Avacopan for the Treatment of Anti-Neutrophil Cytoplasmic Auto-antibody (ANCA)-Associated Vasculitis

ChemoCentryx, Inc.

Arthritis Advisory Committee

May 6, 2021

Avacopan Introduction

Thomas J. Schall, Ph.D.

President, Chief Executive Officer

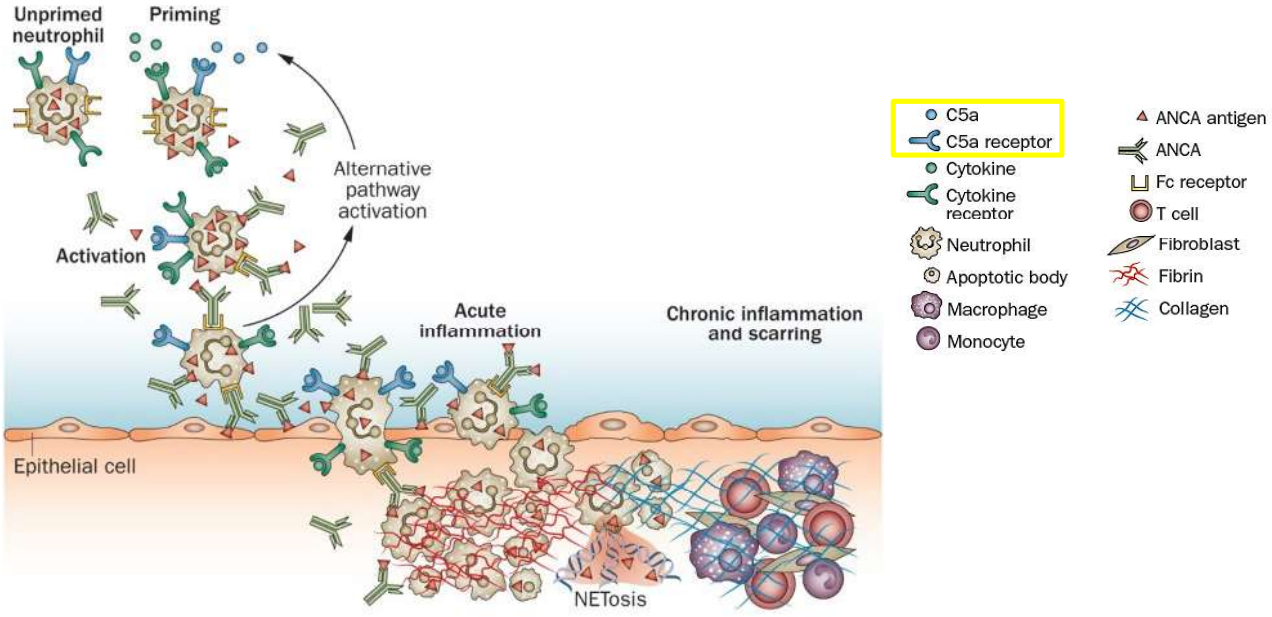
ChemoCentryx, Inc.

Avacopan: First-in-Class, Targeted Therapy for ANCA-Associated Vasculitis

- ANCA-associated vasculitis is rare, severe, and often fatal autoimmune disease
  - Anti-neutrophil cytoplasmic auto-antibodies (ANCA) involved in pathogenesis
  - Inflammation of small vessels, can affect any organ
  - Commonly affects kidneys
- Glucocorticoid treatment associated with significant toxicities
- Despite current therapies, > 1 in 10 patients die within first year of diagnosis[1,2]

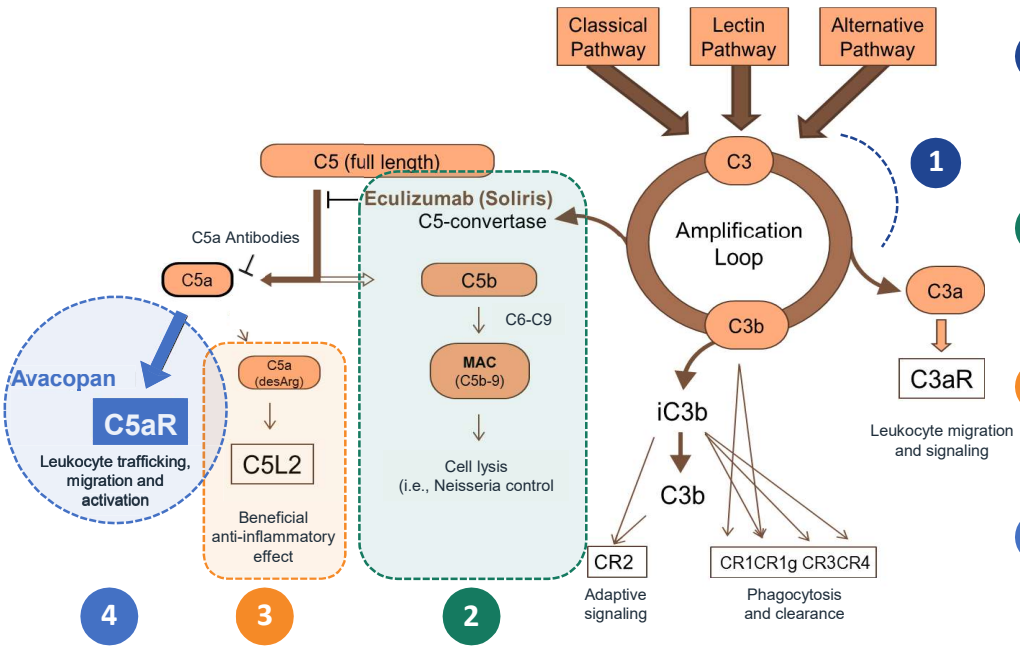
1. Heijl et al., 2017; 2. Little et al., 2010

Central Role of C5a in Pathogenesis of ANCA-Associated Vasculitis



Jennette and Falk, 2014

Avacopan: Highly Potent and Selective C5aR Inhibitor



1. Avacopan avoids long-term biological consequences of 'upstream' complement inhibition
2. Does not block C5b-9 production; leaves host defense mechanism membrane attack complex (MAC) in place
3. Preserves beneficial functions of C5L2 pathway
4. Targets 'downstream' complement pathway

Avacopan in ANCA-Associated Vasculitis

Pirow Bekker, MD, PhD

Clinical Lead
Avacopan Clinical Development Program
ChemoCentryx, Inc.

Avacopan Proposed Indication and Dose

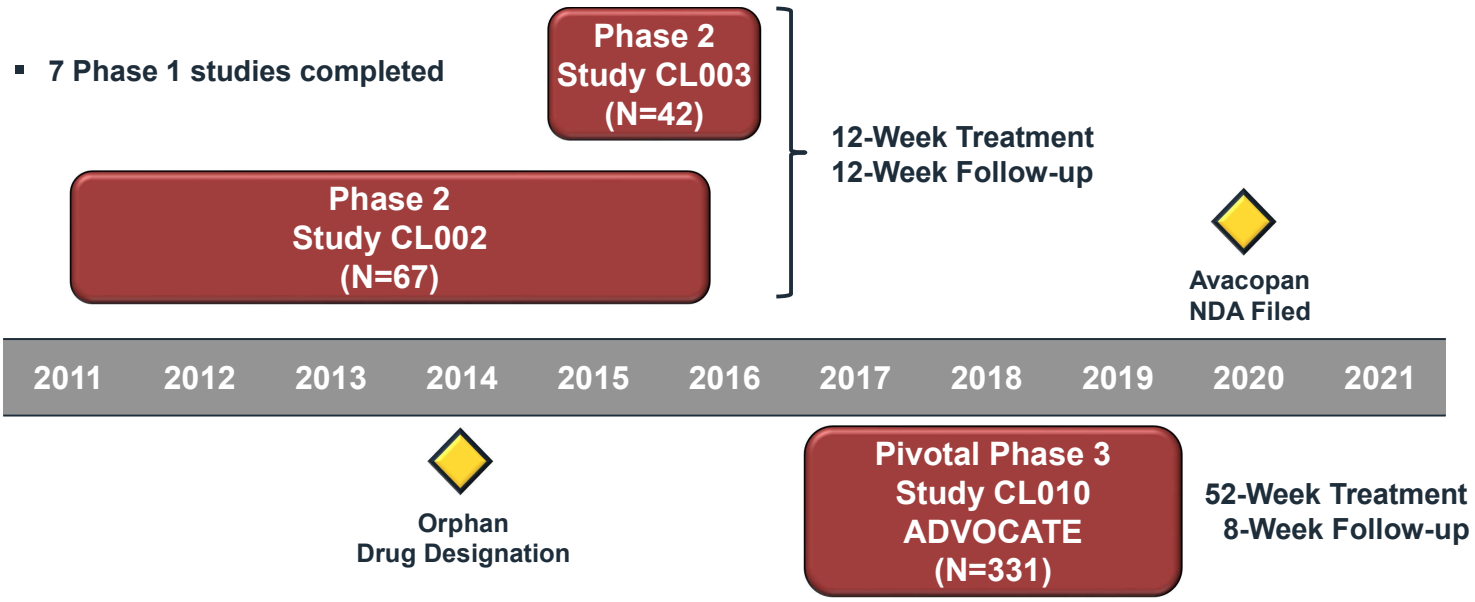
Proposed Indication

…for the treatment of adult patients with anti-neutrophil cytoplasmic auto-antibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis and microscopic polyangiitis).

Proposed Dose

30 mg avacopan taken twice daily with food

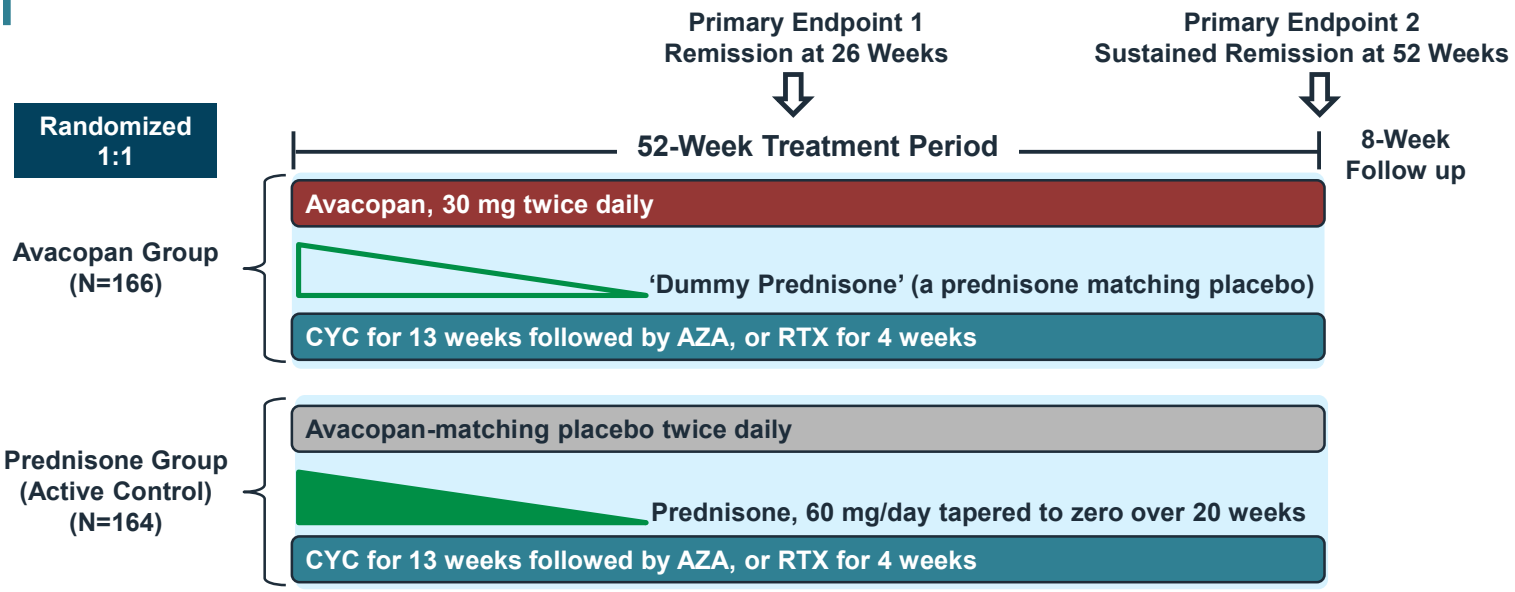
Avacopan Clinical Development Program in ANCA-Associated Vasculitis



