Avacopan - a C5a Receptor Inhibitor for the Treatment of Anti-Neutrophil Cytoplasmic Auto-antibody (ANCA)-Associated Vasculitis

ChemoCentryx, Inc.

Arthritis Advisory Committee

May 6, 2021

Avacopan in ANCA-Associated Vasculitis

Pirow Bekker, MD, PhD

Clinical Lead
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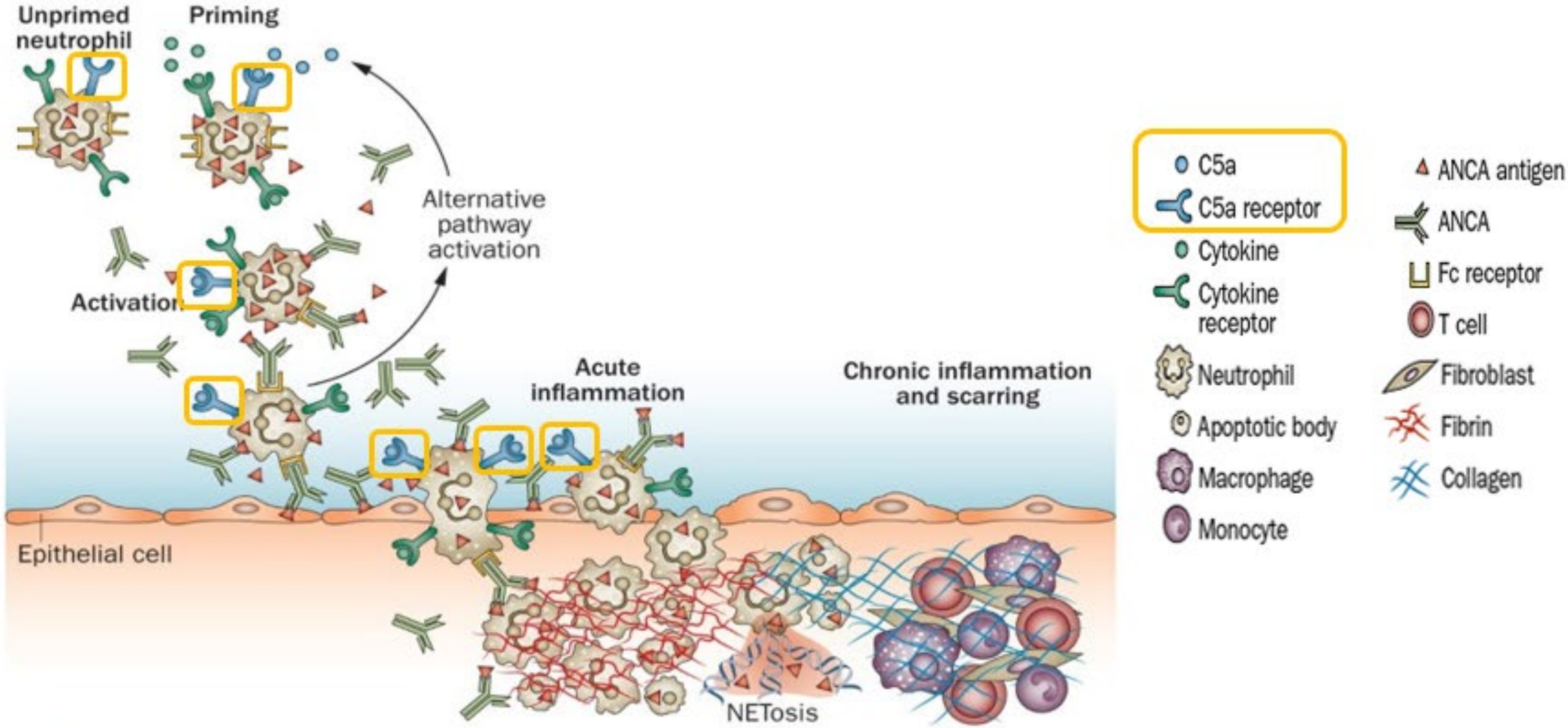
Focus for Today's Presentation

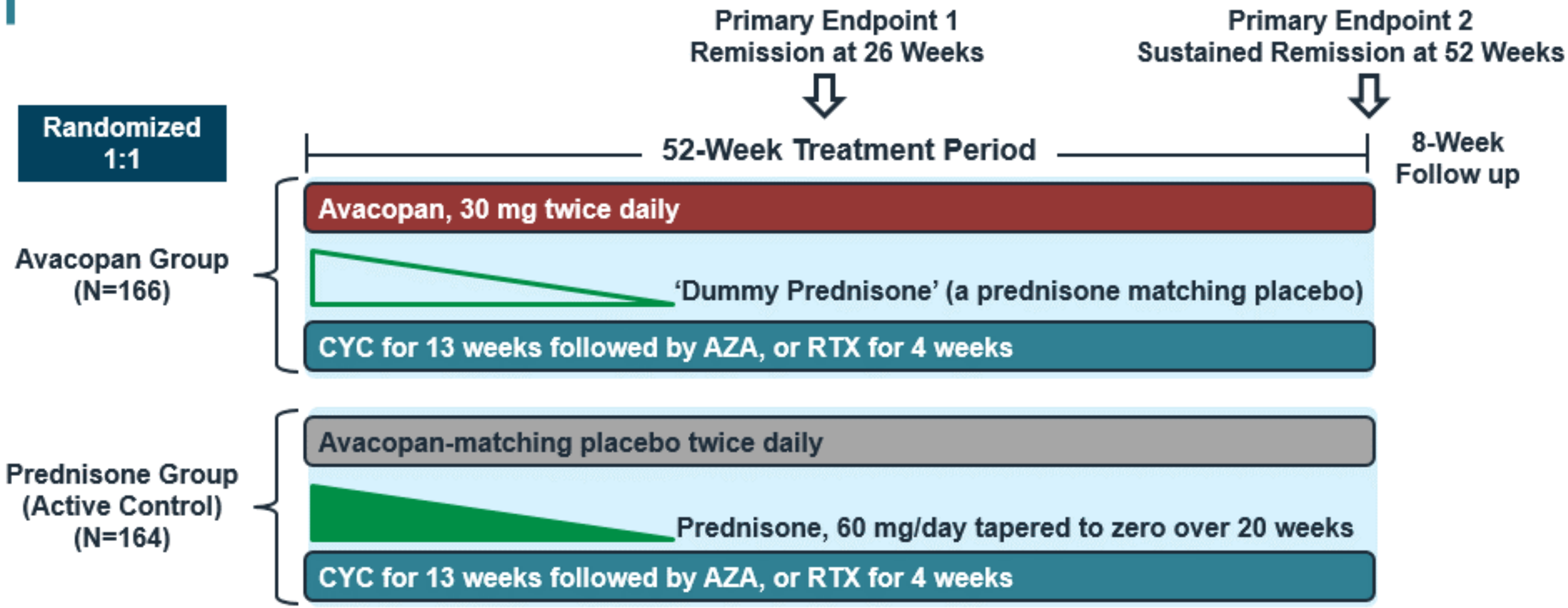
- Study design
- Primary endpoints
  - Remission at Week 26
  - Sustained remission at Week 52
- Secondary endpoints
  - Relapse
  - Renal function
  - Glucocorticoid use and toxicity
- Safety
- Indication

