vasculitis Activity Score
CADTH	Canadian Agency for Drugs and Technologies in Health
CDEC	Canadian Drug Expert Committee
CWS	Cumulative Worsening Score
CYC	cyclophosphamide
CYP3A4	cytochrome P450 3A4
eGFR	estimated glomerular filtration rate
EGPA	eosinophilic granulomatosis with polyangiitis
ENT	ear, nose and throat
ESKD	end-stage kidney disease
GC	Glucocorticoid
GTI	Glucocorticoid Toxicity Index
GPA	granulomatosis with polyangiitis
HRQoL	health-related quality of life
LFT	liver function test
MPA	microscopic polyangiitis
MPO	myeloperoxidase
PR3	proteinase 3
PJP	Pneumocystis jirovecii pneumonia
RTX	rituximab
ULN	upper limit of normal

ANCA-associated vasculitis (AAV)

- Small-vessel vasculitides that include:
  - Granulomatosis with polyangiitis (GPA)
  - Microscopic polyangiitis (MPA)
  - Eosinophilic granulomatosis with polyangiitis (EGPA)

- In most cases, associated with autoantibodies (ANCAs) against one of two proteins located in the granules of neutrophils:
  - Proteinase 3 (PR3)
  - Myeloperoxidase (MPO)

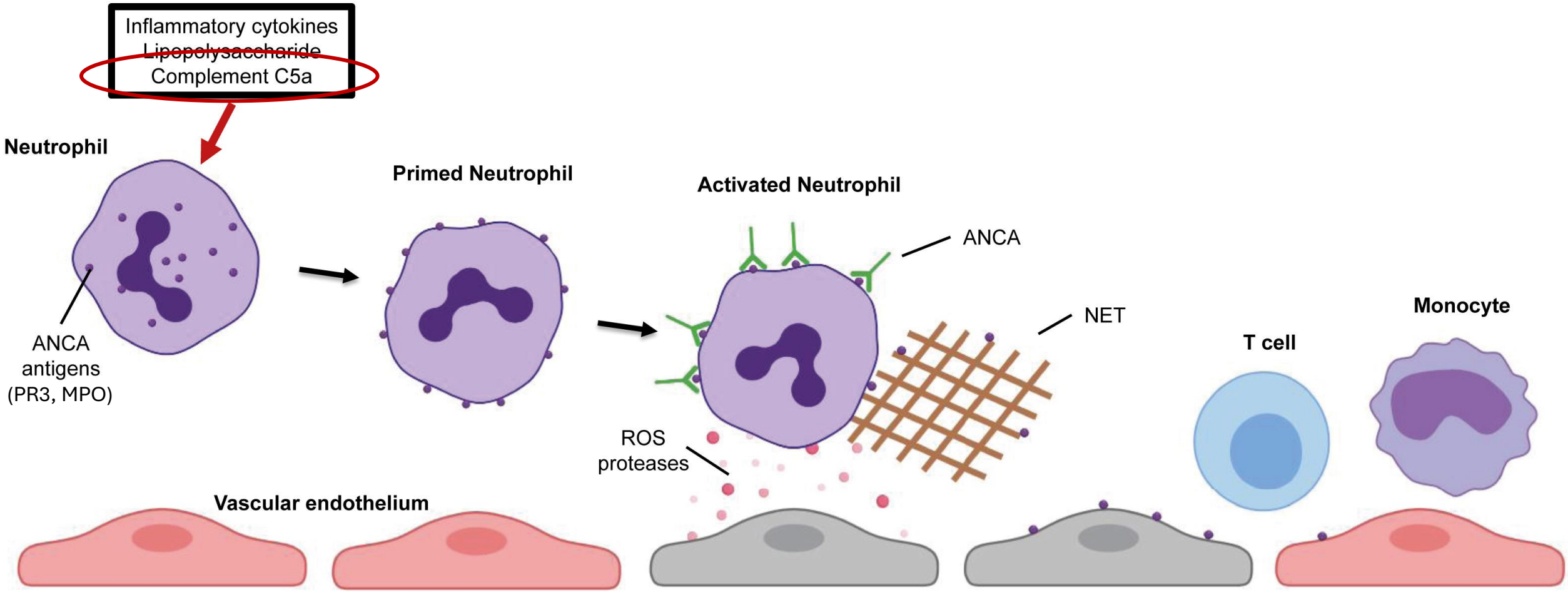
Cortazar FB. ANCA-Associated Kidney Disease. In: National Kidney Foundation Primer on Kidney Diseases (8th edition);. Elsevier;2023, p.176-86.

Characteristics and Clinical Manifestations of AAV

	GPA	MPA
Estimated prevalence	50-250 per million	25-150 per million
Associated ANCA	Mainly PR3-ANCA	Mainly MPO-ANCA
Clinical manifestations		
Constitutional	Fever, arthralgia, myalgia	
Skin	Purpura	
ENT	Frequent; crusting rhinitis, destructive sinusitis, saddle-nose deformity, nasal septum deformity, otitis media, decreased/loss of smell or taste, gum hypertrophy/pain	Few patients; not specific, not destructive, not granulomatous
Lung	Lung solid and/or excavated nodules, alveolar hemorrhage, bronchial and/or subglottic stenosis	Alveolar hemorrhage
Kidney	Pauci-immune, necrotizing, and often crescentic glomerulonephritis	

CanVasc. Vasculitides. 2022 [cited 04Nov2024]. Available from: URL: https://canvasc.ca/vasculitides/
Eur J Rheumatol. 2022 Jul;9(3):153-166. Elsevier. National Kidney Foundation Primer on Kidney Diseases. Elsevier;2023.