ADVOCATE Study Design

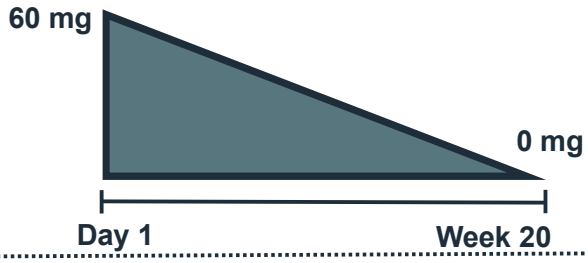
- Sponsor originally proposed a 26-week study with non-inferiority assessment
- Sponsor originally modeled the Phase 3 study on a previous trial (the 26-week,197-patient RAVE study) which led to approval of rituximab in US and Europe
- Europe: a 26-week non-inferiority study with supportive secondary endpoints, e.g., reduced glucocorticoid toxicity deemed acceptable
- In US 26-week non-inferiority would not be sufficient
- Ultimate agreement in US (Nov 2016) to revised study: increasing size and duration (52 weeks); adding a hierarchical analysis to include superiority

ADVOCATE Pivotal Phase 3 Study Design



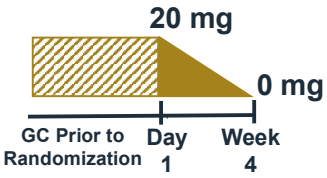
AZA = azathioprine
CYC = cyclophosphamide
RTX = rituximab

Understanding the Sources of Glucocorticoids (GC) in ADVOCATE Study



1. Scheduled daily oral prednisone to prednisone group
   - Provided in kits (blinded)
   - 2450 mg total

2. GC required as rituximab pre-medication = ~500 mg for 4 RTX infusions in first 4 weeks



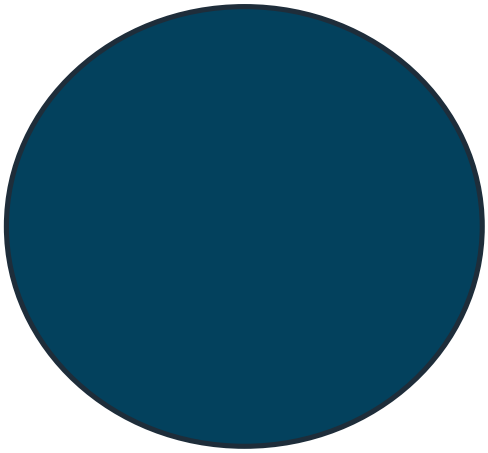
3. GC use following pre-randomization exposure
   - Oral tapering in first 4 weeks of GC given during screening

4. Other prescribed GC

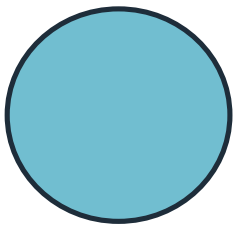
More Relevant Than Overall Incidence: Total GC Exposure Over Treatment Period

Prednisone Group
- Median prednisone load 2939 mg
- Mean prednisone load 3655 mg

Eliminating need for daily prednisone:
- Reduced median total GC load 86%
- Reduced mean total GC load 63%



Avacopan Group
- Median prednisone load 400 mg
- Mean prednisone load 1349 mg



Avacopan Clinical Data Demonstrate Positive Benefit-Risk Profile

- Allows patients to achieve and sustain remission while reducing toxicities associated with glucocorticoids
- Phase 3 study primary endpoints met
- Higher sustained remission and reduced risk of relapse
- Clinically meaningful improvements in kidney function and health-related quality of life
- Favorable safety profile
- Fulfills several unmet medical needs

Agenda

Disease Background and Unmet Need	**David Jayne, MD** Professor of Clinical Autoimmunity, University of Cambridge Director of the Vasculitis and Lupus Service, Addenbrooke's Hospital
Avacopan Efficacy	**Peter A. Merkel, MD, MPH** Chief, Division of Rheumatology Director, Penn Vasculitis Center University of Pennsylvania
Avacopan Safety	**David Jayne, MD**
Clinical Perspective	**Peter A. Merkel, MD, MPH**

Additional Experts

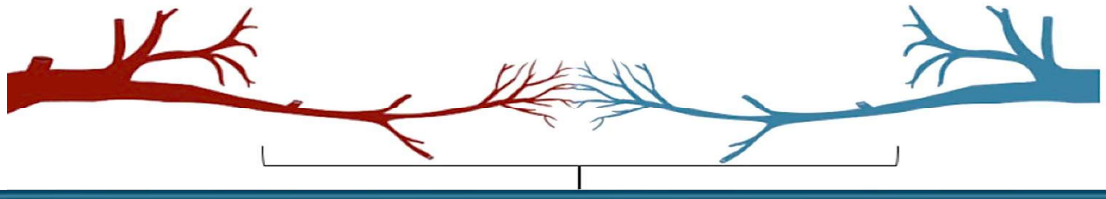
John Niles, MD
Director, Vasculitis and Glomerulonephritis Center
Nephrology Division
Massachusetts General Hospital

John Stone, MD, MPH
Director, Clinical Rheumatology
Massachusetts General Hospital

Disease Background and Unmet Need

David Jayne, MD
Professor of Clinical Autoimmunity
University of Cambridge, United Kingdom
Director, Vasculitis and Lupus Service
Addenbrooke's Hospital
President, European Vasculitis Society (EUVAS)

ANCA-Associated Vasculitis: Heterogenous Group of Systemic Autoimmune Diseases



Necrotizing vasculitis affecting small to medium-sized blood vessels[1-3]

Granulomatosis with Polyangiitis (GPA)	Microscopic Polyangiitis (MPA)

- **Conditions demonstrate distinct pathological profiles yet overlapping clinical characteristics[4,5]**

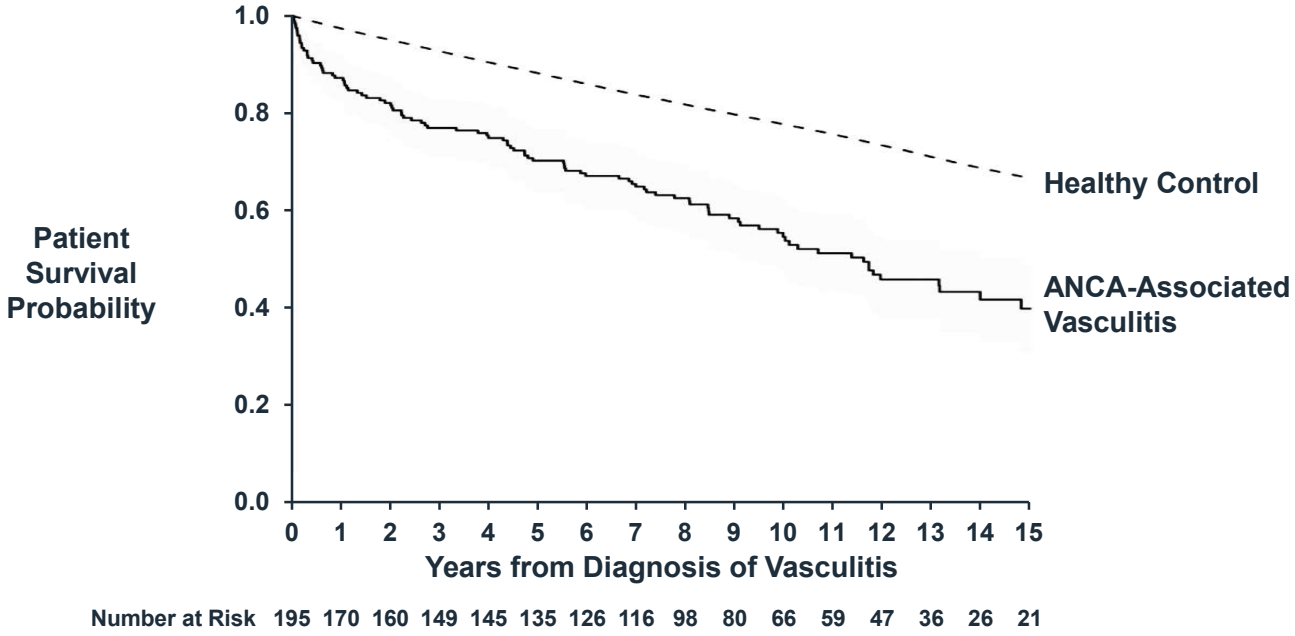
1. Yates and Watts, 2017; 2. Al-Hussain et al., 2017; 3. Chen, Jayne, and Zhao, 2017; 4. Brunini, et al., 2016; 5. Hutton, et al., 2017

ANCA-Associated Vasculitis is Rare, Serious, and Life-Threatening Disease

- US incidence = 3.3 cases per 100,000 adults every year[1]
- Clinical features vary based on disease stage and organ involvement
- Can affect any organ, frequently kidneys and respiratory tract
  - 80 to 90% of patients present with renal or another organ-threatening manifestation[2]
- 11 to 12% of patients die within first year of diagnosis
  - Medications were major cause of deaths (60%)[3,4]

1. Berti et al., 2017; 2. Lamprecht et al., 2018; 3. Little et al., 2010; 4. Heijl et al., 2017

Decreased Survival Probability in Patients with ANCA-Associated Vasculitis



Heijl C et al., 2017

Primary Goals of Managing ANCA-Associated Vasculitis[1-4]

- Rapid diagnosis
- Prompt treatment initiation
- Early remission achievement to prevent organ damage
- Limit glucocorticoid use to prevent associated toxicity
- Prevent relapses

1. Miller et al., 2010; 2. Pearce et al., 2018; 3. Demiselle et al., 2017; 4. Ntatsaki, et al., 2014

Current Treatments for ANCA-Associated Vasculitis

	Current Treatment		
Initial Treatment	**Glucocorticoid treatment** ▪ High-dose IV, followed by tapering regimen of oral glucocorticoids	+	**Immunosuppressants** ▪ IV or oral cyclophosphamide ▪ Rituximab
Maintenance Treatment	▪ Glucocorticoids ▪ Azathioprine ▪ Methotrexate ▪ Mycophenolate mofetil ▪ Repeated administration of rituximab		

- Despite current therapies, mortality remains high
- Many sustain damage from disease- or therapy-related toxicities

Significant Concerns Remain with Current Treatments for ANCA-Associated Vasculitis

- High relapse rate with some treatments
- Limited efficacy on renal function
- Detrimental effect on health-related quality of life
- High level of toxicity

Current Treatments Provide Low Sustained Remission and High Relapse Rates

- Relapses associated with increased tissue and organ damage[1]
- Additional toxicities from glucocorticoid treatment[2]
- RAVE Study[3]
  - Looked at relapse-free remission at 18 months
  - 39% of patients following single course of rituximab
  - 33% of patients in cyclophosphamide / azathioprine group
  - Induction with rituximab without maintenance therapy unlikely to prevent future relapse
- Reduced relapse rate with rituximab, but safety concerns remain

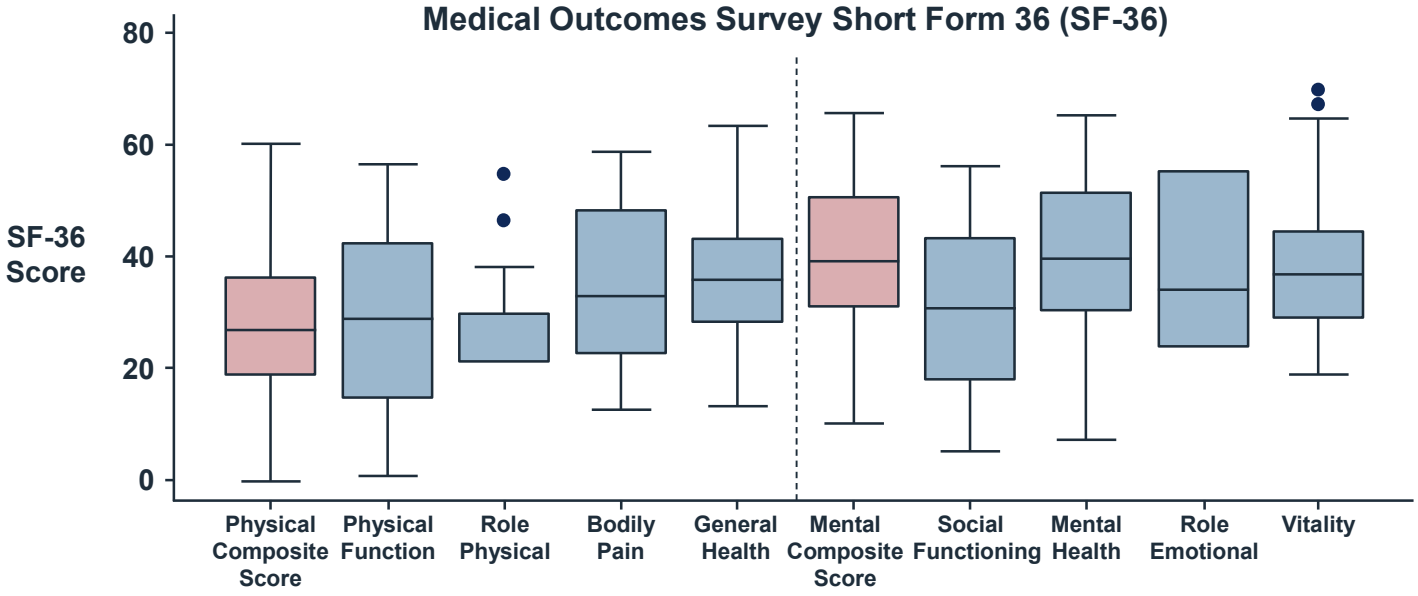
1. Robson et al., 2015; 2. Yates et al., 2016; 3. Specks et al., 2013