Central Role of C5aR in Pathogenesis of ANCA-Associated Vasculitis



Jennette and Falk, 2014

ADVOCATE Pivotal Phase 3 Study Design



AZA = azathioprine
CYC = cyclophosphamide
RTX = rituximab

Key Efficacy Results

Peter A. Merkel, MD, MPH

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

ADVOCATE Included Two Primary Endpoints

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

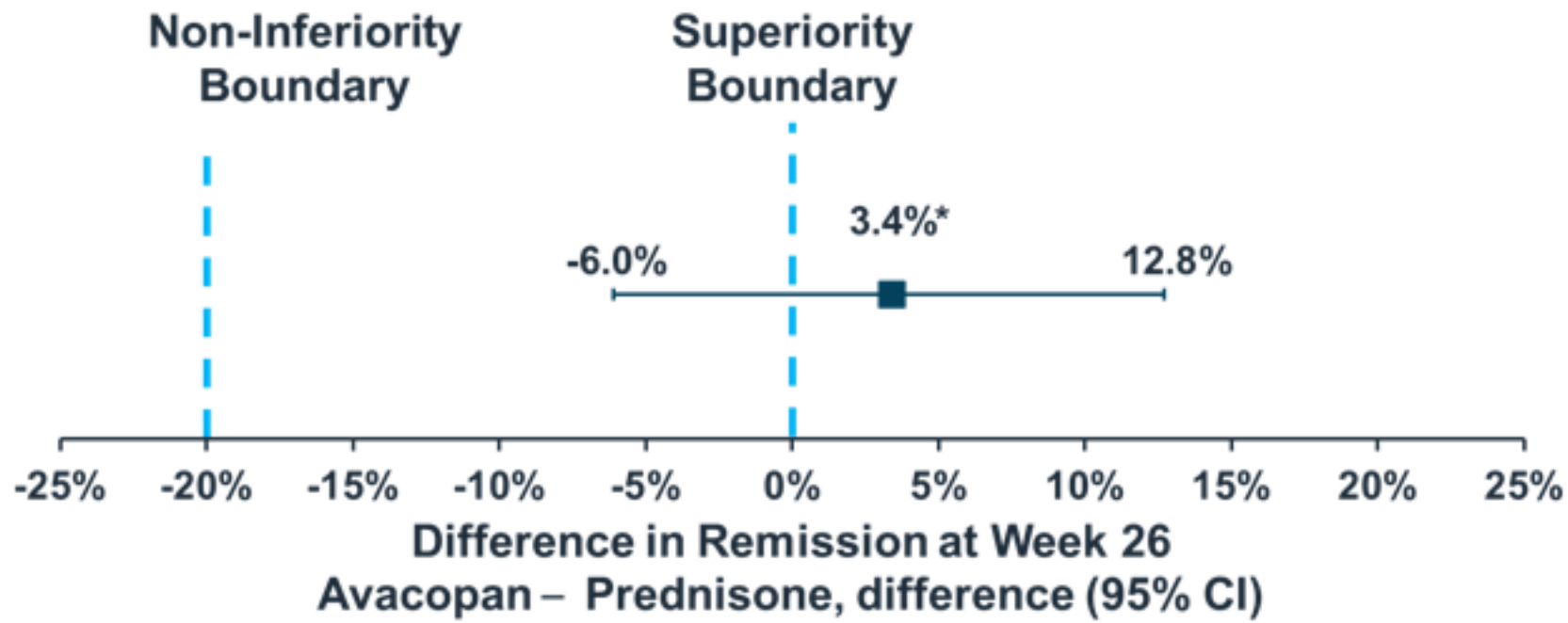
- Both endpoints based on Birmingham Vasculitis Activity Score (BVAS): validated tool used to capture vasculitis disease activity
- Both endpoints analyzed for non-inferiority and superiority at end of study
- Type I error controlled with a gatekeeping procedure

Birmingham Vasculitis Activity Score (BVAS) Assessment

- Adjudication Committee consisting of vasculitis experts adjudicated BVAS results in blinded fashion according to pre-defined charter
- Consistent with FDA guidance, other vasculitis clinical trials, and pre-specified analysis plan
- Adjudicated results pre-specified as primary results
- High consistency with Investigator assessments (95% at Week 52)
- Discrepancies due to items which were scored without supporting disease activity

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%)		