Pathogenesis of AAV

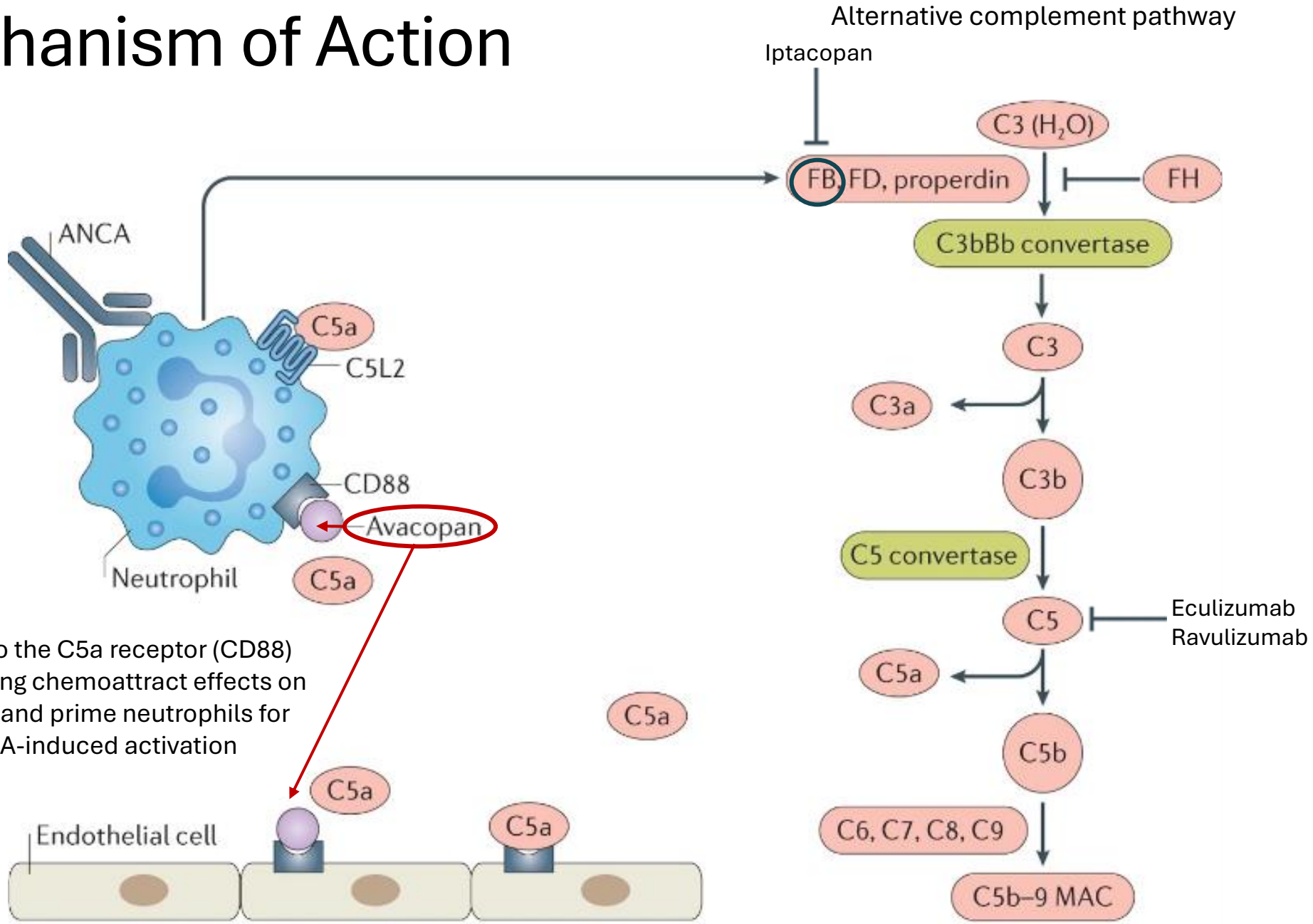


ROS = reactive oxygen species; NET = neutrophil extracellular trap

Am J Kidney Dis. 2020 Jan;75(1):124-137.

Avacopan Mechanism of Action

Avacopan is a small molecule C5a receptor antagonist that blocks the pro-inflammatory effects of C5a



C5a binds to the C5a receptor (CD88) to exert strong chemoattract effects on neutrophils and prime neutrophils for further ANCA-induced activation

FB = factor B, FD = factor D, FH = factor H, MAC = membrane attack complex

Nat Rev Nephrol. 2017 Aug;13(8):448-450.

CanVasc 2020: Treatment of AAV with Renal Involvement (without avacopan)

INDUCTION OF REMISSION (3-6 MONTHS)

Rituximab + high-dose GC
OR
Cyclophosphamide (PO or IV) + high-dose GC

Urgent plasma exchange not recommended in most patients

Initiate GC tapering within 2 weeks of induction therapy.
Consider a reduced-dose GC tapering protocol.

MAINTENENACE OF REMISSION (AT LEAST 24-48 MONTHS)

Rituximab + low-dose GC*
OR
Azathioprine + low-dose GC*
OR
Methotrexate + low-dose GC*

*Optimal duration of low-dose GC for maintenance therapy is unknown

J Rheumatol. 2021 Apr;48(4):555-566.

KDIGO 2024: Treatment of AAV with Renal Involvement (without avacopan)

INDUCTION OF REMISSION (3-6 MONTHS)

Rituximab + GC taper
Reduced-dose GC tapering protocol preferred – withdraw GC by 6 months
OR
Cyclophosphamide (PO or IV) + GC taper
Reduced-dose GC tapering protocol preferred – reduce PO prednisone to 5 mg/day by 5 months
OR
Rituximab + cyclophosphamide (IV) + GC taper
Reduced-dose GC tapering protocol preferred

Consider plasma exchange for:
Patients with SCr > 300 umol/L, patients requiring dialysis or with rapidly increasing SCr, or patients with diffuse alveolar hemorrhage who have hypoxemia

↓

MAINTENENACE OF REMISSION (18-48 MONTHS)

Switch to azathioprine + taper off GC → Discontinue azathioprine
Consider methotrexate (if eGFR > 60 mL/min/1.73 m^2) or mycophenolate mofetil as alternatives to azathioprine in patients who are intolerant of azathioprine
OR
Continue rituximab → Discontinue rituximab

Kidney Int. 2024 Mar;105(3S):S71-S116.

Reduced-Dose Glucocorticoid Tapering Protocol

Daily Prednisone Dose in PEXIVAS Trial (mg)						
Week	Standard			Reduced-dose		
	<50 kg	50-75 kg	>75 kg	<50 kg	50-75 kg	>75 kg
	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse
1	50	60	75	50	60	75
2	50	60	75	25	30	40
3-4	40	50	60	20	25	30
5-6	30	40	50	15	20	25
7-8	20	30	40	12.5	15	20
9-10	15	20	30	10	12.5	15
11-12	15	15	25	7.5	10	12.5
13-14	12.5	20	20	6	7.5	10
15-16	10	10	15	5	5	7.5
17-18	10	10	15	5	5	7.5
19-20	7.5	7.5	10	5	5	5
21-22	7.5	7.5	7.5	5	5	5
23-52	5	5	5	5	5	5
>52	Investigators' local practice			Investigators' local practice		

Compared to standard dose regimen, reduced-dose regimen was:

- Non-inferior with respect to composite endpoint of all-cause death or ESKD
- Associated with fewer serious infections at 1 year

N Engl J Med. 2020 Feb 13;382(7):622-631.

ADVOCATE Trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 18, 2021 VOL. 384 NO. 7

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 Feb 18;384(7):599-609.

Design	52-week, phase 3, randomized, double-blind, double-dummy, controlled trial across 143 centers internationally with 8 weeks of follow-up	
Population (N=331)	<u>Key inclusion criteria:</u> • Aged ≥ 12 years with newly-diagnosed or relapsed AAV requiring treatment with cyclophosphamide or rituximab • Clinical diagnosis of GPA or MPA • Positive test for anti-PR3 or anti-MPO antibodies (current or historic) • Birmingham Vasculitis Activity Score (BVAS)*: ≥1 major item, or ≥3 minor items, or ≥2 renal items of proteinuria and hematuria • eGFR ≥15 mL/min/1.73 m^2 (MDRD)	<u>Key exclusion criteria:</u> • Any other multi-system autoimmune disease • Kidney transplant recipient • Alveolar hemorrhage requiring invasive pulmonary ventilation support • Required dialysis or plasma exchange within last 12 weeks • Received immunosuppression recently** or taking azathioprine, methotrexate, or mycophenolate mofetil at screening and unwilling to discontinue use • Evidence of hepatic disease • Pregnant or breastfeeding

*Composite measure of signs and symptoms in 9 organ systems. Scores range 0 to 63, and higher scores indicate more extensive disease activity

**Includes the following (refer to protocol for others): IV glucocorticoid (>3000 mg methylprednisolone equivalent) within last 4 weeks; oral glucocorticoid (>10 mg/day prednisone equivalent) continuously within last 6 weeks; cyclophosphamide within last 12 weeks; rituximab or other B-cell antibody within last 52 weeks, or within last 26 weeks if B-cell reconstitution occurred

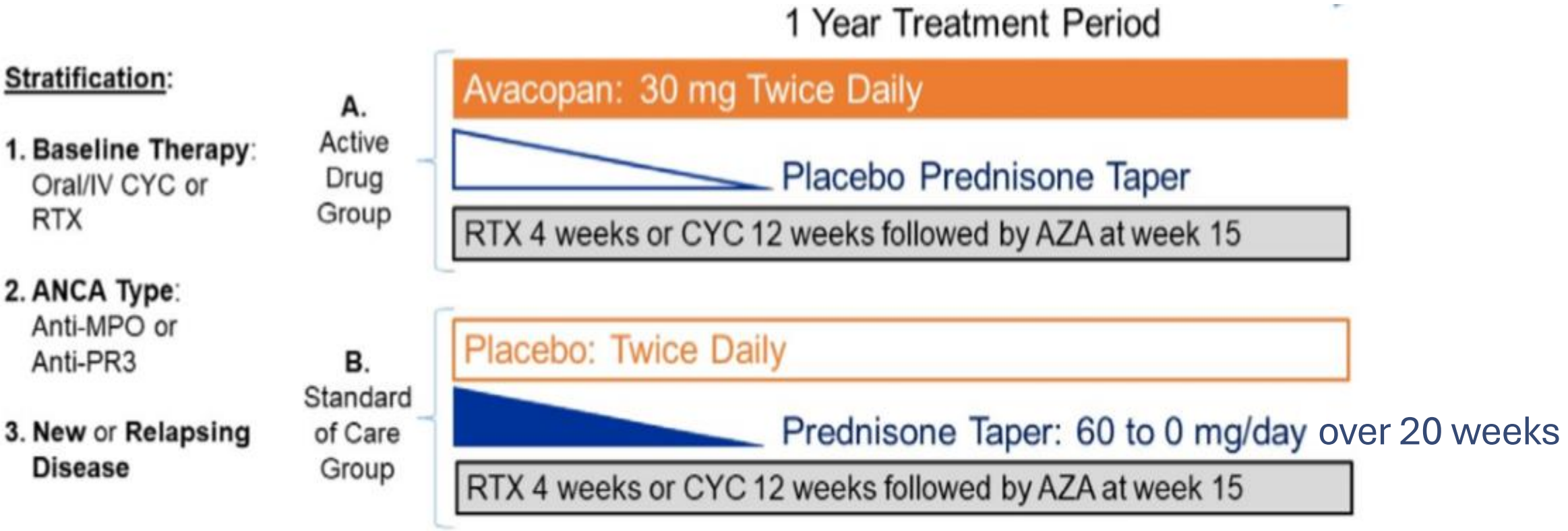
N Engl J Med. 2021 Feb 18;384(7):599-609.