Current Treatments Have Limited Efficacy on Renal Function

- Renal involvement common in patients with GPA or MPA
  - Occurring > 70% of patients
  - Worse prognosis than patients without renal involvement[1]
- Post-hoc analysis of RAVE study showed limited efficacy on estimated glomerular filtration rate (eGFR) over time[2]
  - Similar for rituximab and cyclophosphamide / azathioprine groups
- Treatment should focus on renal function improvement

1. Corral-Gudino et al., 2011; 2. Geetha et al., 2015

Patients with ANCA-Associated Vasculitis Often Have Impaired Health-Related QoL



Adapted from Walsh M et al., 2011

Glucocorticoids Associated with Emotional, Physical, and Social Effects

- High doses can cause initial euphoria, affect sleep patterns and cause daytime fatigue
- Depression, anxiety, and irritability often reported
- Myopathy may lead to reduced physical function
- Weight gain and changes in appearance widely reported
  - Increased appetite
  - Moon-shaped face
  - Unwanted attention to underlying disease

Robson et al., 2018

High Level of Toxicity with Current Therapies, Including Glucocorticoids

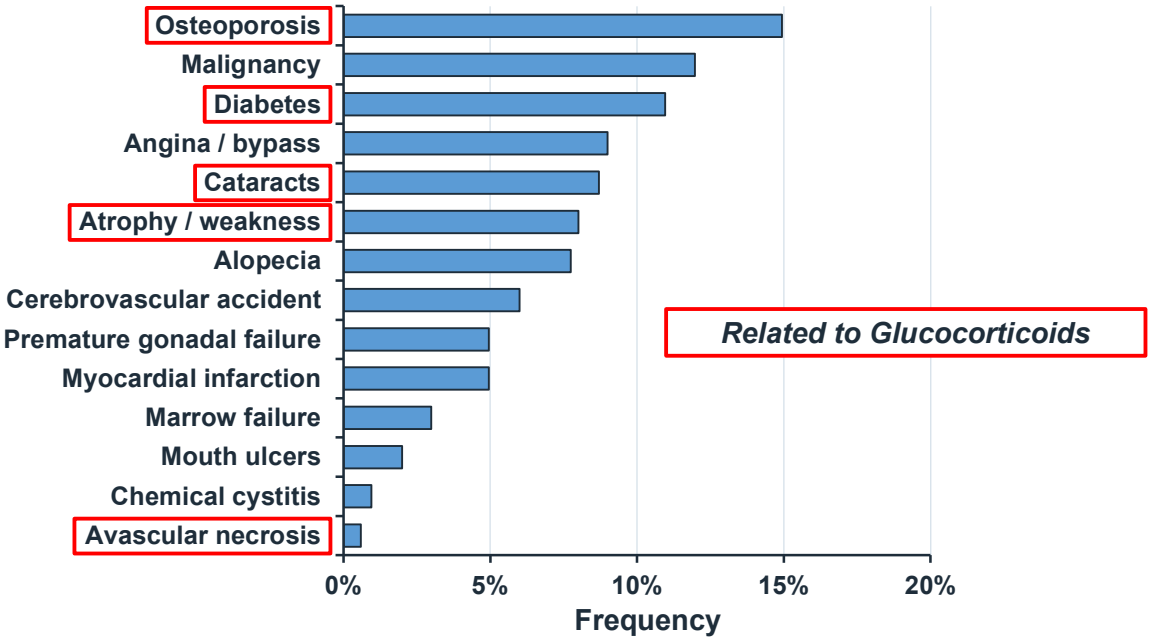
Glucocorticoid use associated with significant toxicity[1, 2]

- Infection
- New onset or worsening diabetes
- Hyperlipidemia
- Hypertension and cardiovascular disease

- Myopathy
- Osteoporosis
- Skin disorders
- Neuropsychiatric disorders
- Immune suppression

1. Little et al., 2010; 2. Robson et al., 2015

Treatment-Related Organ Damage Common in Patients with ANCA-Associated Vasculitis



Robson et al., 2015

Patients with ANCA-Associated Vasculitis Need Treatment to Address Unmet Needs

- Successful alternative therapies should
  - Suppress disease activity long-term
  - Reduce relapse rates
  - Improve renal function
  - Improve health-related quality of life
  - Minimize treatment-related toxicity
  - Allow patients to reduce or eliminate oral glucocorticoids

Avacopan Efficacy

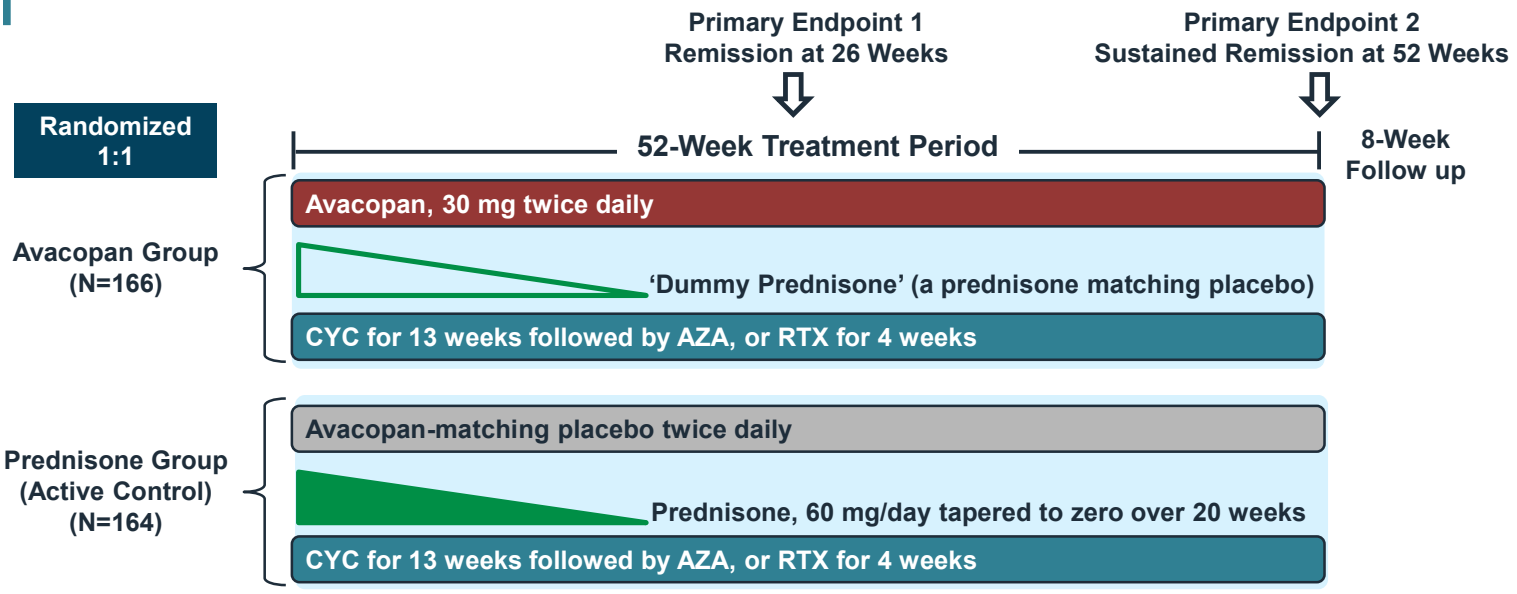
Peter A. Merkel, MD, MPH

Chief, Division of Rheumatology
Director, Penn Vasculitis Center
University of Pennsylvania

ADVOCATE Study Evaluated Avacopan Efficacy and Safety While Eliminating Glucocorticoids

- Pivotal Phase 3 randomized, double-blind, double-dummy, active-controlled clinical trial
- Eligibility criteria
  - Diagnosis of GPA or MPA
  - Positive test for ANCA with antibodies to either proteinase-3 (PR3) or myeloperoxidase (MPO)
  - Newly-diagnosed or relapsing active ANCA-associated vasculitis

ADVOCATE Pivotal Phase 3 Study Design



AZA = azathioprine
CYC = cyclophosphamide
RTX = rituximab

Key Considerations of ADVOCATE Study Design

- Study arm with no glucocorticoids and no avacopan not considered feasible or ethical
- Glucocorticoid taper in control arm standardized according to best medical practice and expert consensus
- Impossible to conduct a trial in ANCA-associated vasculitis without allowing some glucocorticoids, e.g., as pre-medication for rituximab
- Background therapy with cyclophosphamide and rituximab given according to best practices and prescribing information at the time

No Re-Treatment in Rituximab Stratum

- Consistent with treatment practice and rituximab label at time of study launch
- Consistent with RAVE study, where rituximab group, without maintenance treatment, was non-inferior to cyclophosphamide group at 6, 12, and 18 months[1]
- No maintenance treatment in rituximab stratum allowed for assessment of avacopan in true placebo-controlled manner at Week 52
  - Placebo control is gold standard for efficacy assessment

[1]Specks et al., 2013

Patients Stratified Based on 3 Factors

1. Background immunosuppressive therapy: rituximab, IV cyclophosphamide, or oral cyclophosphamide
2. ANCA type: PR3 or MPO
3. Newly-diagnosed or relapsing ANCA-associated vasculitis

ADVOCATE Included Two Primary Endpoints

1. Remission at Week 26
2. Sustained remission at Week 52

   - Both endpoints based on Birmingham Vasculitis Activity Score (BVAS): validated tool used to capture vasculitis disease activity

Primary Endpoints Based on Birmingham Vasculitis Activity Score (BVAS)

- Captures disease activity in 9 organ systems
- Score range from 0 – 63, higher score = greater disease activity
- Definition of Remission at Week 26 and Sustained Remission at Week 52
  - BVAS = 0
  - Not taking glucocorticoids for vasculitis within prior 4 weeks
- Not in Sustained Remission if relapse occurred after Remission at Week 26
- Relapse = return of disease activity with ≥ 1 BVAS major item, ≥ 3 non-major items, OR 1 or 2 non-major items for ≥ 2 consecutive visits
- Blinded adjudication committee reviewed investigator-assessed BVAS
  - Adjudicated data used for primary endpoint analyses according to pre-specified plan

Statistical Hierarchy for Primary Endpoints

- Tested sequentially using gatekeeping procedure to maintain Type I error at 0.05
  1. Non-inferiority at Week 26
  2. Non-inferiority at Week 52
  3. Superiority at Week 52
  4. Superiority at Week 26
- Study declared successful if, at minimum, first test met

Key Secondary Endpoints Included Clinically-Important Patient Outcomes

Relapse	▪ Return of disease activity after achieving remission
Glucocorticoid Toxicity	▪ Glucocorticoid Toxicity Index (GTI)
Kidney Function	▪ Estimated glomerular filtration rate (eGFR) ▪ Urinary albumin:creatinine ratio (UACR)
Health-Related Quality of Life	▪ Medical Outcomes Survey Short Form 36 version 2 (SF-36 v2) ▪ EuroQuality of Life-5 Domains-5 Levels (EQ-5D-5L)

ADVOCATE Patient Disposition: 91% of Patients Completed Week 60 in Each Treatment Group

	Avacopan (N=166)	Prednisone (N=165)
ITT and Safety Population*	**166 (100%)**	**164 (99%)**
Completed Week 26	**155 (93%)**	**154 (93%)**
Completed Week 52	**151 (91%)**	**152 (92%)**
Completed Week 60	**151 (91%)**	**150 (91%)**
Early withdrawal from study	**15 (9%)**	**15 (9%)**
Adverse event	3 (2%)	6 (4%)
Withdrawal by patient	6 (4%)	3 (2%)
Investigator decision	3 (2%)	4 (2%)
Lost to follow-up	1 (0.6%)	2 (1%)
Other	2 (1%)	0 (0%)
Death	**2 (1%)**	**4 (2%)**

*** All randomized patients who received at least one dose of study drug (avacopan/prednisone)**

ADVOCATE: Baseline Demographics Well Balanced Between Treatment Groups

	Avacopan (N=166)	Prednisone (N=164)
Age (years) at screening, mean ± SD	61.2 ± 14.6	60.5 ± 14.5
Sex, (%)		
Male	59%	54%
Female	41%	46%
Race, (%)		
White	83%	85%
Asian	10%	9%
Black or African American	2%	1%
Other	5%	4%
Multiple	0	0.6%