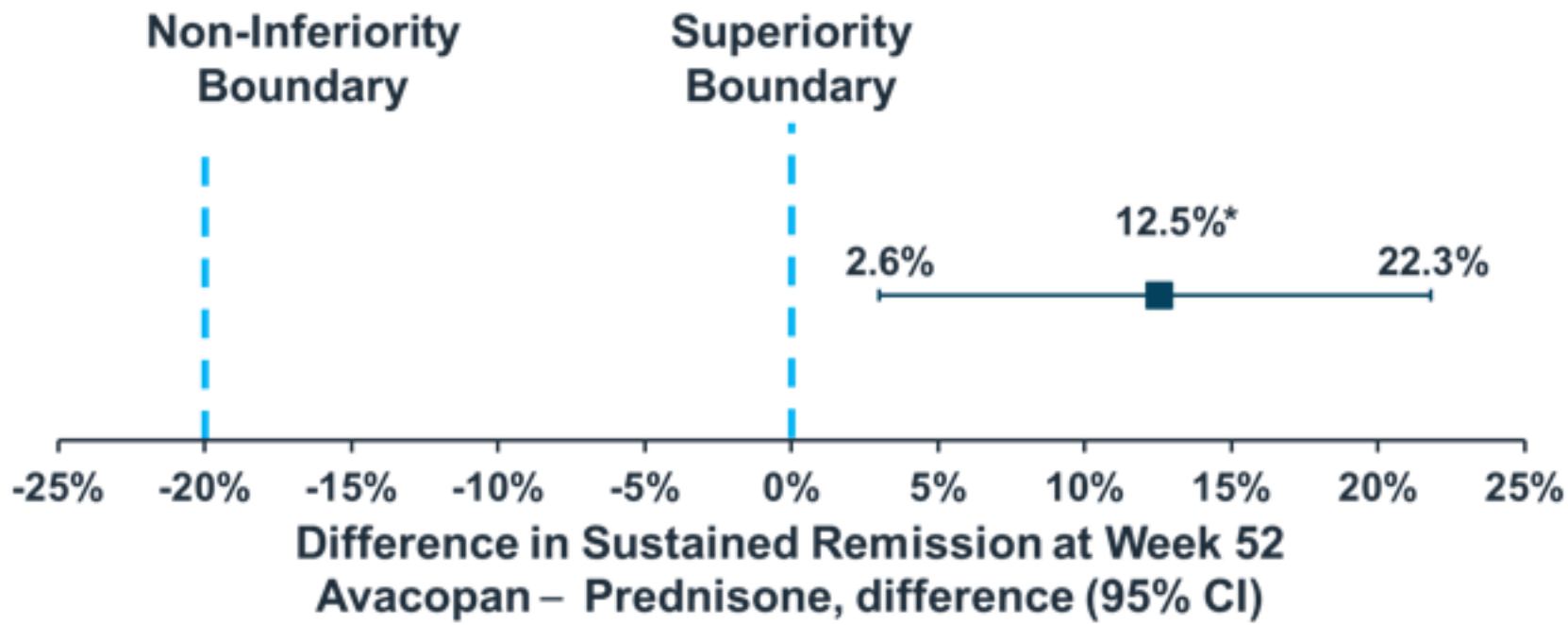


Jayne et al., 2021,
N Engl J Med

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

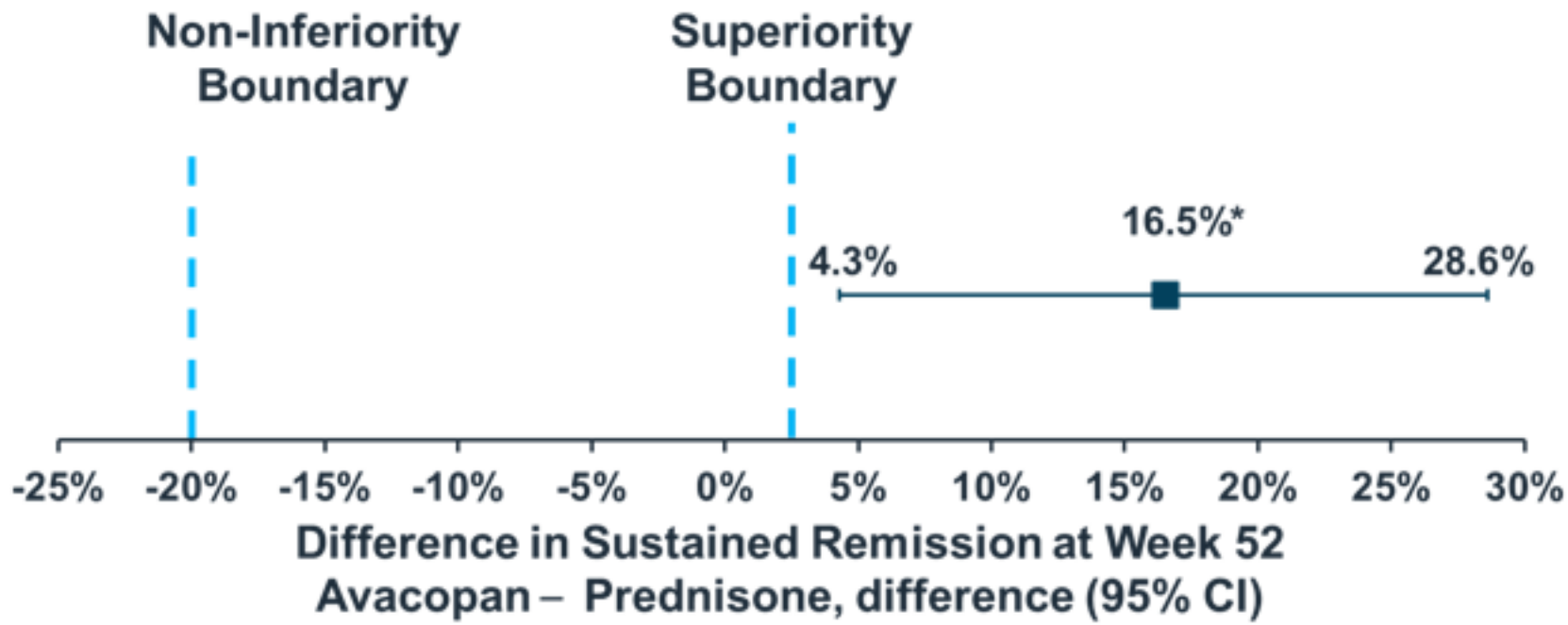
No Re-Treatment in Rituximab Stratum

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

1. Specks et al., 2013

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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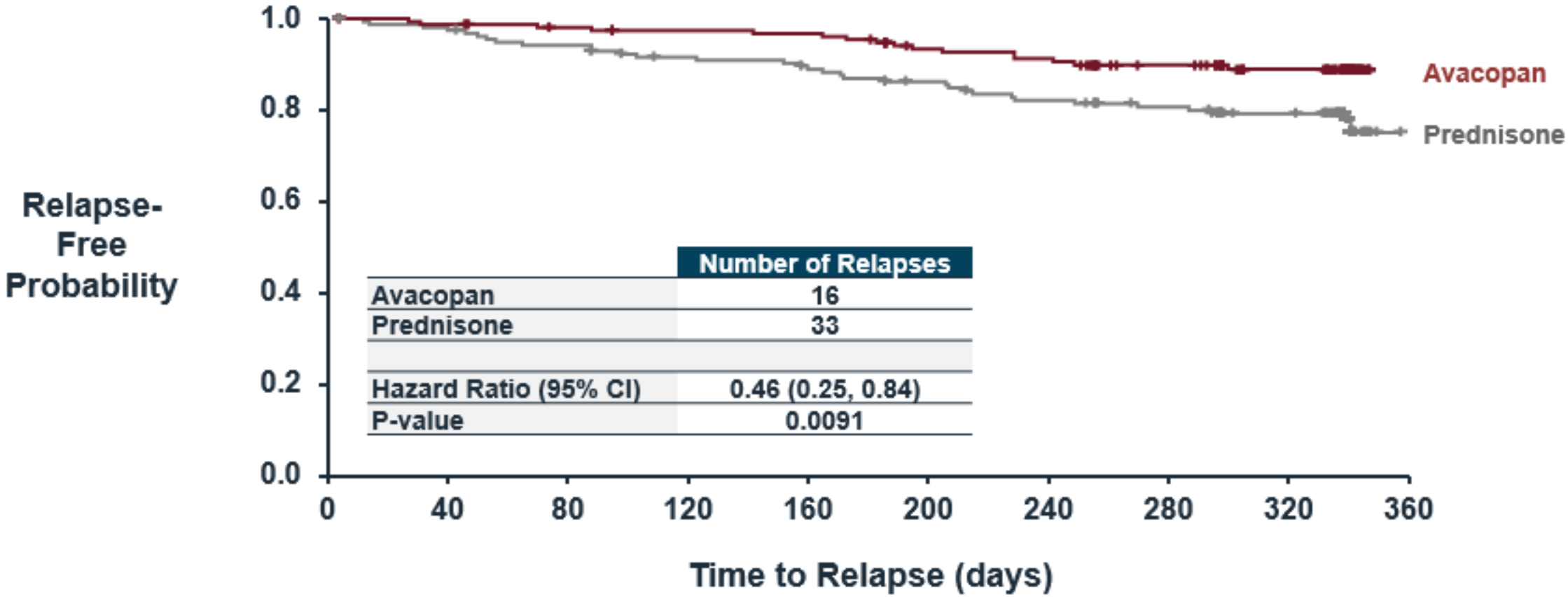
Lower Risk of Relapse in Avacopan Compared to Prednisone Group