Treatment in all patients	**Glucocorticoid from screening period (≤14 day period)**	Required to be tapered to ≤20 mg/day prednisone-equivalent by Day 1 of study, and tapered off by Week 4
	Options for induction and maintenance* (Days 1 to 364)	1. IV cyclophosphamide q2-3 weeks x 13 weeks, then PO azathioprine starting at Week 15 2. PO cyclophosphamide x 14 weeks, then PO azathioprine starting at Week 15 3. Rituximab 375 mg/m^2 IV weekly x 4 weeks; no maintenance
	Additional glucocorticoids as needed	Allowed for: • ≥1 major BVAS and no improvement/stabilization within first 4 weeks, or worsening of disease • Non-vasculitis reasons (e.g., adrenal insufficiency, allergies) • Pre-medication for rituximab infusions
	Prophylactic therapy	Prophylaxis against PJP and osteoporosis, and gastroprotection
Intervention	Avacopan 30 mg PO BID	
Control	Prednisone, tapered according to protocol and discontinued by Week 21	

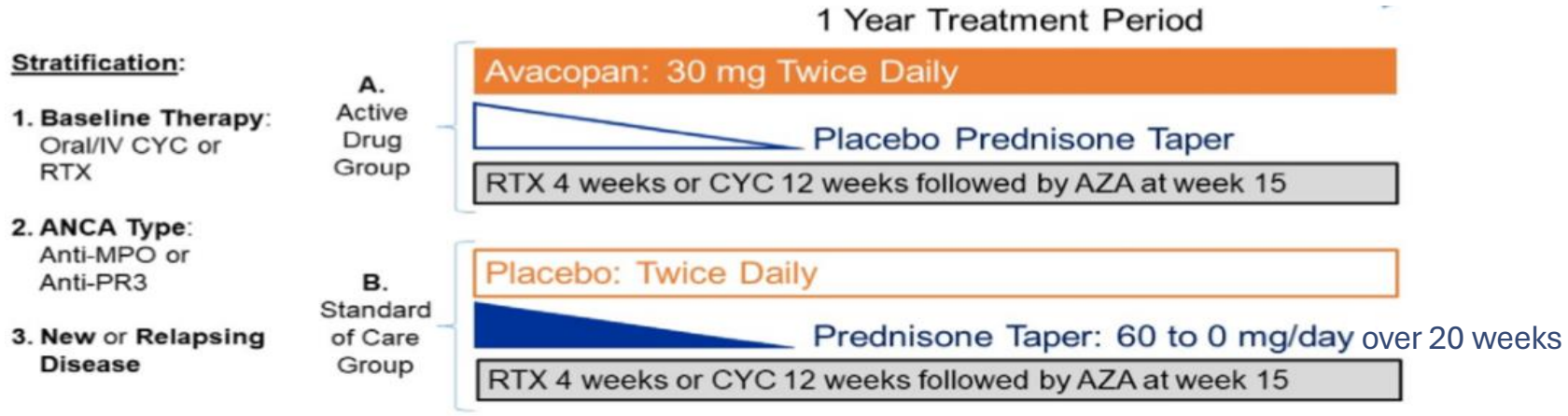
*Dosing: IV cyclophosphamide – 15 mg/kg (max 1.2 g) IV on Day 1 and Weeks 2, 4, 7, 10, 13 (dose adjusted based on age and eGFR); PO cyclophosphamide – 2 mg/kg/day (max 200 mg/day) (dose adjusted based on age and eGFR); PO azathioprine – 1 mg/kg/day, with titration up to 2 mg/kg/day

N Engl J Med. 2021 Feb 18;384(7):599-609.

ADVOCATE Trial Design



N Engl J Med. 2021 Feb 18;384(7):599-609.



Daily Prednisone Dose (mg)				
Study Week	Adults		Adolescents	
	≥55 kg	<55 kg	>37 kg	≤37 kg
1	60	45	45	30
2	45	45	45	30
3	30	30	30	30
4-6	25	25	25	25
7-8	20	20	20	20
9-10	15	15	15	15
11-14	10	10	10	10
15-20	5	5	5	5
21-52	0	0	0	0

N Engl J Med. 2021 Feb 18;384(7):599-609.

Primary outcomes	**<u>Tested for non-inferiority (margin of 20%) and superiority:</u>**
	• **Clinical remission at 26 weeks**
	  • BVAS of 0 and no glucocorticoids for 4 weeks before Week 26
	• **Sustained remission at 52 weeks**
	  • BVAS of 0 and no glucocorticoids for 4 weeks before Week 52
	  • Not considered to be in sustained remission if patient was in remission at Week 26 but relapsed* afterwards

Key secondary outcomes	**<u>No adjustment of confidence intervals for multiplicity; no definite conclusions can be drawn:</u>**
	Glucocorticoid Toxicity Index (GTI) during first 26 weeks, measured by:
	  • Cumulative Worsening Score (GTI-CWS)
	  • Aggregate Improvement Score (GTI-AIS)
	• Relapse* (time-to-event analysis)
	• Change in eGFR from baseline
	• Change in HRQoL from baseline, assessed with SF-36 and EQ-5D-5L

Other secondary outcomes included: change in urinary ACR, change in urinary monocyte-chemoattractant protein-1:creatinine ratio; change in Vasculitis Damage Index

*Relapse defined as return of vasculitis activity on the basis of ≥1 major BVAS item or ≥3 minor BVAS items, or 1-2 minor BVAS items for at least 2 consecutive trial visits

N Engl J Med. 2021 Feb 18;384(7):599-609.

Demographic and Clinical Characteristics of Patients at Baseline		
	Avacopan (n=166)	**Prednisone (n=164)**
Age – yrs, mean ± SD	61.2 ± 14.6	60.5 ± 14.5
Male – no. (%)	98 (59.0)	88 (53.7)
Vasculitis disease status – no. (%)		
Newly diagnosed	115 (69.3)	114 (69.5)
Relapsed	51 (30.7)	50 (30.5)
ANCA status – no. (%)		
PR3-positive	72 (43.4)	70 (42.7)
MPO-positive	94 (56.6)	94 (57.3)
Type of vasculitis – no. (%)		
GPA	91 (54.8)	90 (54.9)
MPA	75 (45.2)	74 (45.1)
BVAS – mean ± SD	16.3 ± 5.9	16.2 ± 5.7

N Engl J Med. 2021 Feb 18;384(7):599-609.

Demographic and Clinical Characteristics of Patients at Baseline - *continued*

	Avacopan (n=166)	Prednisone (n=164)
Organ involvement – no. (%)		
Renal	134 (80.7)	134 (81.7)
General	111 (66.9)	114 (69.5)
Ear, nose, and throat	75 (45.2)	69 (42.1)
Chest	71 (42.8)	71 (43.3)
Nervous system	38 (22.9)	31 (18.9)
Mucous membranes or eyes	26 (15.7)	40 (24.4)
Cutaneous	24 (14.5)	23 (14.0)
Cardiovascular	6 (3.6)	3 (1.8)
Abdominal	4 (2.4)	1 (0.6)
Patients with renal disease at baseline based on BVAS		
eGFR (mL/min/1.73 m^2) – mean ± SD*	44.6 ± 2.4	45.6 ± 2.4
Urinary ACR (mg/mmol) – geometric mean (range)**	43.3 (20.0-64.6)	31.2 (11.0-53.7)

*Evaluated in 131 and 134 patients in avacopan and prednisone groups, respectively

**Evaluated in 125 and 128 patients in avacopan and prednisone groups, respectively

N Engl J Med. 2021 Feb 18;384(7):599-609.