ADVOCATE: Baseline Disease Characteristics

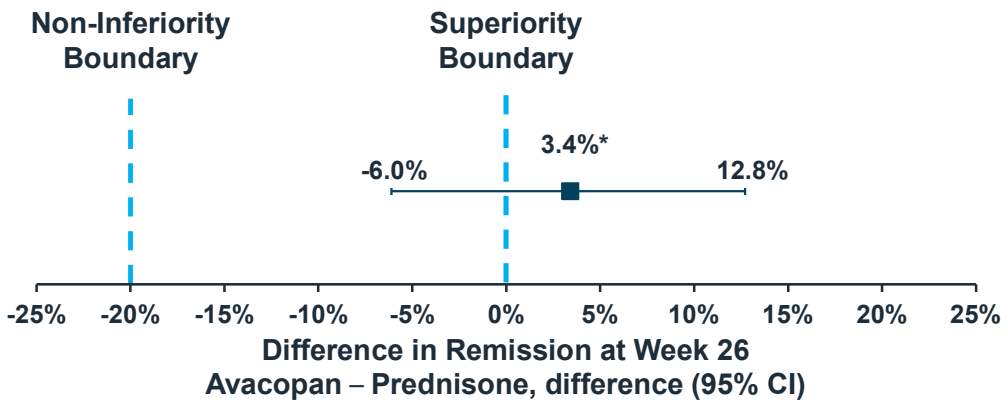
	Avacopan (N=166)	Prednisone (N=164)
ANCA-Associated Vasculitis status		
Newly diagnosed	69%	70%
Relapsed	31%	31%
ANCA type		
Proteinase 3 positive	43%	43%
Myeloperoxidase positive	57%	57%
ANCA disease type		
Granulomatosis with polyangiitis	55%	55%
Microscopic polyangiitis	45%	45%
Background standard of care therapy		
Rituximab	65%	65%
Cyclophosphamide IV / Oral	36%	35%
BVAS, mean ± SD Median (range)	16.3 ± 5.9 15.0 (5, 37)	16.2 ± 5.7 15.5 (5, 33)
eGFR (mL/min/1.73 m^2), mean ± SD	50.7 ± 31.0	52.9 ± 32.7

ADVOCATE: BVAS Items at Baseline

Organ involvement (based on BVAS), % of pts	Avacopan (N=166)	Prednisone (N=164)
Renal	81%	82%
General	67%	70%
Ear, nose and throat	45%	42%
Chest	43%	43%
Nervous system	23%	19%
Mucous membranes/eyes	16%	24%
Cutaneous	15%	14%
Cardiovascular	4%	2%
Abdominal	2%	0.6%

Primary Endpoint: Avacopan Non-Inferior to Prednisone in Week 26 Clinical Remission

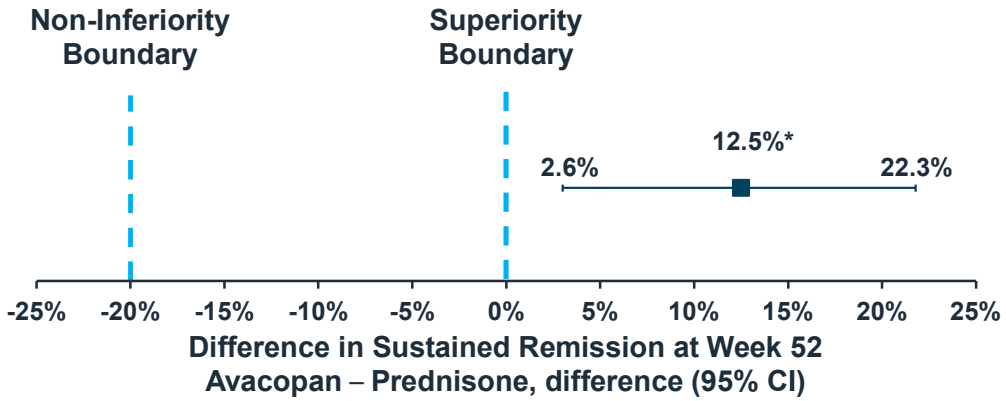
	Patients Achieving Clinical Remission n (%)	Non-Inferiority p-value	Superiority p-value
Avacopan (N=166)	120 (72.3%)	< 0.0001	0.2387
Prednisone (N=164)	115 (70.1%)		



*Summary score estimate of common difference in remission rates (Agresti 2013) by using inverse-variance stratum weights

Primary Endpoint: Avacopan Superior to Prednisone in Week 52 Sustained Remission

	Patients Achieving Sustained Remission n (%)	Non-Inferiority p-value	Superiority p-value
Avacopan (N=166)	109 (65.7%)	< 0.0001	0.0066
Prednisone (N=164)	90 (54.9%)		



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Per Protocol Population Analyses of Primary Endpoints

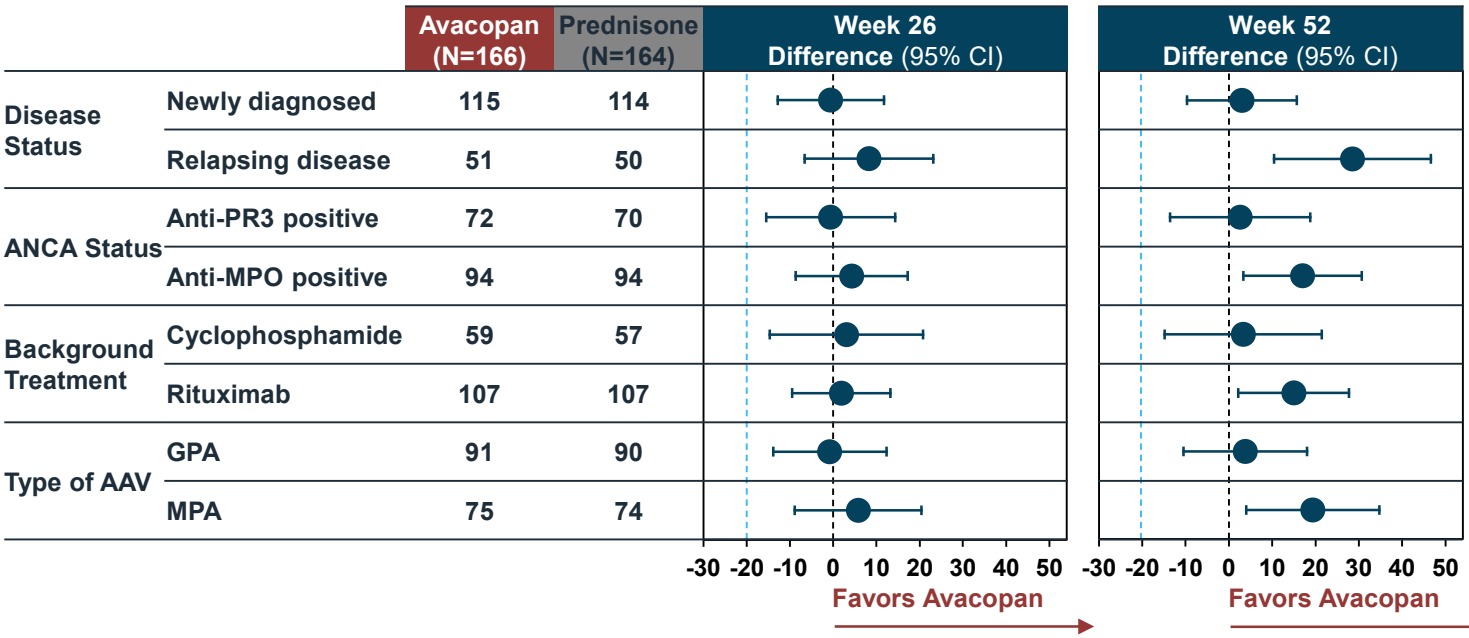
Remission at Week 26

Treatment	n	%	Diff. in %	Estimate of Common Diff. in %	Two-sided 95% CI for Diff. in %	Non-inferior p-value	Superior p-value
Avacopan (N=162)	110	67.9	0.2	2.0	-7.6, 11.6	<0.0001	0.3419
Prednisone (N=161)	109	67.7					

Sustained Remission at Week 52

Treatment	n	%	Diff. in %	Estimate of Common Diff. in %	Two-sided 95% CI for Diff. in %	Non-inferior p-value	Superior p-value
Avacopan (N=162)	95	58.6	8.3	11.0	1.0, 21.1	<0.0001	0.0159
Prednisone (N=161)	81	50.3					

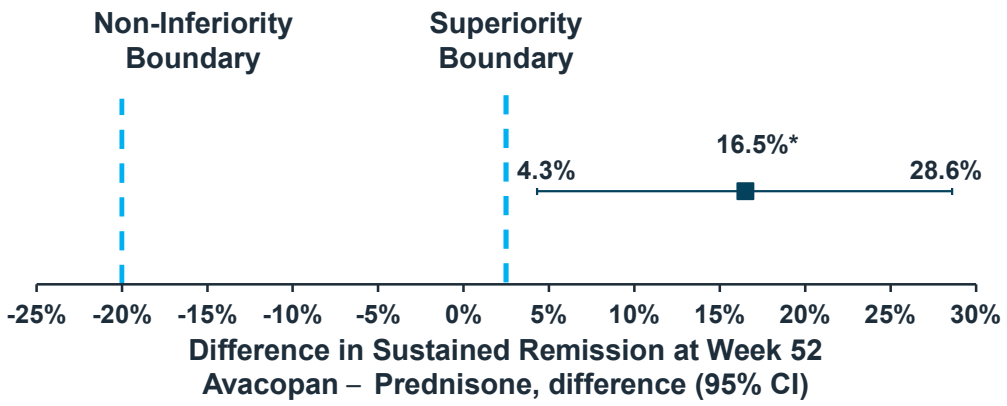
Avacopan without Daily Prednisone Effective Across Subgroups



Blue dashed line represents non-inferiority margin

Week 52 Sustained Remission in Rituximab Stratum

	Patients Achieving Sustained Remission n (%)	Non-Inferiority p-value	Superiority p-value
Avacopan (N=107)	76 (71.0%)	<0.0001	0.0040
Prednisone (N=107)	60 (56.1%)		



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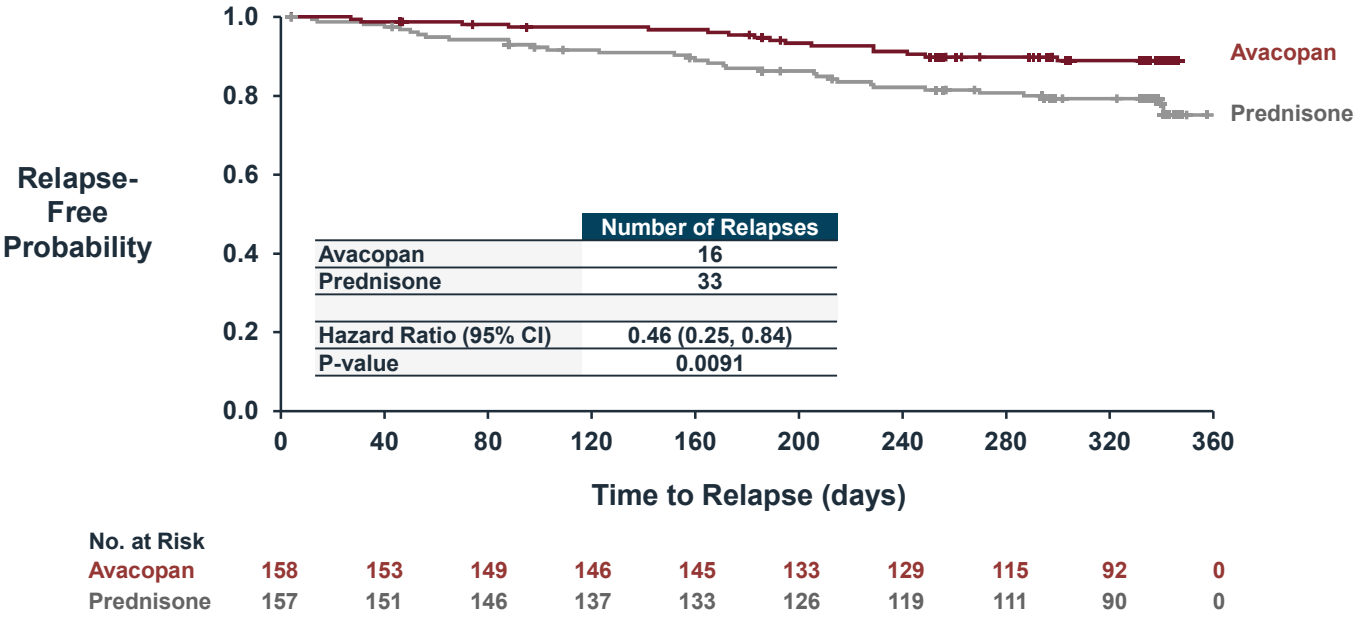
Lower Risk of Relapse in Avacopan Compared to Prednisone Group