	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

Jayne et al., 2021, N Engl J Med

Kidney Function and Health-Related Quality of Life

David Jayne, MD

Professor of Clinical Autoimmunity

University of Cambridge, United Kingdom

Director, Vasculitis and Lupus Service

Addenbrooke's Hospital

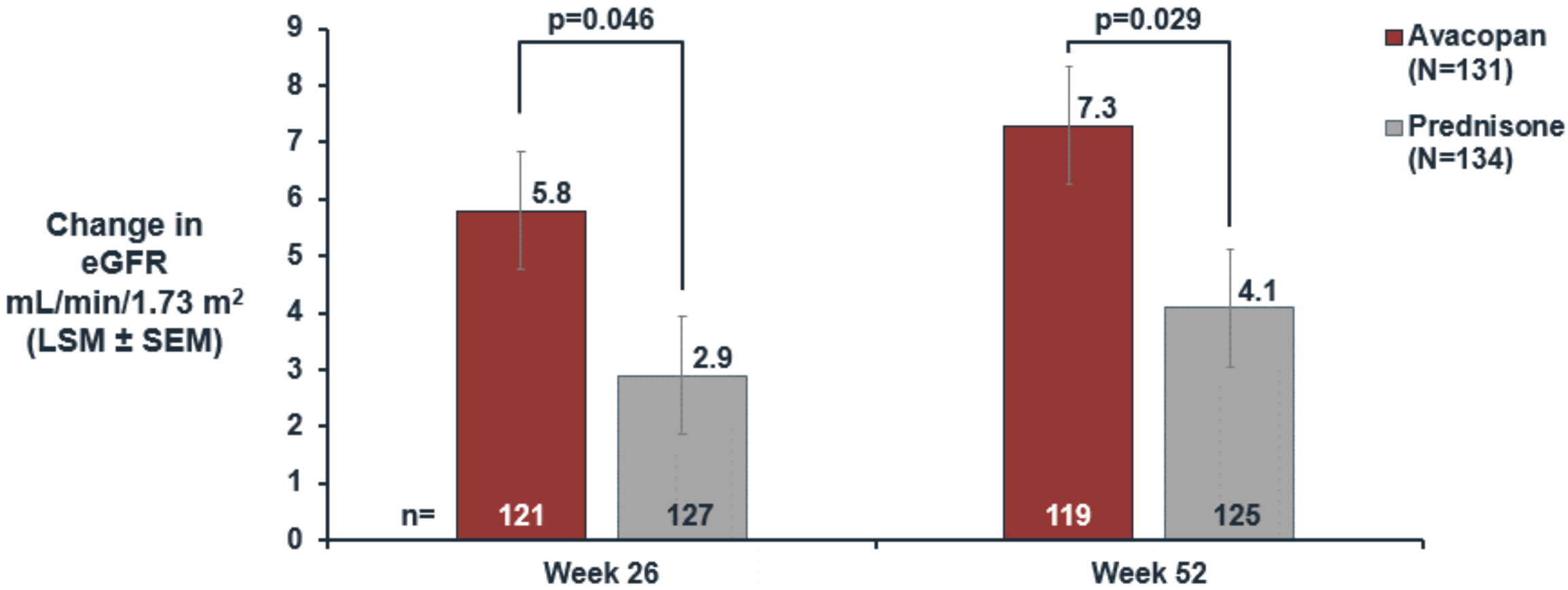
President, European Vasculitis Society (EUVAS)

Why Important to Evaluate Kidney Function?

- Renal vasculitis common in ANCA-associated vasculitis
  - 81% of patients in ADVOCATE had renal involvement
- Difficult historically to improve kidney function with medications
- Recent large meta-analysis[1] showed that 0.75 mL/min/year in eGFR between treatment groups is clinically relevant in chronic kidney disease

1. Inker et al., 2019

Secondary Endpoint: Change from Baseline in Estimated Glomerular Filtration Rate

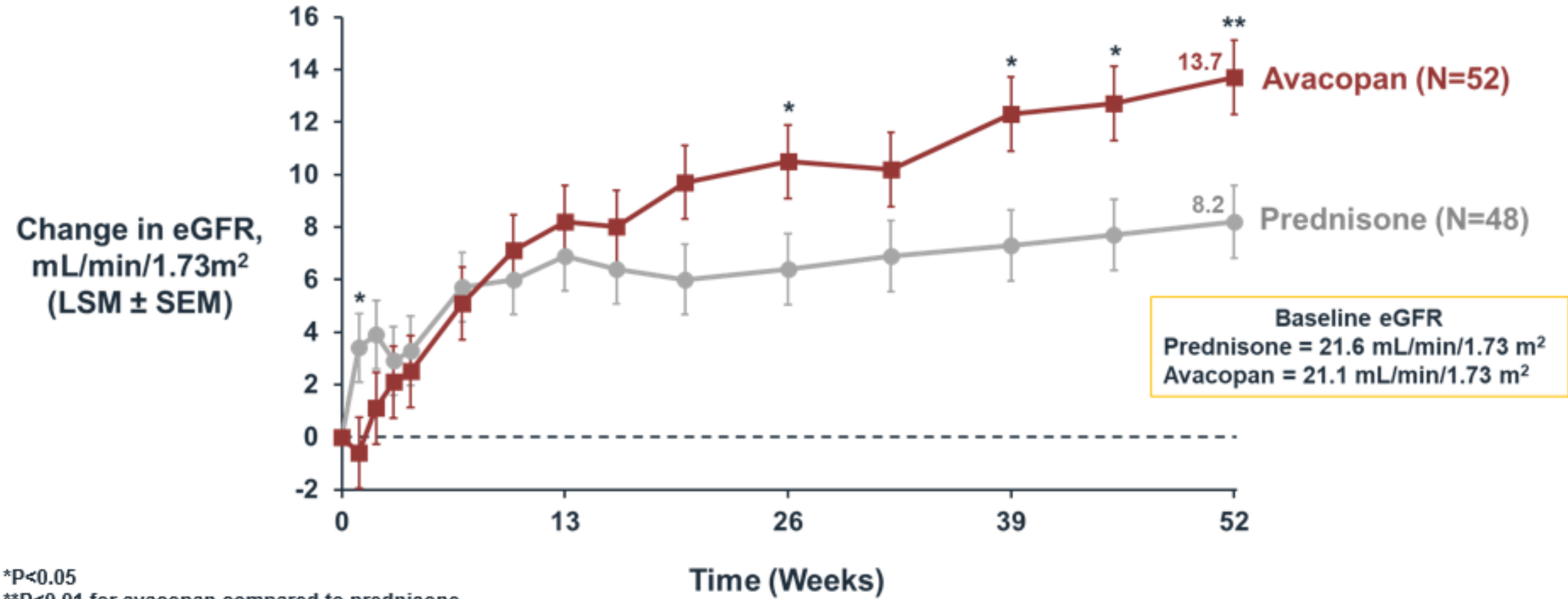


Measured in patients with baseline renal disease
eGFR based on serum creatinine
Clinically relevant difference: 0.75 mL/min (Inker et al, 2019)