Medication Characteristics of Patients		
	Avacopan (n=166)	**Prednisone (n=164)**
Glucocorticoid use in screening period – no. (%)		
Use of any glucocorticoids	125 (75.3)	135 (82.3)
IV glucocorticoid	63 (38.0)	73 (44.5)
PO glucocorticoid	99 (59.6)	113 (68.9)
Daily prednisone-equivalent dose, mg – mean ± SD	64.8 ± 81.9	69.9 ± 82.7
Immunosuppressant induction treatment – no. (%)		
IV rituximab	107 (64.5)	107 (65.2)
IV cyclophosphamide	51 (30.7)	51 (31.1)
PO cyclophosphamide	8 (4.8)	6 (3.7)

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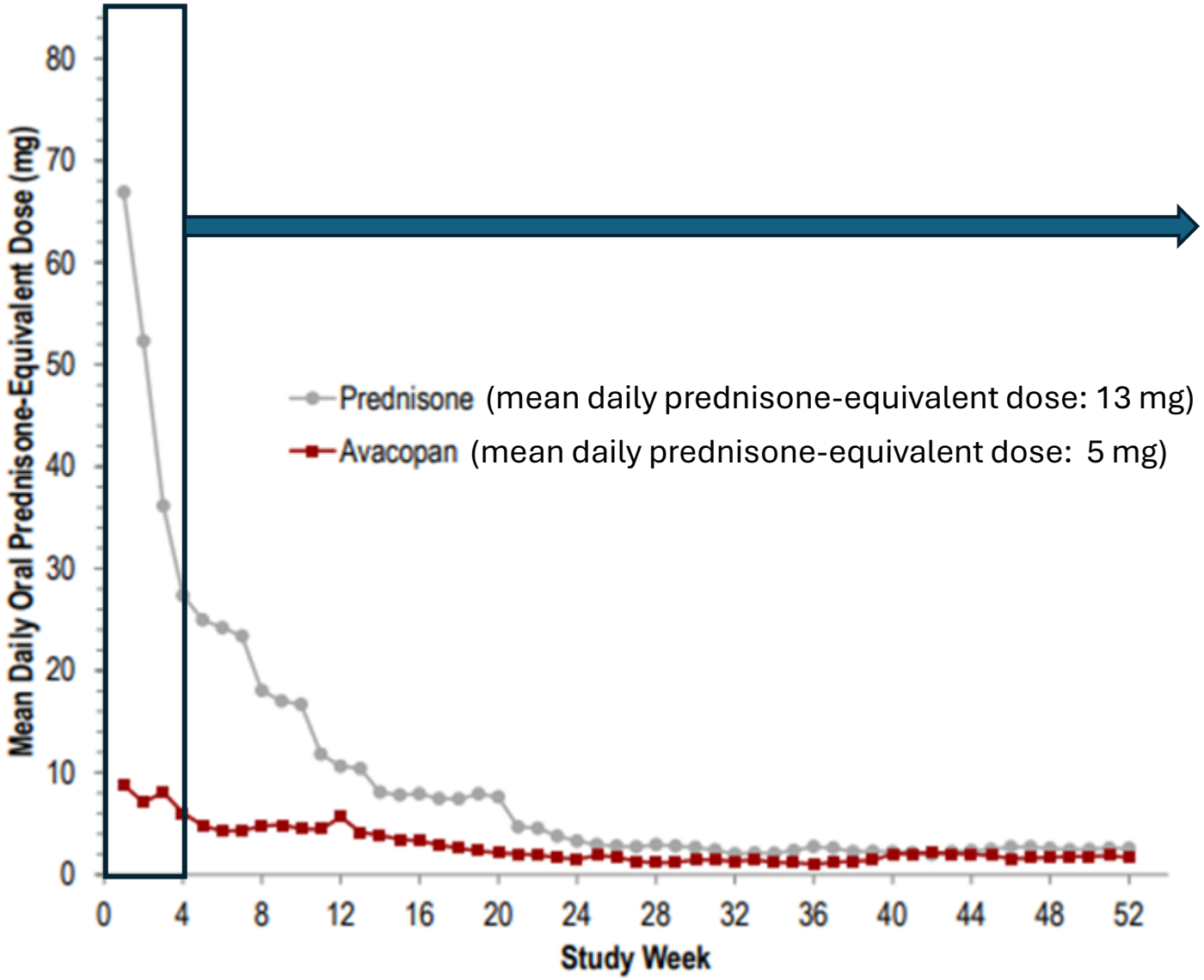
Glucocorticoid Use During Treatment Period



In first 4 weeks, 67.6% of patients received IV glucocorticoids; majority were for rituximab pre-medication

Sources of non-protocol PO glucocorticoids throughout the study included 4-week taper, use for adrenal insufficiency, and limited use for minor worsening or persistence of vasculitis

N Engl J Med. 2021 Feb 18;384(7):599-609.

Results – Primary Outcomes

Primary Outcome – no. (%)	Avacopan (n=166)	Prednisone (n=164)	Difference (95% CI)	One-sided p-value for non-inferiority	p-value for superiority
Remission at week 26	120 (72.3)	115 (70.1)	3.4 (-6.0 to 12.8)	<0.001	0.24
Sustained remission at week 52	109 (65.7)	90 (54.9)	12.5 (2.6 to 22.3)	<0.001	0.007

N Engl J Med. 2021 Feb 18;384(7):599-609.

Results – Glucocorticoid Toxicity Index (GTI)

	Avacopan (n=166)	Prednisone (n=164)	Difference (95% CI)
GTI-CWS*, least squares mean ± SE			
Week 13	25.7 ± 3.4	36.6 ± 3.4	-11.0 (-19.7 to -2.2)
Week 26	39.7 ± 3.4	56.6 ± 3.4	-16.8 (-25.6 to -8.0)
GIT-AWS, least squares mean ± SE**			
Week 13	9.9 ± 3.4	23.2 ± 3.5	-13.3 (-22.2 to -4.4)
Week 26	11.2 ± 3.5	23.4 ± 3.5	-12.1 (-21.1 to -3.2)

Sample sizes differed by timepoint for these outcome measures
Minimum clinically important difference for GTI is 10
*Ranges 0 to 410, with higher scores indicating greater severity of toxic effects
*Ranges -317 to 410, with higher scores indicating greater severity of toxic effects

N Engl J Med. 2021 Feb 18;384(7):599-609.
Semin Arthritis Rheum. 2022 Aug;55:152010.