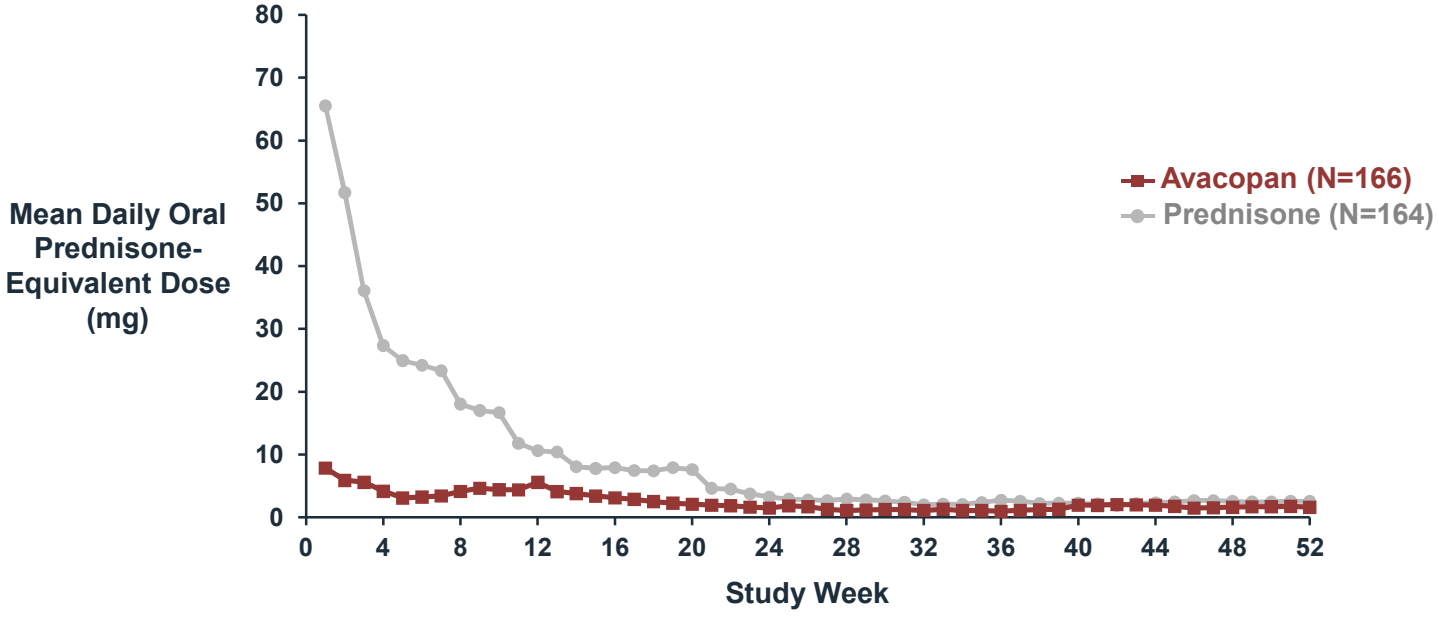


	Number of Relapses
Avacopan	16
Prednisone	33
Hazard Ratio (95% CI)	0.46 (0.25, 0.84)
P-value	0.0091

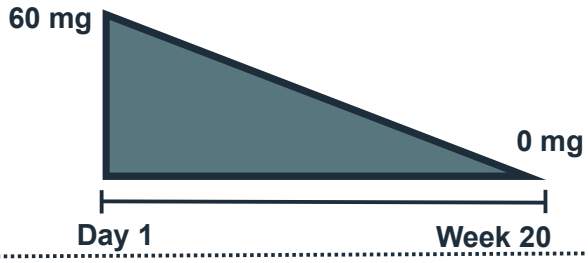
No. at Risk										
Avacopan	158	153	149	146	145	133	129	115	92	0
Prednisone	157	151	146	137	133	126	119	111	90	0

Time to relapse defined as time from when BVAS = 0 first achieved up to time when relapse occurred

Oral Glucocorticoid Dose by Study Week



Understanding the Sources of Glucocorticoids (GC) in ADVOCATE Study



1. Scheduled daily oral prednisone to prednisone group
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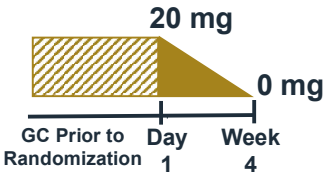
   - 2450 mg total

2. GC required as rituximab pre-medication = ~500 mg for 4 RTX infusions in first 4 weeks

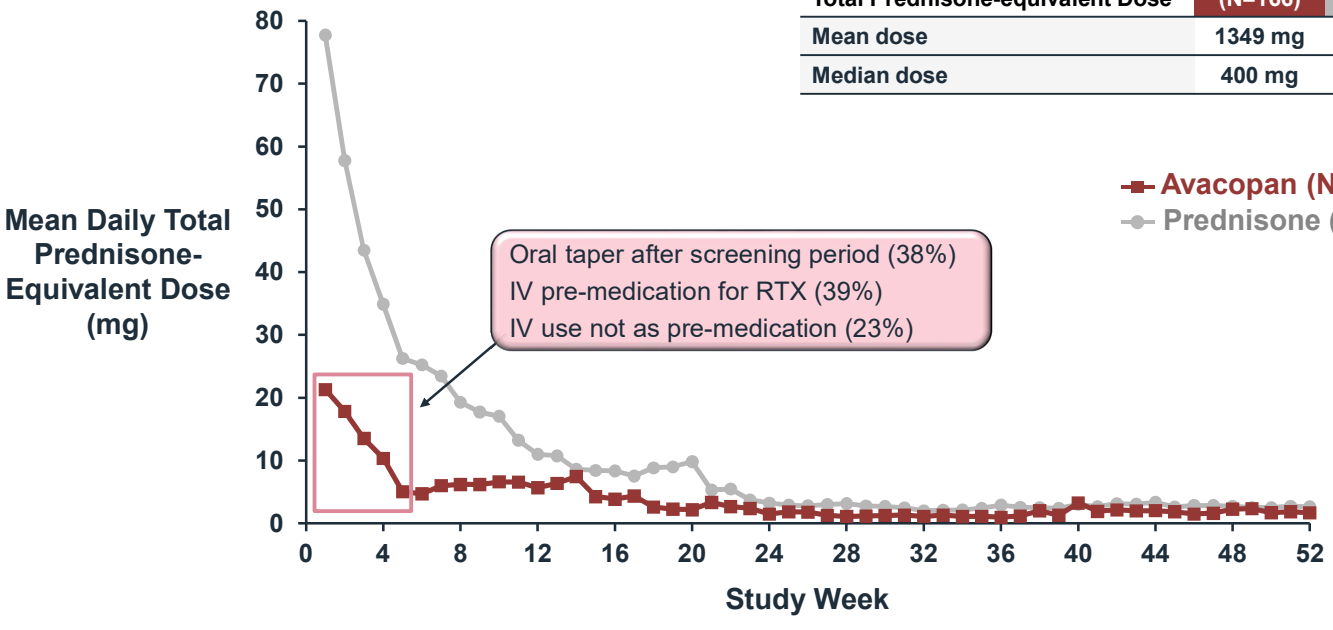


3. GC use following pre-randomization exposure
   - Oral tapering in first 4 weeks of GC given during screening

4. Other prescribed GC

All Glucocorticoid Dose by Study Week

Total Prednisone-equivalent Dose	Avacopan (N=166)	Prednisone (N=164)
Mean dose	1349 mg	3655 mg
Median dose	400 mg	2939 mg



Patient Incidence of Extra Glucocorticoid Use by Study Period

	Avacopan (N=166) n (%)	Prednisone (N=164) n (%)
Day 1 to Week 4	138 (83%)	141 (86%)
Week 4 to Week 26	52 (31%)	56 (34%)
Week 26 to Week 52	45 (27%)	64 (39%)

- Incidence of glucocorticoid use only high within first 4 weeks
  - Oral taper after screening period
  - IV pre-medication for rituximab
  - IV use not as pre-medication

Summary of Glucocorticoid Use

- Elimination of daily oral glucocorticoid use with avacopan
- Substantial reduction in overall glucocorticoid use
- Most additional glucocorticoid use within first 4 weeks
  - Mainly due to rituximab pre-medication and taper after pre-study use

Secondary Endpoint: Glucocorticoid Toxicity Index (GTI)[1, 2]

- GTI is a standardized, weighted, validated instrument that measures **change** in glucocorticoid toxicity
- Created by international group of 17 experts representing 11 subspecialties[1]
- Methodology employed identical to that used in multiple ACR/EULAR Classification Criteria efforts:
  - Multicriteria decision analysis
  - Validation in real patients[2]

1. Miloslavsky et al., 2016; 2. McDowell, et al., 2020

GTI: A Clinician-Facing Instrument Relying on Patient Input

- Several domains require direct patient interaction and consideration of the impact of glucocorticoid toxicity on their lives:
  - Myopathy domain – assessment of patients' muscle strength and its impact on day-to-day function
  - Skin toxicity domain – assessments that consider impact on activities of daily living
  - Neuropsychiatric effects domain – assessment of day-to-day functioning as impacted by insomnia, depression, other

Glucocorticoid Toxicity Index Components

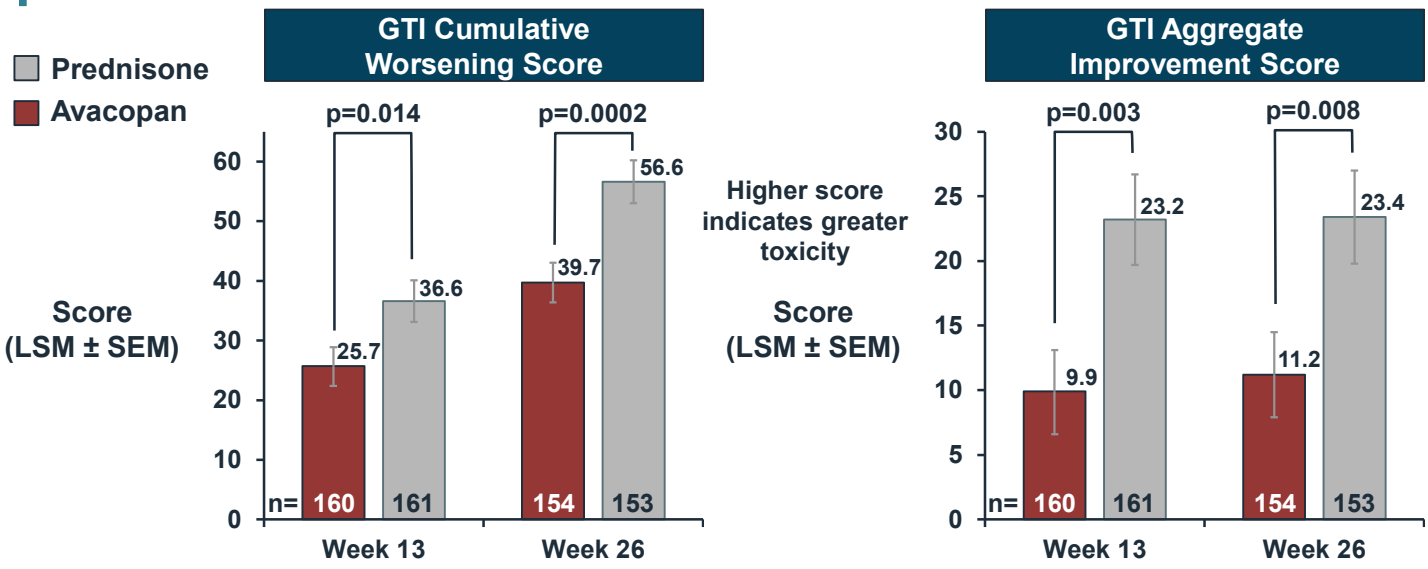
Cumulative Worsening Score (CWS)

- Reflects cumulative toxicity over time
- Score can only increase or stay the same

Aggregate Improvement Score (AIS)