Jayne et al., 2021, N Engl J Med

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

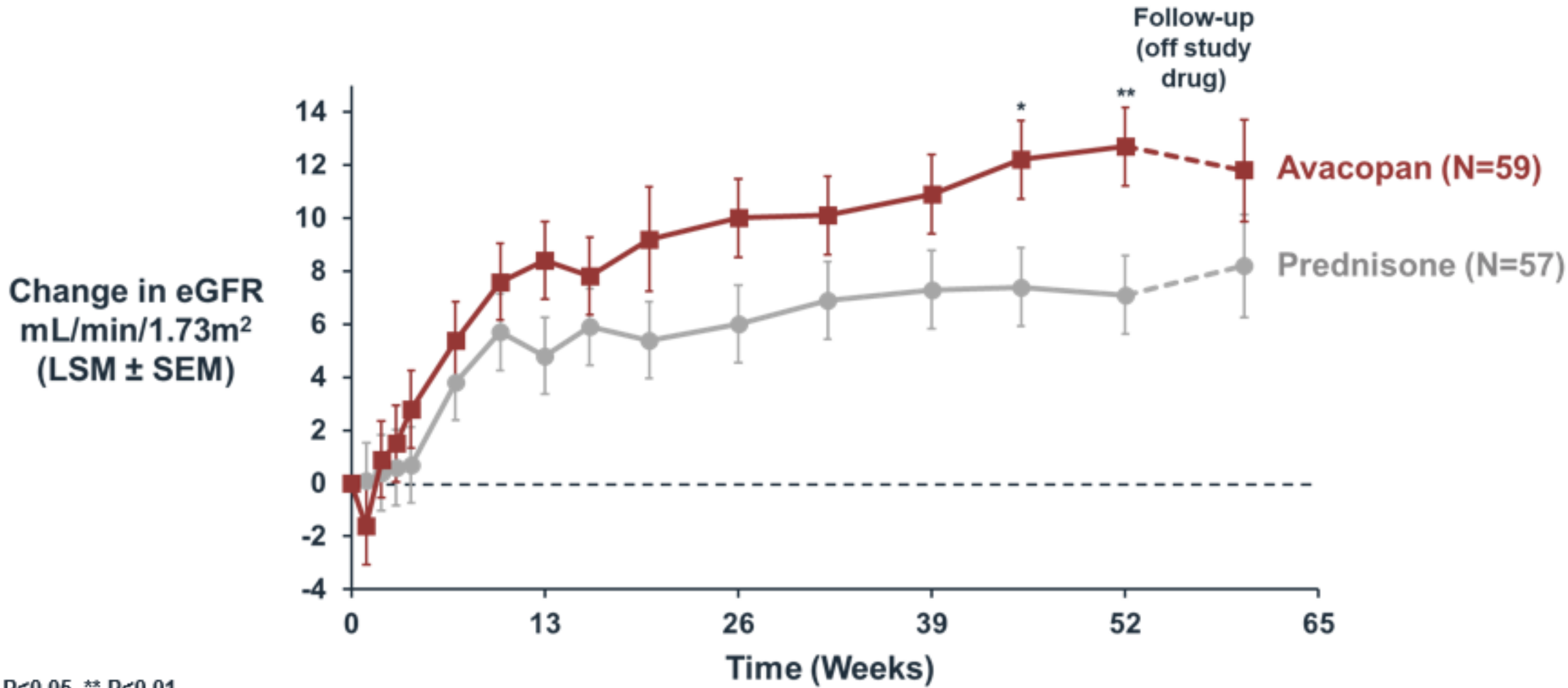
Pre-specified Analysis in Patients with Stage 4 Kidney Disease: Greater Improvement in Renal Function in Patients with eGFR < 30 at Baseline



*P<0.05
**P<0.01 for avacopan compared to prednisone
Note that <30 mL/min classified as severe impairment / Stage 4 kidney disease