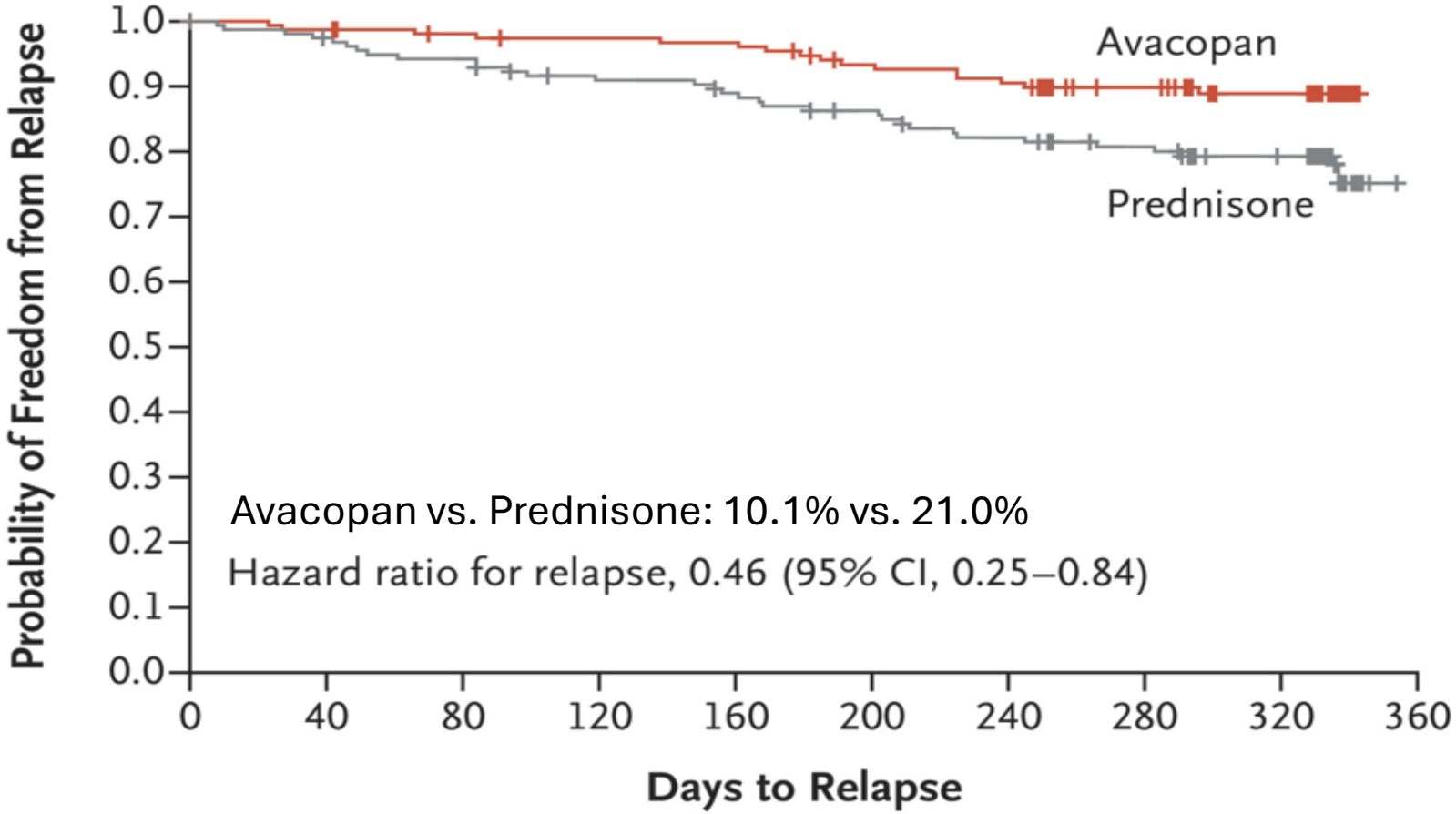
Results – Health-Related Quality of Life

	Avacopan (n=166)	Prednisone (n=164)	Difference (95% CI)
SF-36 physical component score*			
Baseline, mean ± SD	39.2 ± 3.4	40.1 ± 0.8	--
Change from baseline to Week 26, least-squares mean ± SE	4.45 ± 0.73	1.34 ± 0.74	3.10 (1.17 to 5.03)
Change from baseline to Week 52, least-squares mean ± SE	4.98 ± 0.74	2.63 ± 0.75	2.35 (0.40 to 4.31)
EQ-5D-5L visual analogue scale**			
Baseline, mean ± SD	65.8 ± 0.74	63.4 ± 1.8	--
Change from baseline to Week 26, least-squares mean ± SE	9.1 ± 1.4	5.5 ± 1.4	3.6 (-0.1 to 7.2)
Change from baseline to Week 52, least-squares mean ± SE	13.0 ± 1.4	7.1 ± 1.4	5.9 (2.3 to 9.6)

Only select HRQoL results are presented here
Sample sizes differed by timepoint for these outcome measures
*Minimal clinically important difference is 2.5. Ranges from 0 to 100, with higher scores indicating better QoL.
**Minimally clinically important difference is 5.0. Ranges from 0 to 100, with higher scores indicating better QoL.

N Engl J Med. 2021 Feb 18;384(7):599-609.
Lancet Rheumatol 2023; 5: e451–60.

Results – Relapse



No. at Risk

Avacopan	158	153	149	146	145	133	129	115	92	0
Prednisone	157	151	146	137	133	126	119	111	90	0

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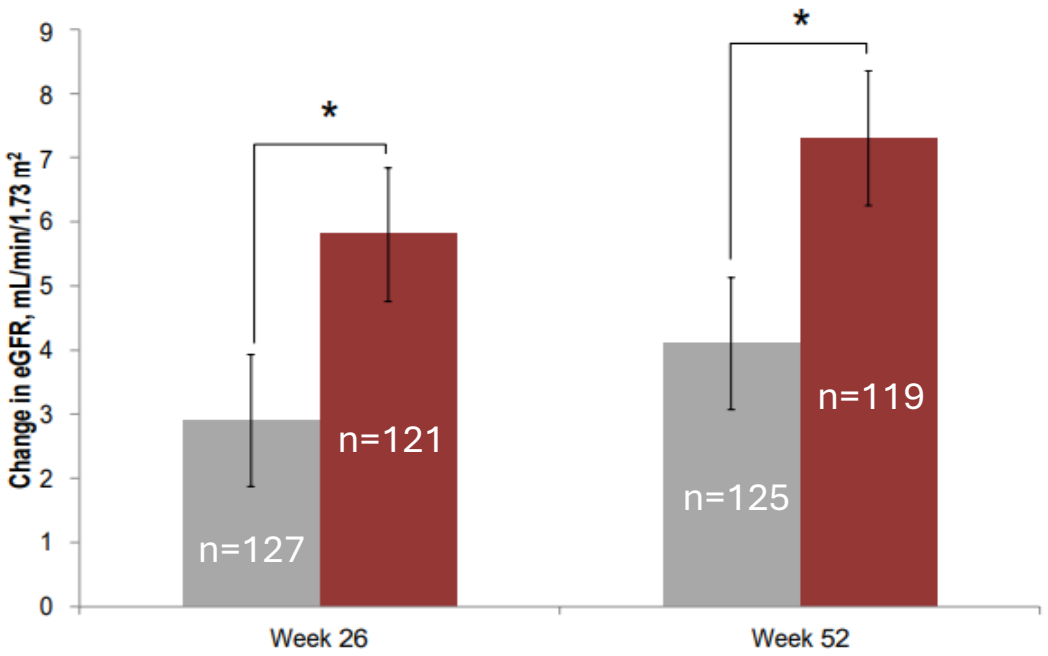
Results – Change in eGFR from baseline