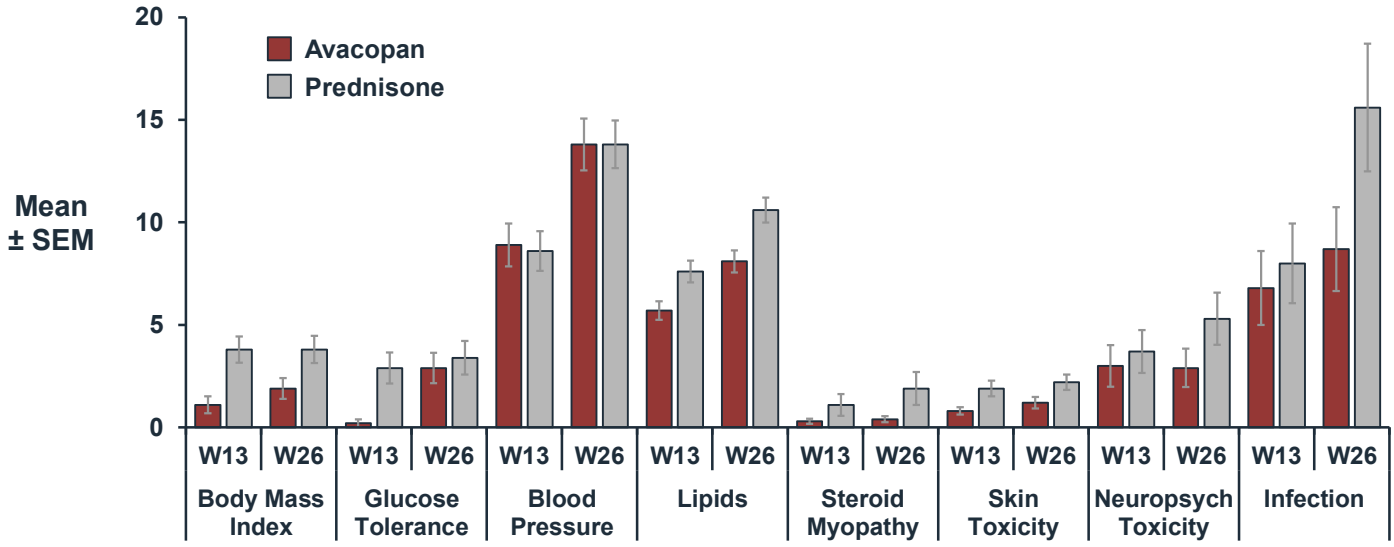
- Reflects both worsening and improvement in toxicity
- Score can increase, decrease, or stay the same

Glucocorticoid-Related Toxicity Reduced with Avacopan Compared to Prednisone

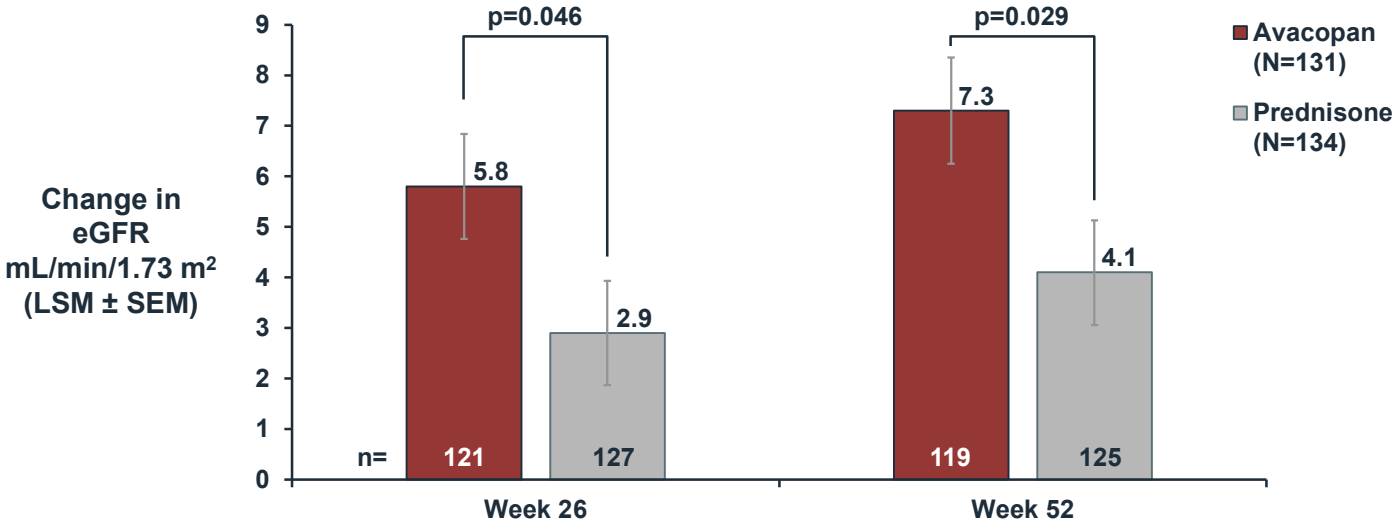


Differences of ≥10 points are clinically important (McDowell et al, 2020)

Glucocorticoid Toxicity: GTI Cumulative Worsening Score Components



Change from Baseline in Estimated Glomerular Filtration Rate

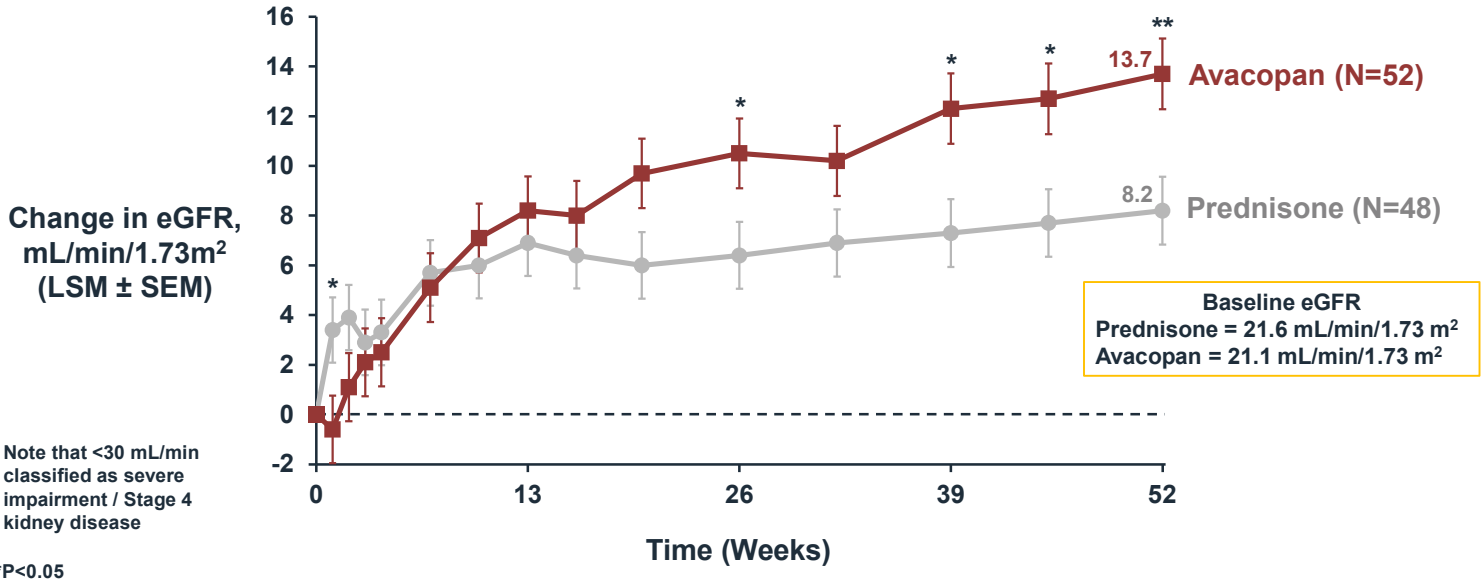


Measured in patients with baseline renal disease
eGFR based on serum creatinine

Baseline eGFR
Prednisone = 45.6 mL/min/1.73 m²
Avacopan = 44.6 mL/min/1.73 m²

CO-61

Pre-specified Analysis in Patients with Stage 4 Kidney Disease: Greater Improvement in Renal Function in Patients with eGFR < 30 at Baseline