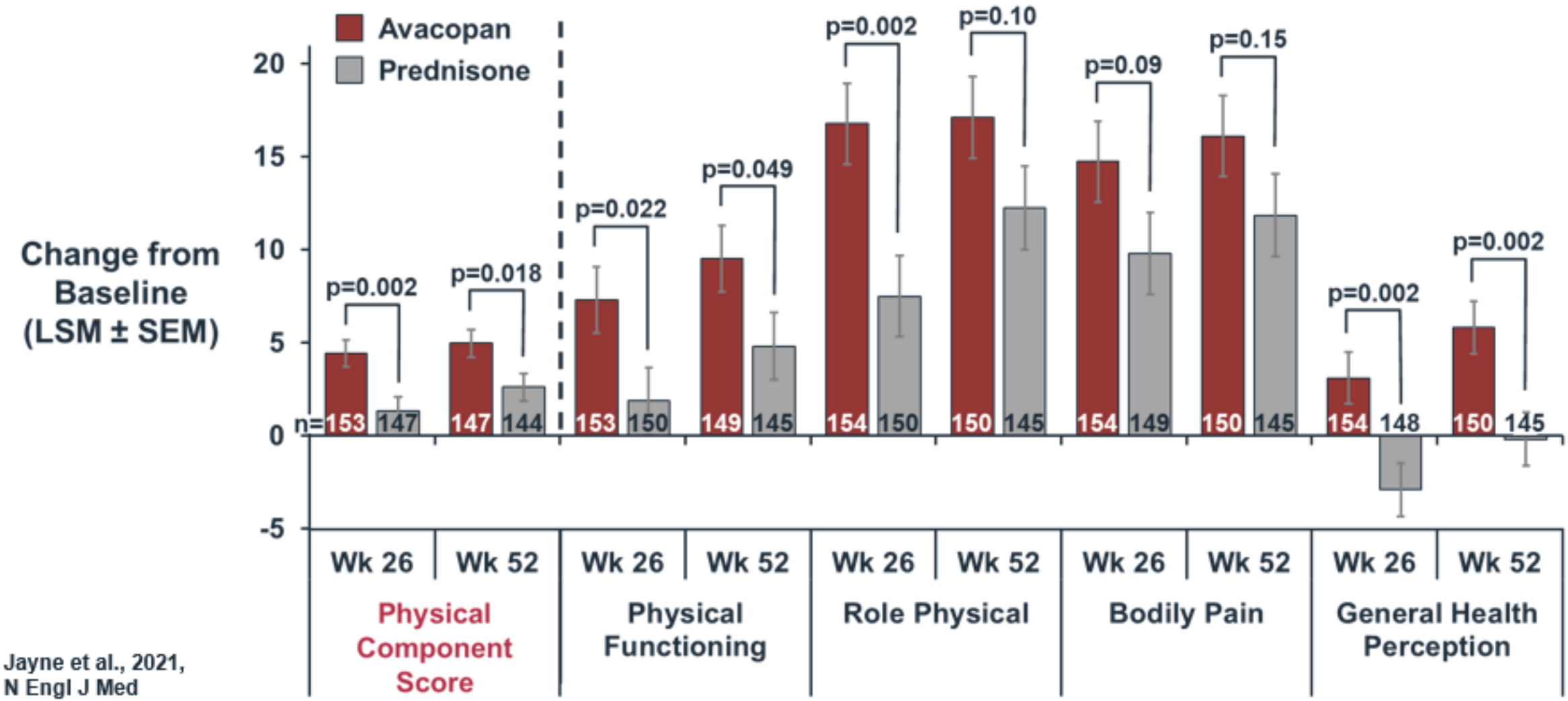
Jayne et al., 2021, N Engl J Med

eGFR Change in Patients with eGFR < 60, UACR ≥ 300 mg/g Creatinine, and U-RBC ≥ 10/hpf



* P<0.05, ** P<0.01
Avacopan vs. Prednisone

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

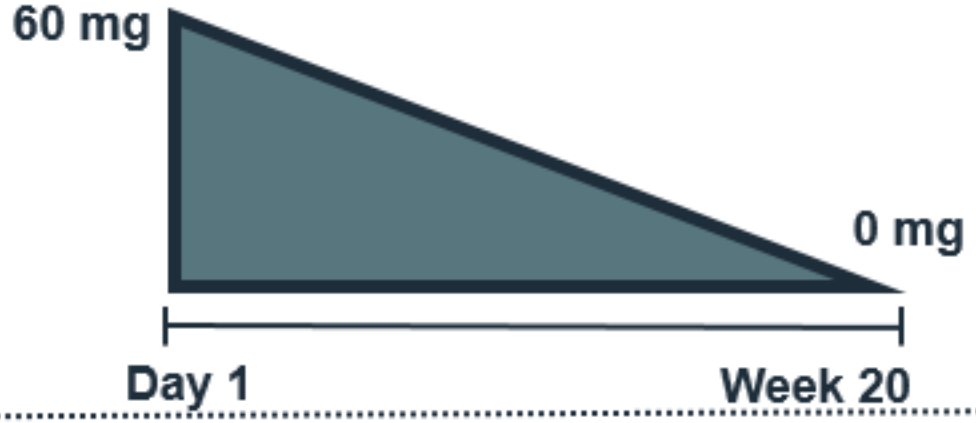


Jayne et al., 2021, N Engl J Med

Glucocorticoid Use and Safety

Pirow Bekker, MD, PhD

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

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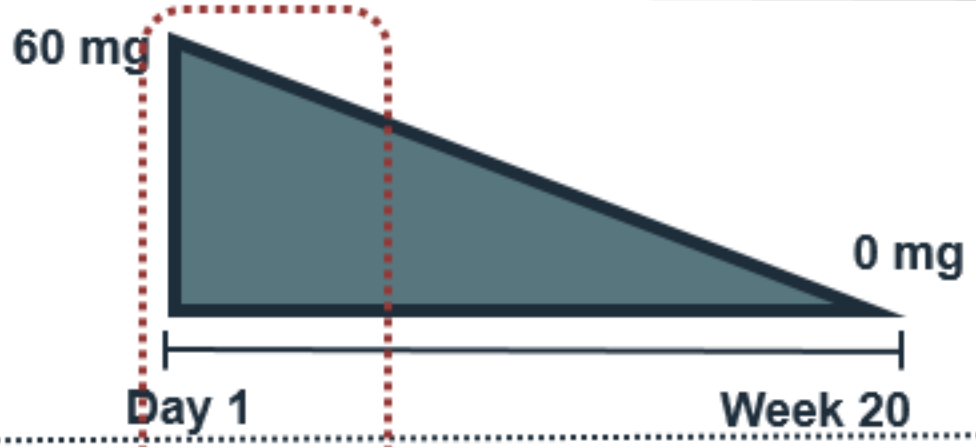

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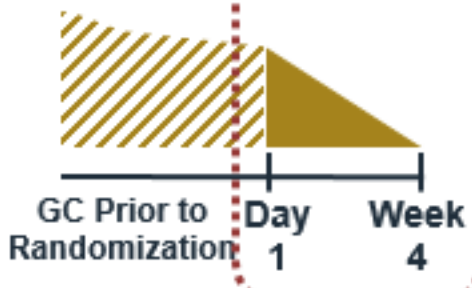