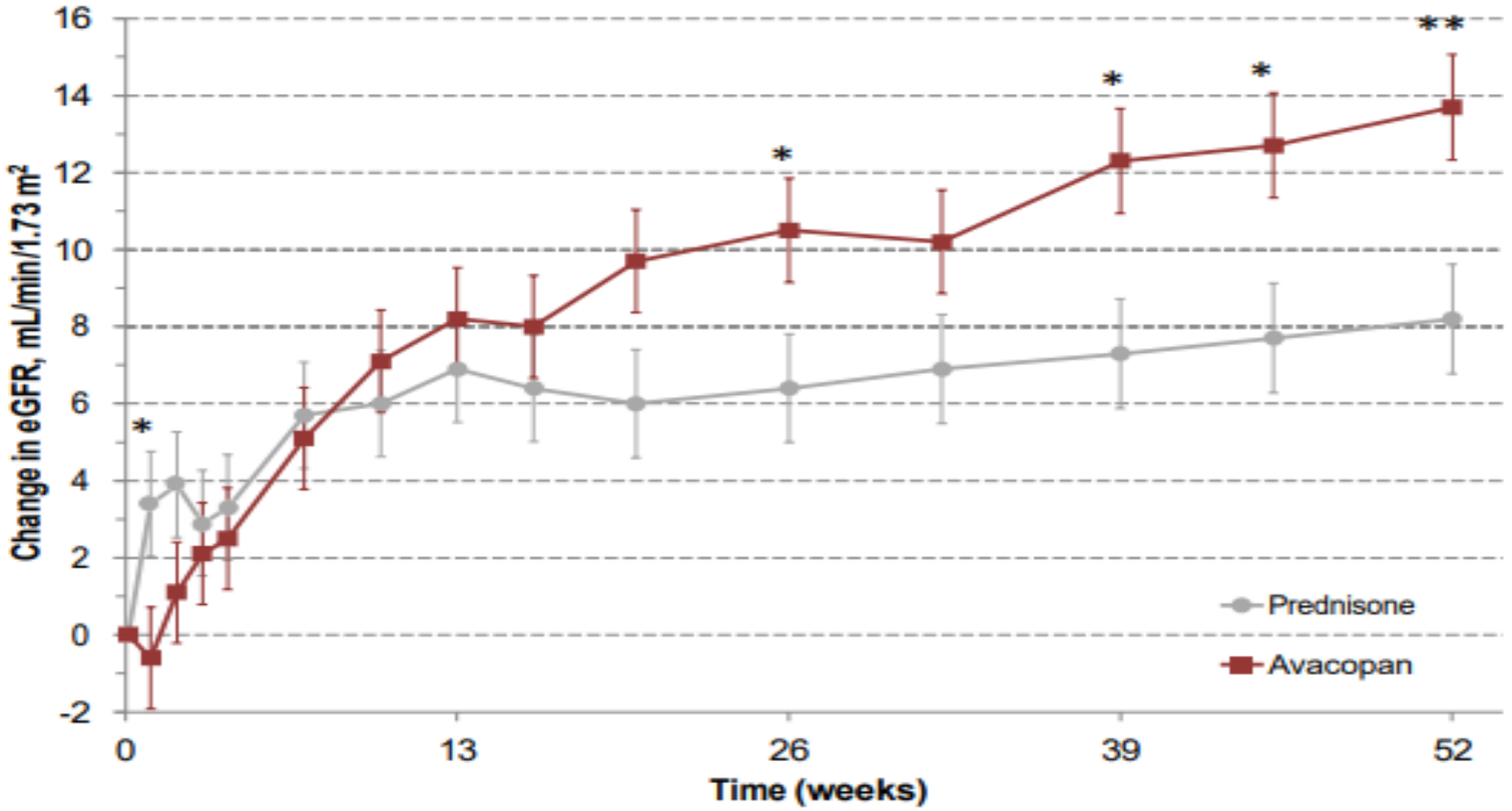
*Indicates 95% confidence intervals of differences between avacopan and prednisone group that do not include 0

Patients with renal disease at baseline based on BVAS	Avacopan (n=131)	Prednisone (n=134)	Difference (95% CI)
eGFR (mL/min/1.73 m²)			
Baseline, mean ± SD	44.6 ± 2.4	45.6 ± 2.4	--
Change from baseline to Week 26, least-squares mean ± SE	5.8 ± 1.0	2.9 ± 1.0	2.9 (0.1 to 5.8)
Change from baseline to Week 52, least-squares mean ± SE	7.3 ± 1.0	4.1 ± 1.0	3.2 (0.3 to 6.1)
Sample sizes differed by timepoint for this outcome measure			

N Engl J Med. 2021 Feb 18;384(7):599-609.

Results of Post-Hoc Analyses – Change in eGFR in subgroups with low baseline eGFR

eGFR < 30 mL/min/1.73 m^2 at baseline



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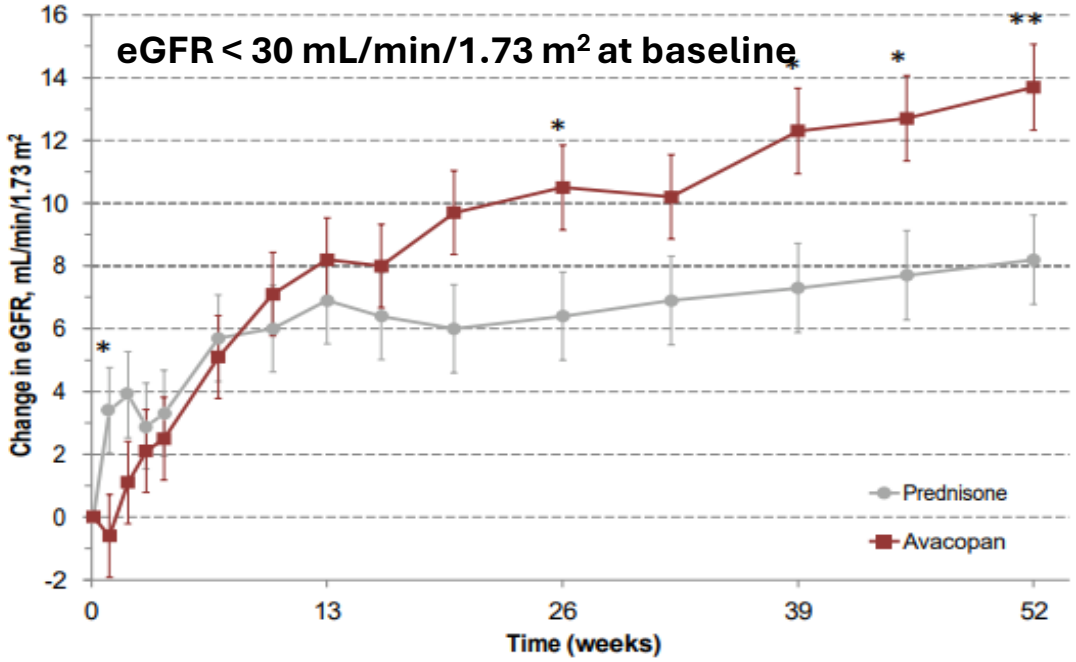
Results of Post-Hoc Analyses – Change in eGFR in subgroups with low baseline eGFR



Patients with eGFR < 30 mL/min/1.73 m² at baseline			
	Avacopan (n=52)	**Prednisone (n=48)**	**Difference (95% CI)**
eGFR (mL/min/1.73 m²)			
Baseline, mean ± SD	21.1 ± 0.6	21.6 ± 0.7	--
Change from baseline to Week 52, least-squares mean ± SE	13.7 ± 1.4	8.2 ± 1.4	5.6 (1.7 to 9.5)

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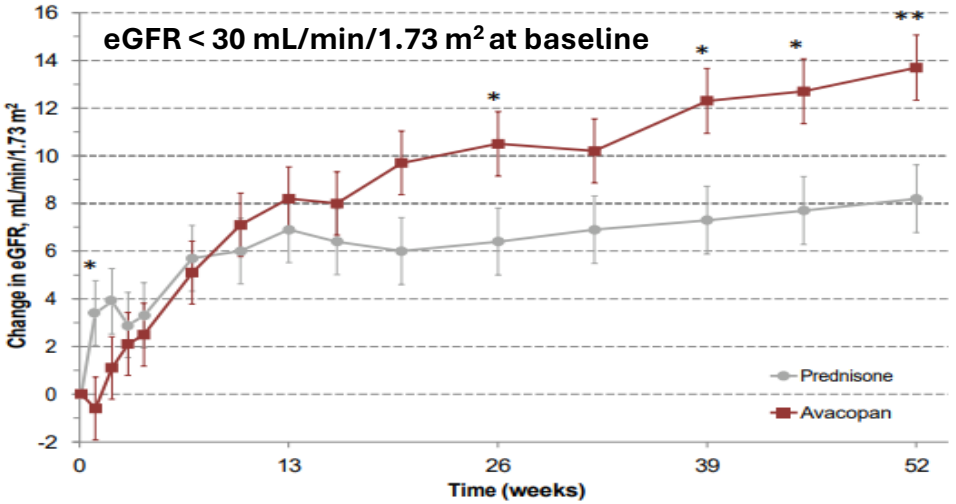
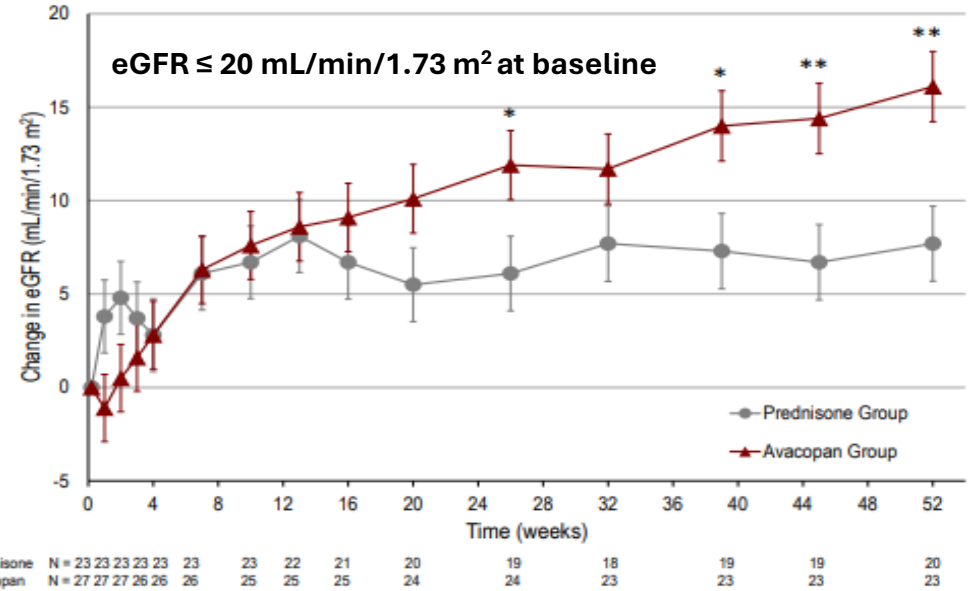
Results of Post-Hoc Analyses – Change in eGFR in subgroups with low baseline eGFR