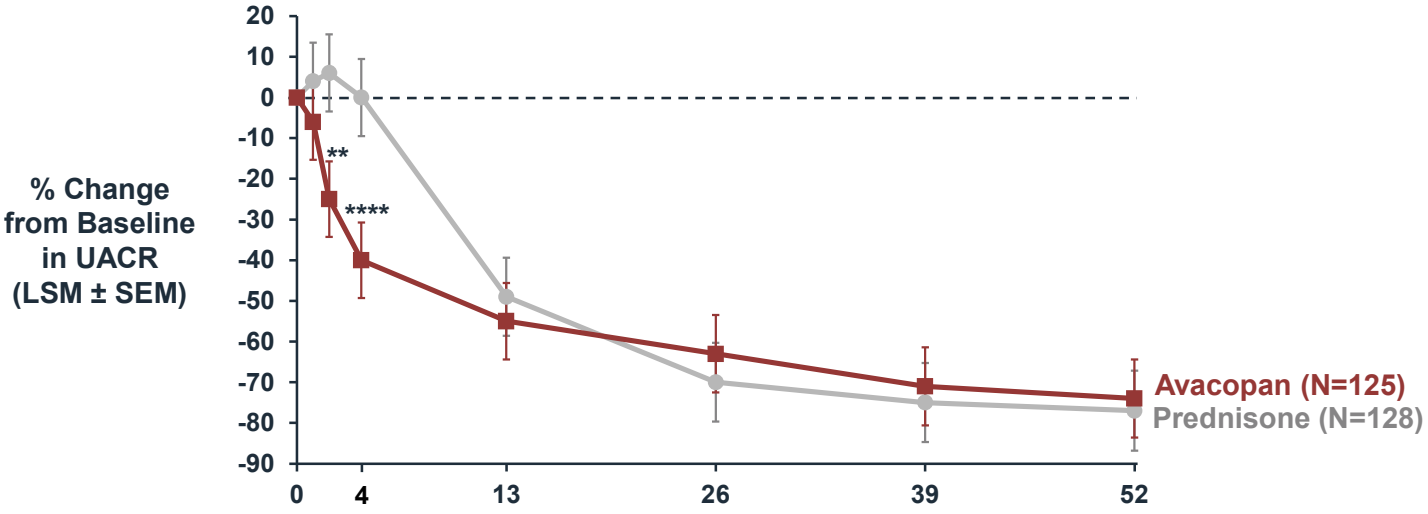


Note that <30 mL/min classified as severe impairment / Stage 4 kidney disease

*P<0.05
**P<0.01 for avacopan compared to prednisone

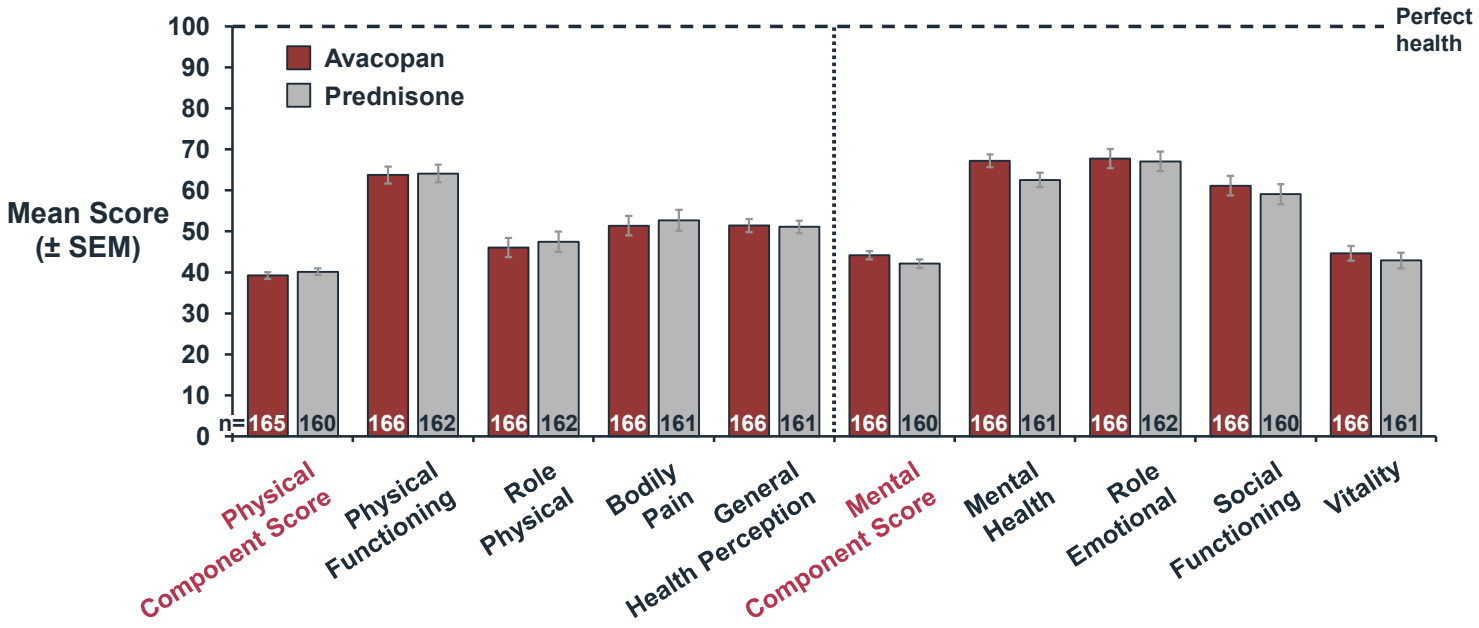
CO-62

Early Improvement in Urinary Albumin:Creatinine Ratio in Avacopan Group

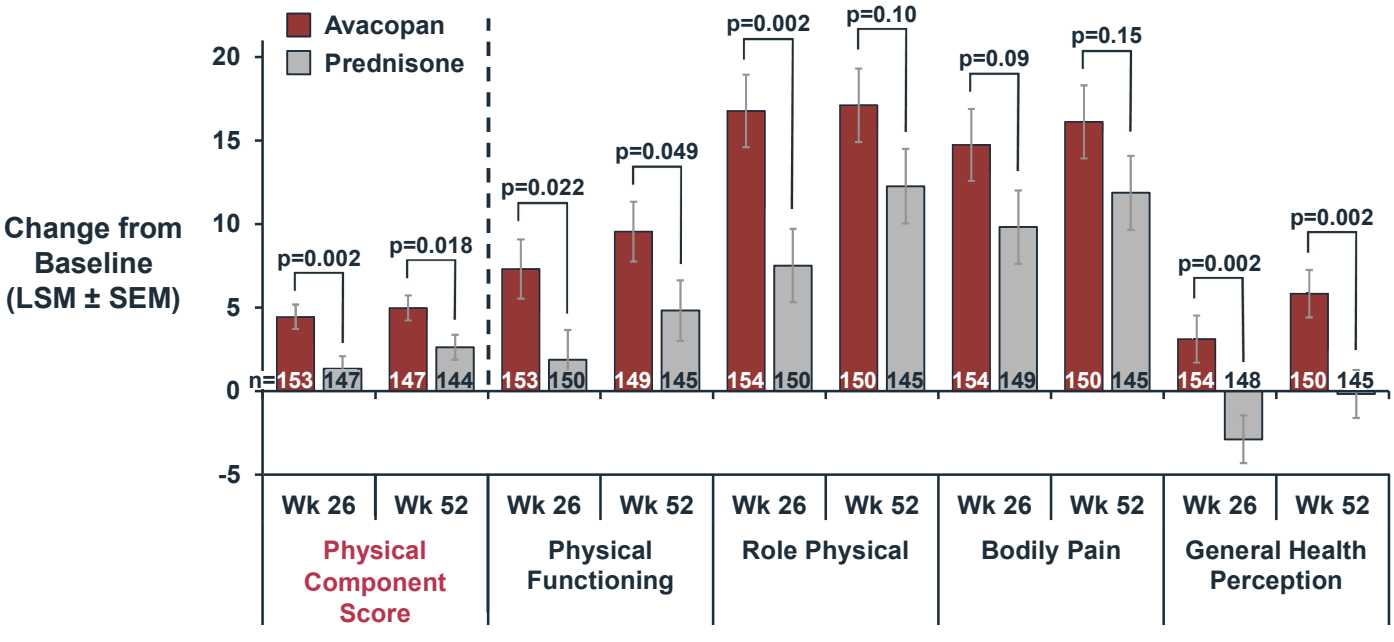


Measured in patients with baseline albuminuria
****p < 0.0001
**p < 0.01 for avacopan compared to prednisone

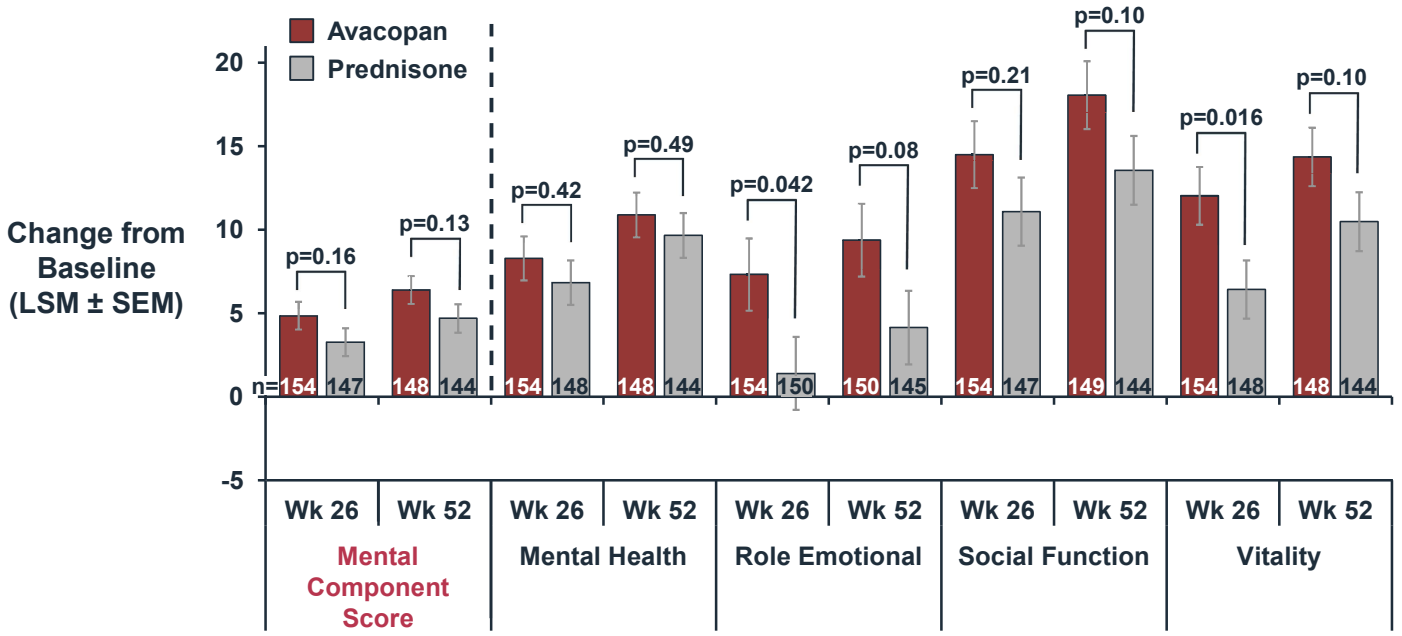
Impaired QOL at Baseline Measured by SF-36



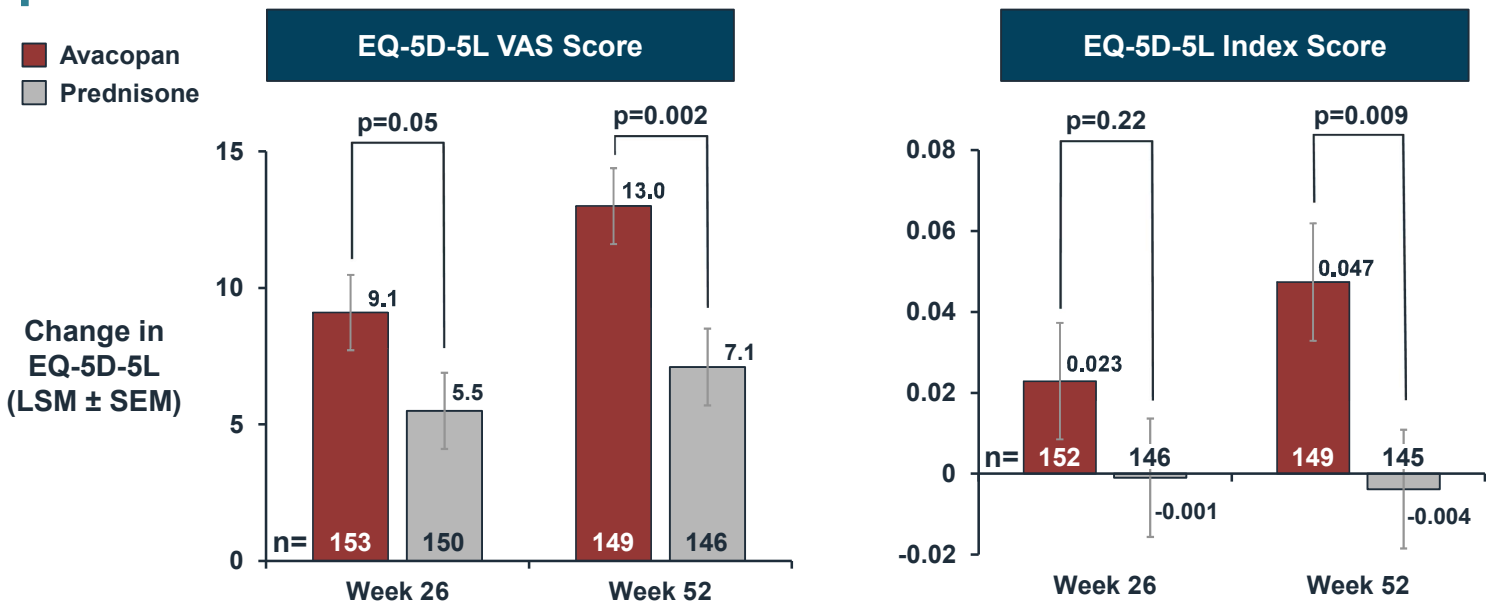
Avacopan Improved Health-Related QoL: SF-36 Physical Component Domains



SF-36 Mental Component Domains



Significant Improvement in EQ-5D-5L at Week 52 with Avacopan Compared to Prednisone



VAS = visual analogue scale (0-100)

ADVOCATE Demonstrated Meaningful Efficacy of Avacopan

- Both pre-specified primary endpoints met
  - Clinical remission at Week 26
  - Statistically superior sustained remission at Week 52
- Lower risk of relapse with avacopan compared to prednisone
- Less glucocorticoid toxicity
- Greater improvements in kidney function
  - Particularly evident in patients with Stage 4 kidney disease
- Improved health-related quality of life

Safety of Avacopan

David Jayne, MD

Overall Avacopan Safety Exposure

	Patients Receiving Avacopan
Clinical pharmacology studies	**206**
Phase 2 and 3 controlled studies	**239**
Phase 2 CL002	44
Phase 2 CL003	29
Phase 3 CL010 (ADVOCATE)	166
Compassionate use / uncontrolled studies	**23**
Other indications	**310**
Total	**1017**

Avacopan AE Overview Across All Phase 2 and 3 Studies

	Avacopan (N=239) Patients n (%)	Prednisone (N=200) Patients n (%)
AE	**233 (98%)**	**195 (97%)**
Severe AE	**51 (22%)**	**45 (22%)**
Serious AE	**94 (40%)**	**82 (39%)**
Life-threatening	**10 (4%)**	**14 (6%)**
Death	**2 (1%)**	**4 (2%)**
AEs leading to study medication discontinuation	**35 (15%)**	**32 (16%)**

Phase 3 ADVOCATE Study AE Overview

	Avacopan (N=166)		Prednisone (N=164)	
	Patients n (%)	Events n	Patients n (%)	Events n
AE	164 (99%)	1779	161 (98%)	2139
Severe AE	39 (24%)	71	41 (25%)	94
Serious AE	70 (42%)	116	74 (45%)	166
Life-threatening	8 (5%)	8	14 (9%)	22
Death	2 (1%)	2	4 (2%)	4
AEs leading to study medication discontinuation	27 (16%)	27	28 (17%)	28

ADVOCATE: Most Commonly Reported AEs (≥ 15%)

	Avacopan (N=166)		Prednisone (N=164)	
	Patients n (%)	Events n	Patients n (%)	Events n
Any AE	164 (99%)	1779	161 (98%)	2139
Nausea	39 (24%)	54	34 (21%)	46
Edema peripheral	35 (21%)	39	40 (24%)	56
Headache	34 (21%)	43	23 (14%)	30
Arthralgia	31 (19%)	42	36 (22%)	48
Hypertension	30 (18%)	36	29 (18%)	31
Anti-neutrophil cytoplasmic antibody positive vasculitis	26 (16%)	30	34 (21%)	46
Cough	26 (16%)	31	26 (16%)	29
Diarrhea	25 (15%)	33	24 (15%)	31
Nasopharyngitis	25 (15%)	38	30 (18%)	46
Vomiting	25 (15%)	29	21 (13%)	27
Upper respiratory tract infection	24 (15%)	28	24 (15%)	33
Muscle spasms	18 (11%)	23	37 (23%)	47

Deaths in Phase 3 ADVOCATE Study

Patient	AE Leading to Death Preferred Term	Study Day of Last Dose of Study Drug	Study Day of Death
Avacopan			
1	Granulomatosis with polyangiitis	236	315
2	Pneumonia	50	160
Prednisone			
1	Death (unknown cause)	319	359
2	Acute myocardial infarction	113	160
3	Infectious pleural infusion	94	108
4	Diarrhea, vomiting, fungal infection	16	34