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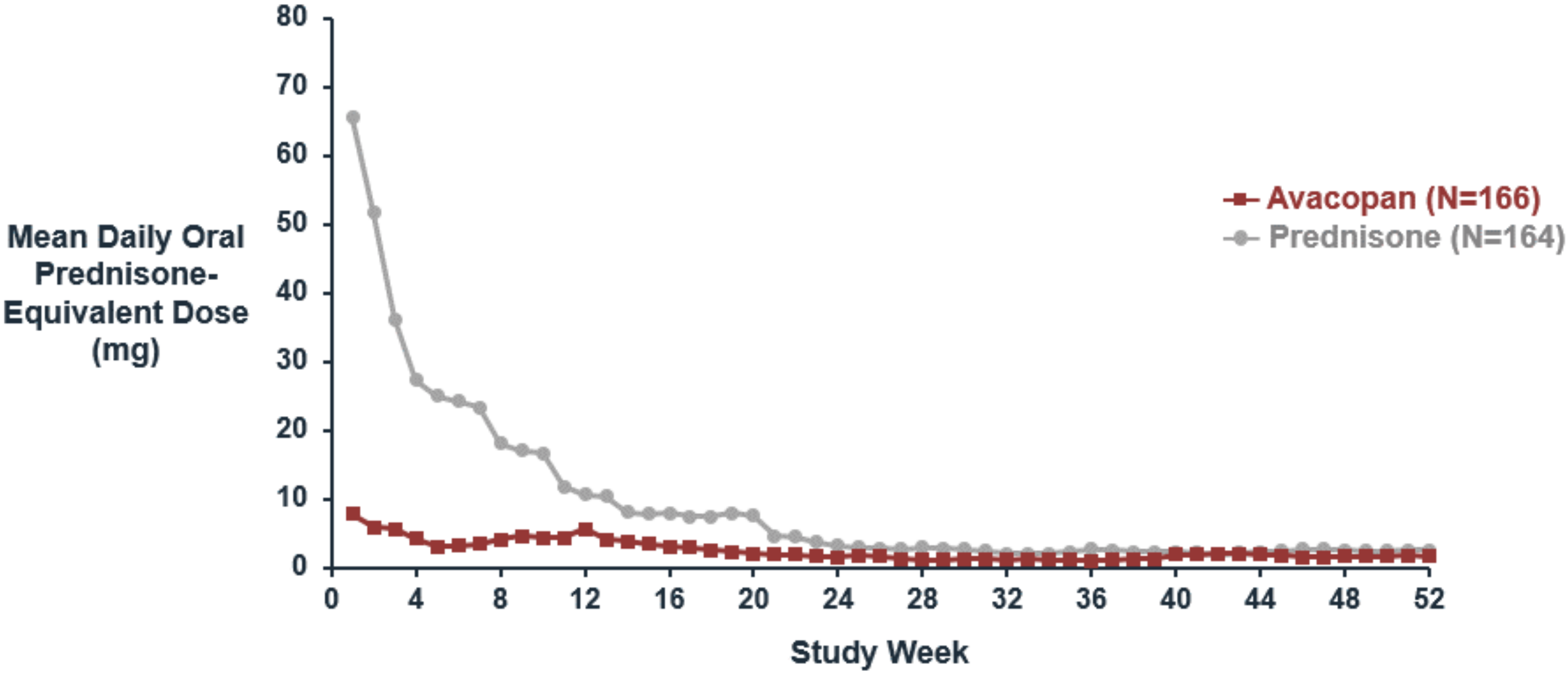
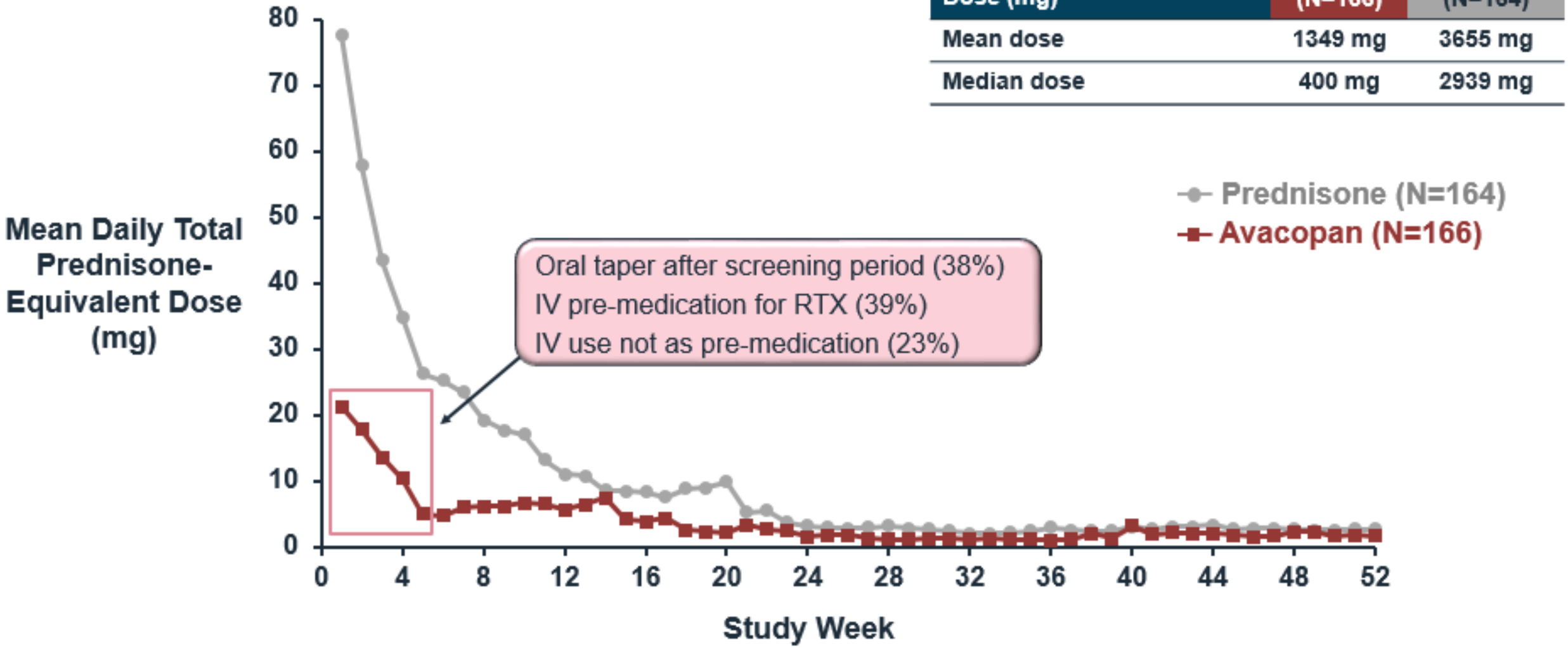
Oral Glucocorticoid Dose by Study Week



All Glucocorticoid Dose by Study Week

Total Prednisone-equivalent Dose (mg)	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

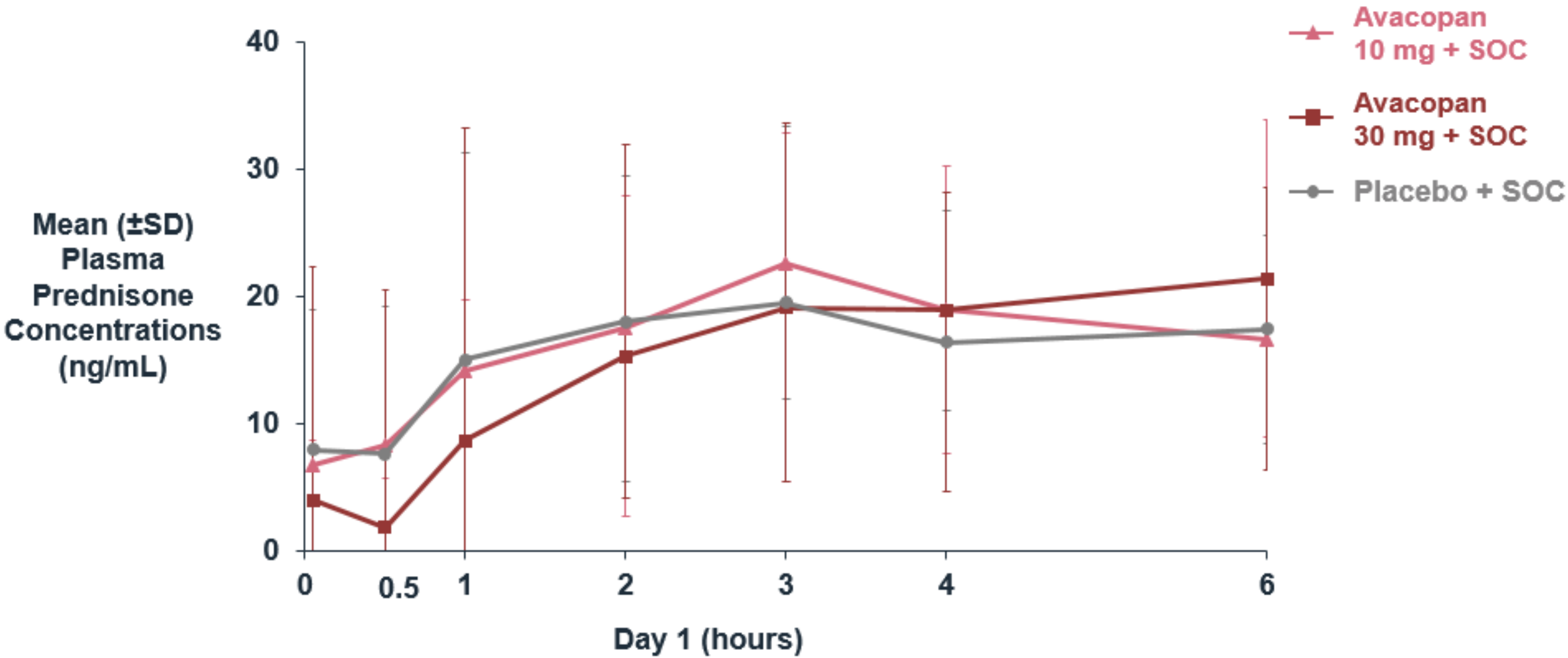
Avacopan is a Weak CYP3A4 Inhibitor Which Does Not Alter Prednisone Exposure