Patients with eGFR < 30 mL/min/1.73 m² at baseline			
	Avacopan (n=52)	Prednisone (n=48)	Difference (95% CI)
eGFR (mL/min/1.73 m²)			
Baseline, mean ± SD	21.1 ± 0.6	21.6 ± 0.7	--
Change from baseline to Week 52, least-squares mean ± SE	13.7 ± 1.4	8.2 ± 1.4	5.6 (1.7 to 9.5)

Patients with eGFR ≤ 20 mL/min/1.73 m² at baseline			
	Avacopan (n=27)	Prednisone (n=23)	Difference (95% CI)
eGFR (mL/min/1.73 m²)			
Baseline, mean ± SD	17.6 ± 1.9	17.5 ± 2.0	--
Change from baseline to Week 52, least-squares mean ± SE	16.1 ± 1.9	7.7 ± 2.0	8.4 (2.9 to 13.8)
Difference in eGFR between groups largely remained at 8-week follow-up after study ended			

Note: Sample sizes differed by timepoint for both post-hoc analyses

N Engl J Med. 2021 Feb 18;384(7):599-609. Kidney Int Rep. 2023 Feb 3;8(4):860-870.

Results – Safety

Adverse Event – no. (%)	Avacopan (n=166)	Prednisone (n=164)
Any adverse event	164 (98.8)	161 (98.2)
Discontinuation of medication due to adverse event	26 (15.7)	29 (17.7)
Serious adverse events		
Any serious adverse event	39 (23.5)	41 (25.0)
Any serious event related to vasculitis worsening	17 (10.2)	23 (14.0)
Any serious event not related to vasculitis worsening	62 (37.3)	64 (39.0)
Serious adverse event of LFT abnormality	9 (5.4)	6 (3.7)
Infection*		
Any infection	113 (68.1)	124 (75.6)
Any serious infection	22 (13.3)	25 (15.2)
Any serious opportunistic infection	6 (3.6)	11 (6.7)
Hepatitis B reactivation**	1 (0.6)	0 (0)
Death	2 (1.2)	4 (2.4)

*No *Neisseria meningitidis* or *Pneumocystis jirovecii* infections were observed

**1 patient had hepatitis B reactivation during the 8-week drug-free period; had received 2 RTX infusions

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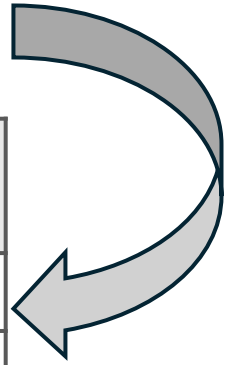
Results – Safety

Adverse Event – no. (%)	Avacopan (n=166)	Prednisone (n=164)
Serious adverse event of LFT abnormality	9 (5.4)	6 (3.7)



LFT Abnormality – no. (%)	Avacopan (n=166)	Prednisone (n=164)
AST >3-5x ULN	6 (3.6)	4 (2.4)
ALT >3-5x ULN	3 (1.8)	0 (0.0)
Bilirubin >1.5-3x ULN	2 (1.2)	1 (0.6)
Bilirubin >3-10x ULN	1 (0.6)	0 (0.0)
All events resolved with withdrawal of trial medication and potentially hepatotoxic drugs, including trimethoprim-sulfamethoxazole		

N Engl J Med. 2021 Feb 18;384(7):599-609.
Otsuka Canada Pharmaceutical Inc. Tavneos Product Monograph Including Patient Information. 22Apr14 [cited 04Nov2024]. Available from: URL: https://pdf.hres.ca/dpd_pm/00065462.PDF

Summary of ADVOCATE Trial

Avacopan vs. Prednisone							
Efficacy					Glucocorticoid Parameters		Safety
Remission at 26 weeks	Sustained remission at 52 weeks	HRQoL	Relapse	Change in eGFR from baseline	Glucocorticoid Use	Glucocorticoid Toxicity Index	Serious adverse events
↔	↓	↑	↓	↑ with greater renal recovery observed in those with lower baseline eGFR	↓	↓	↔ but higher incidence of serious adverse event of LFT abnormality

Compared to prednisone taper, avacopan was:

- Non-inferior, but not superior, with respect to remission at Week 26
- Superior with respect to remission at Week 52

N Engl J Med. 2021 Feb 18;384(7):599-609.

Limitations of ADVOCATE Trial

- Requirement for glucocorticoids to be tapered to ≤20 mg/day prednisone-equivalent during the screening period may have excluded patients with worse prognoses

- Deviations from current standards of care
  - No maintenance therapy was given following induction with rituximab
  - In Prednisone arm, prednisone tapering protocol was rapid (even quicker than the low-dose regimen in PEXIVAS)

- Avacopan arm was not truly glucocorticoid-free

- Unable to generalize results to patients with eGFR <15 ml/min/1.73 m^2 or alveolar hemorrhage requiring mechanical ventilation

- Short trial duration

What is avacopan's approved indication?

Health Canada (April 2022)
Avacopan approved for adjunctive treatment of adult patients with severe active AAV (GPA or MPA) in combination with standard background therapy including glucocorticoids. **Avacopan does not eliminate glucocorticoid use.**

Otsuka Canada Pharmaceutical Inc. Tavneos Product Monograph Including Patient Information 22Apr14 [cited 04Nov2024]. Available from: URL: https://pdf.hres.ca/dpd_pm/00065462.PDF

What do guidelines recommend?

	Recommendation/Practice Point
CanVasc 2022 addendum	1. The addition of oral avacopan (30 mg twice daily) can be considered for induction of remission in patients with newly diagnosed or relapsing GPA or MPA treated with cyclophosphamide or rituximab (Category 1B, Strength B) **2. After starting avacopan, a faster glucocorticoid tapering protocol aiming for discontinuation by end of week 4** should be considered (Category 1B, strength B) 3. When initiated as part of induction therapy, avacopan can be **continued for 1 year** (Category 1B, Strength B) • Use avacopan with caution in patients with more severe end-organ manifestations (e.g., eGFR < 15 mL/min/1.73 m^2 or alveolar hemorrhage requiring mechanical ventilation) • Clinicians can choose to follow the ADVOCATE protocol (which includes omission of maintenance therapy after remission induction with rituximab) or rely on maintenance strategies recommended in previous CanVasc guidelines
KDIGO 2024	Practice Point 9.3.1.7: Avacopan may be used as an **alternative to glucocorticoids**. Patients with an increased risk of glucocorticoid toxicity are likely to receive the most benefit from avacopan. Patients with lower GFR may benefit from greater GFR recovery.

J Rheumatol. 2021 Apr;48(4):555-566. Kidney Int. 2024 Mar;105(3S):S71-S116.