1 death occurred during screening period due to acute MI

Most SAEs Related to Underlying ANCA-Associated Vasculitis or Standard Therapies

	Avacopan (N=166)		Prednisone (N=164)	
Preferred Term (≥ 2%)	Patients n (%)	Events n	Patients n (%)	Events n
Any serious AE	70 (42%)	116	74 (45%)	166
ANCA positive vasculitis / GPA / MPA	17 (10%)	17	23 (14%)	28
Pneumonia	8 (5%)	9	6 (4%)	6
Acute kidney injury	3 (2%)	3	1 (0.6%)	2
Urinary tract infection	3 (2%)	3	2 (1%)	2
Hepatic enzyme increased	2 (1%)	2	3 (2%)	3
Pyrexia	2 (1%)	3	3 (2%)	3
Lymphopenia	1 (0.6%)	1	3 (2%)	3

AEs Leading to Study Medication Discontinuation Similar Between Groups

AE ≥ 2 Patients	Avacopan (N=166) n (%)	Prednisone (N=164) n (%)
Any AE leading to discontinuation of study medication	27 (16%)	28 (17%)
ANCA positive vasculitis	4 (2%)	8 (5%)
Hepatic function abnormal	3 (2%)	0 (0%)
Latent tuberculosis	2 (1%)	0 (0%)
Hepatic enzyme increased	1 (0.6%)	2 (1%)
Lymphopenia	0 (0%)	3 (2%)
Thrombocytopenia	0 (0%)	2 (1%)

Lower Incidence of Glucocorticoid Toxicity in Avacopan Group

	Avacopan (N=166) n (%)	Prednisone (N=164) n (%)	Difference % (95% CI)
Any AE of glucocorticoid use*	110 (66%)	132 (81%)	-14.2 (-23.7, -3.8)
Cardiovascular	72 (43%)	85 (52%)	-8.5 (-19.2, 2.6)
Dermatological	14 (8%)	28 (17%)	-8.6 (-16.2, -1.0)
Endocrine / Metabolic	23 (14%)	48 (29%)	-15.4 (-24.3, -6.0)
Gastrointestinal	3 (2%)	4 (2%)	-0.6 (-4.6, 3.1)
Infectious	22 (13%)	25 (15%)	-2.0 (-9.9, 5.7)
Musculoskeletal	19 (11%)	21 (13%)	-1.4 (-8.7, 5.9)
Ophthalmological	7 (4%)	12 (7%)	-3.1 (-8.7, 2.1)
Psychological	27 (16%)	39 (24%)	-7.5 (-16.5, 1.3)

- Difference between groups mainly due to AEs of weight increased, insomnia, hyperlipidemia, adrenal insufficiency, blood glucose increased, and irritability

*Based on EULAR recommendations (van der Goes et al., 2010; Duru et al., 2013)

Pre-Specified Adverse Events of Interest

- Infection
- Hepatic events
- WBC abnormalities (neutropenia / lymphopenia)
- Hypersensitivity

More Infections and Serious Infections in Prednisone Group Compared to Avacopan Group

	Avacopan (N=166) n (%)	Prednisone (N=164) n (%)
Any infection	113 (68%) 233 events	124 (76%) 291 events
Any serious infection	22 (13%) 25 events	25 (15%) 31 events
Any serious opportunistic infection	6 (4%)	11 (7%)
Any severe infection	12 (7%)	10 (6%)
Any infection leading to study withdrawal	4 (2%)	5 (3%)
Any life-threatening infection	1 (0.6%)	2 (1%)
Any infection leading to death	1 (0.6%)	2 (1%)

Most Common Serious Infections (≥ 2 Patients in Any Treatment Group)

	Avacopan (N=166) n (%)	Prednisone (N=164) n (%)
Pneumonia (all terms)*	9 (5%)	9 (6%)
Urinary tract infection	3 (2%)	2 (1%)
Device related infection	2 (1%)	0 (0%)
Influenza	2 (1%)	1 (0.6%)
Herpes zoster	0 (0%)	2 (1%)
Infectious pleural effusion	0 (0%)	2 (1%)
Respiratory syncytial virus infection	0 (0%)	2 (1%)

*Includes pneumonia / pneumonia hemophilus / lower respiratory tract infection / pneumonia bacterial / pneumonia cytomegaloviral

Hepatic Function Test Abnormalities

	Avacopan (N=166) n (%)	Prednisone (N=164) n (%)
Any AE of hepatic function test abnormalities	22 (13%)	19 (12%)
Study medication paused or discontinued	9 (5%)	5 (3%)
Any serious AE	9 (5%)	6 (4%)

- Grade 4 elevations in ALT or AST (> 20x ULN)
  - Avacopan (n=1), Prednisone (n=2)
- Concurrent bilirubin increases
  - Avacopan (n=2), Prednisone (n=1)
- Causality assessment confounded by known hepatotoxic agents
  - Sulfamethoxazole-trimethoprim, acetaminophen, statins, repaglinide, azathioprine, and alcohol
- All patients recovered with withdrawal of study medication and other potentially hepatotoxic drugs

Neutropenia and Lymphopenia Events

		Avacopan (N=166) n (%)	Prednisone (N=164) n (%)
Any AE of WBC count decrease		31 (19%)	39 (24%)
Any SAE of WBC count decrease		4 (2%)	8 (5%)
Leukopenia	Grade 3	1 (0.6%)	3 (2%)
	Grade 4	0 (0%)	0 (0%)
Lymphopenia	Grade 3	47 (28%)	49 (30%)
	Grade 4	4 (2%)	13 (8%)
Neutropenia	Grade 3	4 (2%)	2 (1%)
	Grade 4	0 (0%)	2 (1%)

Leukocytes: Grade 3: < 2.0 $x10^3/\mu L$ - 1.0 $x10^3/\mu L$; Grade 4: < 1.0 $x10^3/\mu L$
Lymphocytes: Grade 3: < 0.5 $x10^3/\mu L$ – 0.2 $x10^3/\mu L$; Grade 4: < 0.2 $x10^3/\mu L$
Neutrophils: Grade 3: < 1.0 $x10^3/\mu L$ – 0.5 $x10^3/\mu L$; Grade 4: < 0.5 $x10^3/\mu L$

Hypersensitivity Events

	Avacopan (N=166) n (%)	Prednisone (N=164) n (%)
Any AE of hypersensitivity	68 (41%)	70 (43%)
Skin and subcutaneous tissue disorders	51 (31%)	55 (34%)
Rash	19 (11%)	13 (8%)
Any serious AE of hypersensitivity	2 (1%)	0 (0%)

- 2 SAEs in avacopan group
  - Angioedema recovered without sequelae
  - Skin necrosis not considered hypersensitivity reaction to avacopan

Creatine Phosphokinase (CPK) Increases

- AE of blood CPK increased occurred in 6 patients in avacopan group and 1 in prednisone group
  - Two Grade 3*
    - One on pravastatin and other on colchicine
  - Rest Grade 1 or 2
  - None serious
  - No cases of rhabdomyolysis or myositis observed

* Grade 1: > ULN – 2.5x ULN; Grade 2: > 2.5x ULN – 5x ULN; Grade 3: > 5x ULN – 10x ULN

Safety Conclusions: Avacopan Safety Profile Favorable Compared to Prednisone

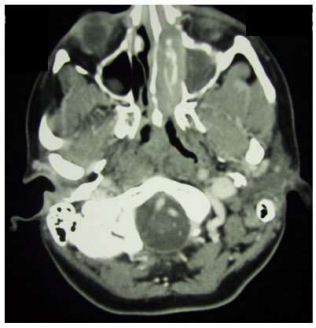
- Lower number of AEs, SAEs, life-threatening AEs, and deaths vs prednisone
- Lower incidence of infections and WBC count decreases
- Hepatic test AEs and angioedema manageable with patient monitoring
- Fewer AEs related to glucocorticoid use
  - Consistent with GTI efficacy results

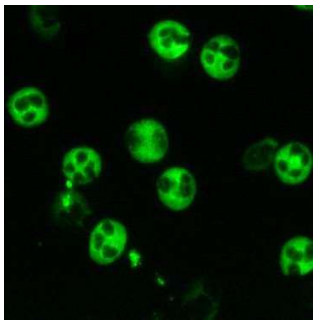
Clinical Perspective

Peter A. Merkel, MD, MPH

51-Year-Old Woman with ANCA-Associated Vasculitis

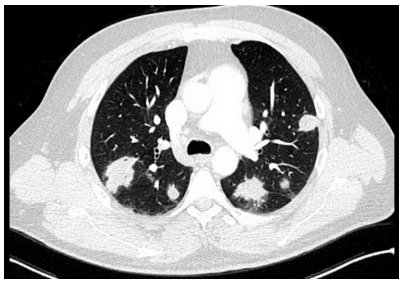
Sinusitis

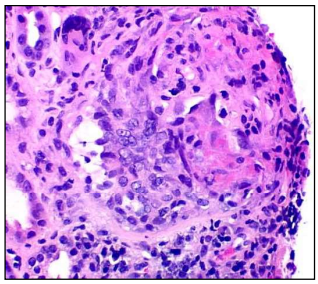




Positive test for ANCA

Pulmonary nodules





Glomerulonephritis

Significant Unmet Needs Remain With Current Treatment of ANCA-Associated Vasculitis

- Rate of relapse remains high
- Irreversible renal impairment quite common
- Patients' quality of life significantly negatively impacted by disease and its treatment
- Glucocorticoids remain major source of toxicity for patients with ANCA-associated vasculitis

Treatment with Glucocorticoids has Substantial Detrimental Effects

- Glucocorticoids have both short- and long-term toxicities
- Months of daily high-dose prednisone associated with many physical and psychological adverse effects
- Longstanding goal of physicians and patients to markedly reduce or eliminate the need for glucocorticoids to treat ANCA-associated vasculitis

ADVOCATE Demonstrated Avacopan's Superior Efficacy Compared to Prednisone

Unmet Needs	ADVOCATE Results
Low sustained remission and high relapse rate	• Remission at 26 weeks (non-inferiority outcome met) • Sustained remission at 52 weeks (superiority outcome met) • Lower risk of relapse compared to prednisone group
Limited efficacy on renal function	• Improvement in eGFR, a measure of kidney function • Particularly evident efficacy in patients with Stage 4 kidney disease
Detrimental effect on health-related QoL	• Improvements in health-related quality of life
High level of toxicity	• Reduction in glucocorticoid-related toxicity (GTI and AEs)

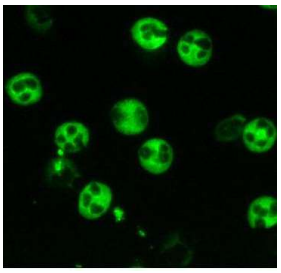
Avacopan Safety Profile Favorable Compared to Prednisone

- Lower number of AEs, SAEs, life-threatening AEs, and deaths in avacopan group
- Lower incidence of infections and AEs of leukopenia in avacopan group compared to prednisone group
- Hepatic AEs and angioedema manageable

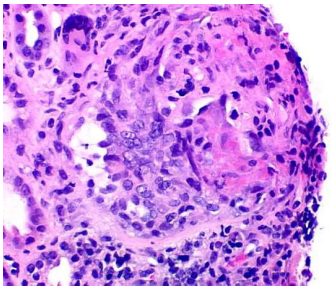
How Might Avacopan be Used in ANCA-Associated Vasculitis?

- Give avacopan instead of daily oral glucocorticoids to achieve remission without side effects of glucocorticoids
- Continue avacopan to sustain remission and protect renal function
- Reduce relapse rate
- Improved quality of life

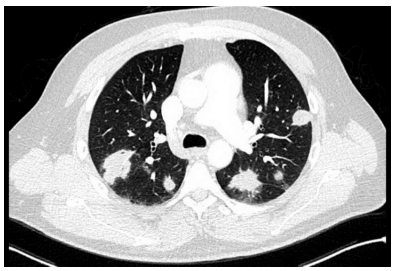
Positive test for ANCA



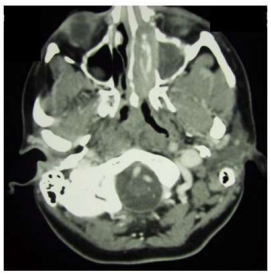
Glomerulonephritis



Pulmonary Nodules



Sinusitis



Avacopan: Major Advance in Treatment of Patients with ANCA-Associated Vasculitis

- Novel mechanism of action that targets disease-specific pathophysiology
- Provides clinically meaningful benefits
- Without substantial toxicities of glucocorticoid use

Avacopan for the Treatment of Anti-Neutrophil Cytoplasmic Auto-antibody (ANCA)-Associated Vasculitis

ChemoCentryx, Inc.

Arthritis Advisory Committee

May 6, 2021