What is done in my Kidney Clinic…

- Start avacopan as early as possible in glucocorticoid taper
- Aim to taper off glucocorticoid within 2-3 months of avacopan initiation
- If avacopan is used in conjunction with rituximab induction therapy, maintenance therapy is not omitted
- Decision for PJP prophylaxis while patient is on avacopan therapy is based on the risk of PJP associated with patient's concomitant immunosuppressant(s)
  - Prophylaxis is prescribed during induction therapy with cyclophosphamide or rituximab (consistent with CanVasc prescribing information)
  - For other immunosuppressants, we refer to "BC Renal Pneumocystis jirovecii Pneumonia Prophylaxis Guidelines in Patients with Glomerulonephritis"
- Discontinue avacopan after 1 year

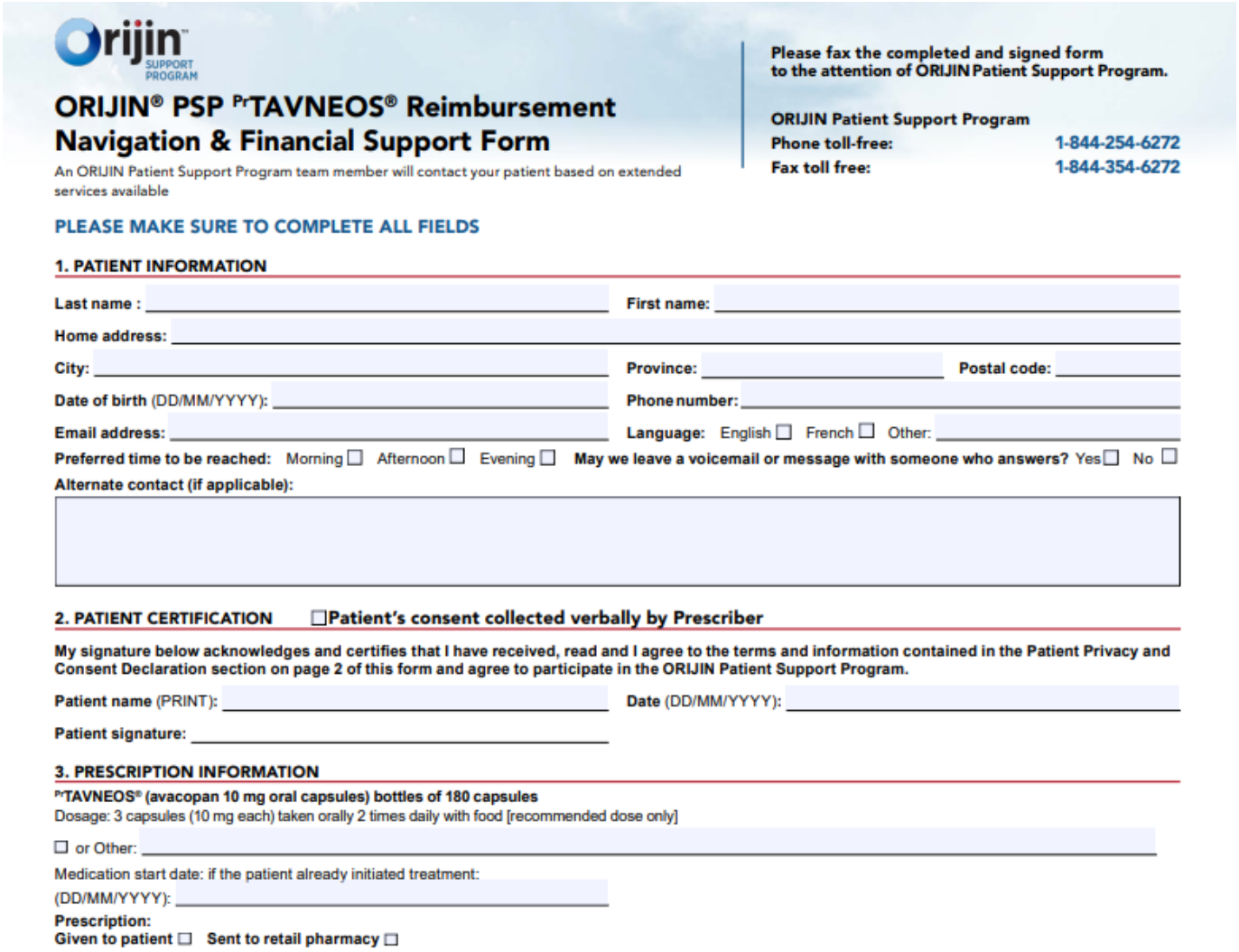
Avacopan Prescribing Information

Dosing	• **30 mg (3 x 10 mg capsules) PO BID with food** • Kidney impairment: No dosage adjustment necessary • Hepatic impairment: Avoid in severe hepatic impairment (Child-Pugh C)
Drug interactions	• **Major substrate and moderate inhibitor of CYP3A4** • Strong and moderate CYP3A4 inducers: Avoid combination • Strong CYP3A4 inhibitors: Reduce avacopan to 30 mg PO daily
Notable adverse effects	• Infections • **Hepatotoxicity (< 5%)** • **Hepatitis B reactivation** • Hypersensitivity reactions
Monitoring	• **LFTs: Baseline, then at least every 4 weeks for first 6 months of therapy, then as clinically indicated** • **Hepatitis B serology: Baseline**
Pregnancy and Lactation	• In the absence of sufficient safety data, avacopan use should be avoided

J Rheumatol. 2021 Apr;48(4):555-566.

Cost of Avacopan

- 1 year supply = ~$79,890
- CADTH CDEC recommended that avacopan not be reimbursed (August 2023)
- Otsuka provides financial support for the first year of therapy through the ORIJIN® Patient Support Program



Orijin SUPPORT PROGRAM

ORIJIN® PSP PrTAVNEOS® Reimbursement Navigation & Financial Support Form

An ORIJIN Patient Support Program team member will contact your patient based on extended services available

Please fax the completed and signed form to the attention of ORIJIN Patient Support Program.

ORIJIN Patient Support Program
Phone toll-free: 1-844-254-6272
Fax toll free: 1-844-354-6272

PLEASE MAKE SURE TO COMPLETE ALL FIELDS

1. PATIENT INFORMATION

Last name : First name:
Home address:
City: Province: Postal code:
Date of birth (DD/MM/YYYY): Phone number:
Email address: Language: English ☐ French ☐ Other:
Preferred time to be reached: Morning ☐ Afternoon ☐ Evening ☐ May we leave a voicemail or message with someone who answers? Yes ☐ No ☐
Alternate contact (if applicable):

2. PATIENT CERTIFICATION ☐Patient's consent collected verbally by Prescriber

My signature below acknowledges and certifies that I have received, read and I agree to the terms and information contained in the Patient Privacy and Consent Declaration section on page 2 of this form and agree to participate in the ORIJIN Patient Support Program.

Patient name (PRINT): Date (DD/MM/YYYY):
Patient signature:

3. PRESCRIPTION INFORMATION

PrTAVNEOS® (avacopan 10 mg oral capsules) bottles of 180 capsules
Dosage: 3 capsules (10 mg each) taken orally 2 times daily with food [recommended dose only]
☐ or Other:
Medication start date: if the patient already initiated treatment:
(DD/MM/YYYY):
Prescription:
Given to patient ☐ Sent to retail pharmacy ☐

CADTH. CADTH Reimbursement Recommendation – Avacopan (Tavneos). Monograph Including Patient Information 28Aug2023 [cited 04Nov2024]. Available from: URL: https://www.cda-amc.ca/sites/default/files/DRR/2023/SR0732REC-Tavneos-KH_BF-KH-meta.pdf

Conclusions

- Avacopan is a glucocorticoid-sparing agent that is an option in the treatment of GPA or MPA
  - Prioritize use in patient at high risk of glucocorticoid toxicity (e.g., high infection risk, preexisting diabetes mellitus, psychiatric disorders, osteoporosis)

- Further studies/data are needed to guide optimal use of avacopan; areas of uncertainty include:
  - Optimal glucocorticoid regimen to be used with avacopan
  - Whether avacopan can be used as a maintenance therapy
  - Role of avacopan in non-severe/limited AAV and in more severe end-organ manifestations of AAV
  - Long-term efficacy and safety of avacopan
  - Optimal duration of avacopan therapy

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Kidney Int. 2024 Mar;105(3S):S71-S116.

Questions?