	Effect on Plasma Levels of CYP3A4 Substrate
Strong CYP3A4 Inhibitor Ketoconazole + Midazolam*, [1]	> 10-fold Midazolam AUC increase
Avacopan + Midazolam*, [2]	1.8-fold Midazolam AUC increase
Strong CYP3A4 Inhibitor Ketoconazole + Prednisone*, [3]	1.5-fold Prednisone AUC increase
Strong CYP3A4 Inhibitor Grapefruit juice + Prednisone*, [4]	No significant effect on Prednisone AUC
Avacopan + Prednisone (Phase 2 study)*, [5]	No significant effect on Prednisone AUC

* CYP3A4 Substrate

1. Olkkola et al., 1994; 2. Drug-Drug Interaction Study CL008_168; 3. Zürcher et al., 1989; 4. Hollander et al., 1995; 5. Blinded Phase 2 Study CL003_168

Phase 2 Study CL003_168 – Plasma Prednisone Concentrations



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

- Captures glucocorticoid toxicities, including infection, hypertension, glucose intolerance, myopathy, neuropsychiatric problems, and changes in weight, lipids, and skin

Cumulative Worsening Score (CWS)

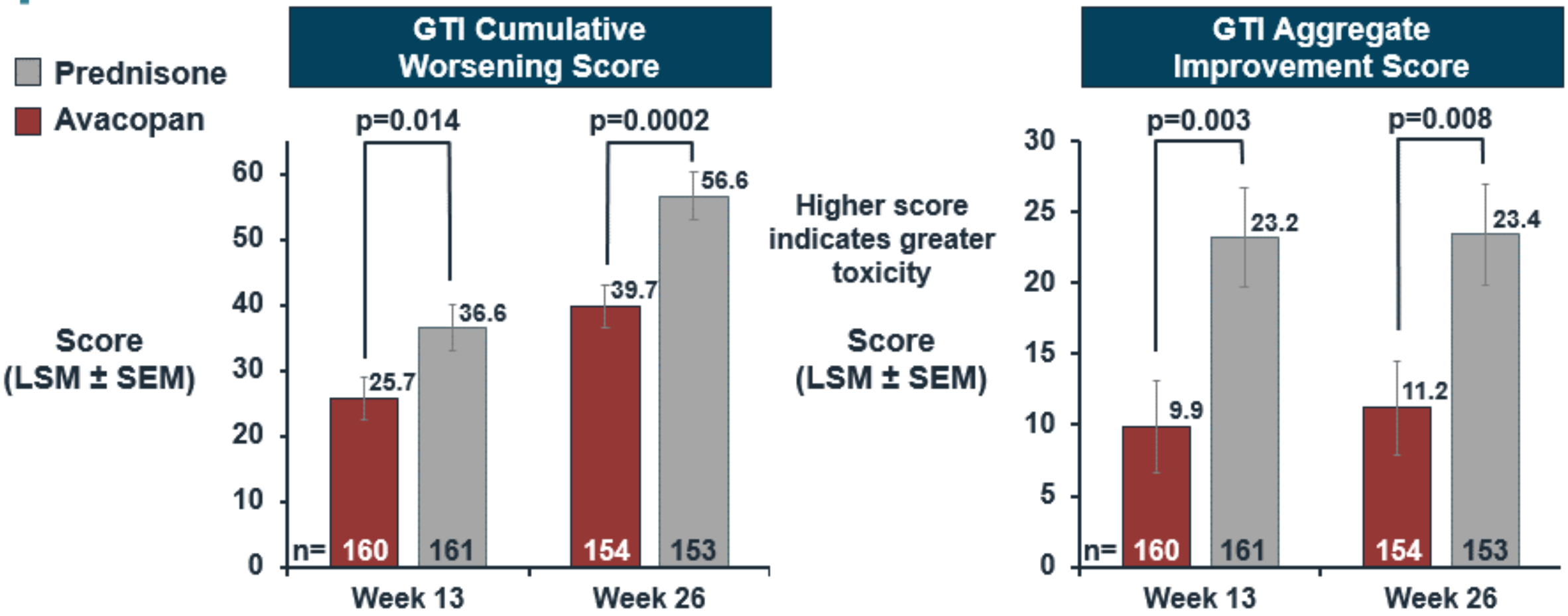
- Captures cumulative toxicity over time
- Score can only increase or stay the same

Aggregate Improvement Score (AIS)

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

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

Glucocorticoid-Related Toxicity Reduced with Avacopan Group Compared to Prednisone Group



Jayne et al., 2021, N Engl J Med

Differences of ≥10 points are clinically important (McDowell et al, 2021)

Phase 3 ADVOCATE Study Adverse Event Overview

	Avacopan (N=166)		Prednisone (N=164)	
	Patients n (%)	Events n	Patients n (%)	Events n
Adverse event (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

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
  - All patients in trial received prophylaxis for pneumocystis; known hepatic burden in these agents
  - Sulfamethoxazole-trimethoprim, acetaminophen, statins, repaglinide, azathioprine and alcohol
- All patients recovered with withdrawal of study medication and other potentially hepatotoxic drugs

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%)

- No *Neisseria meningitidis* infections

Current Therapy Unmet Needs

- High level of toxicity with current therapy
- Low sustained remission and high relapse rate
- Limited efficacy on renal function
- Detrimental effect on health-related QoL

Avacopan Addresses Unmet Needs

A first potential alternative to daily oral prednisone for ANCA-associated vasculitis

- Achieving and sustaining remission in absence of daily scheduled oral prednisone
- Lower risk of relapse

- Potential alternative to repeated rituximab dosing (sparing B cell and Ig-depletion)

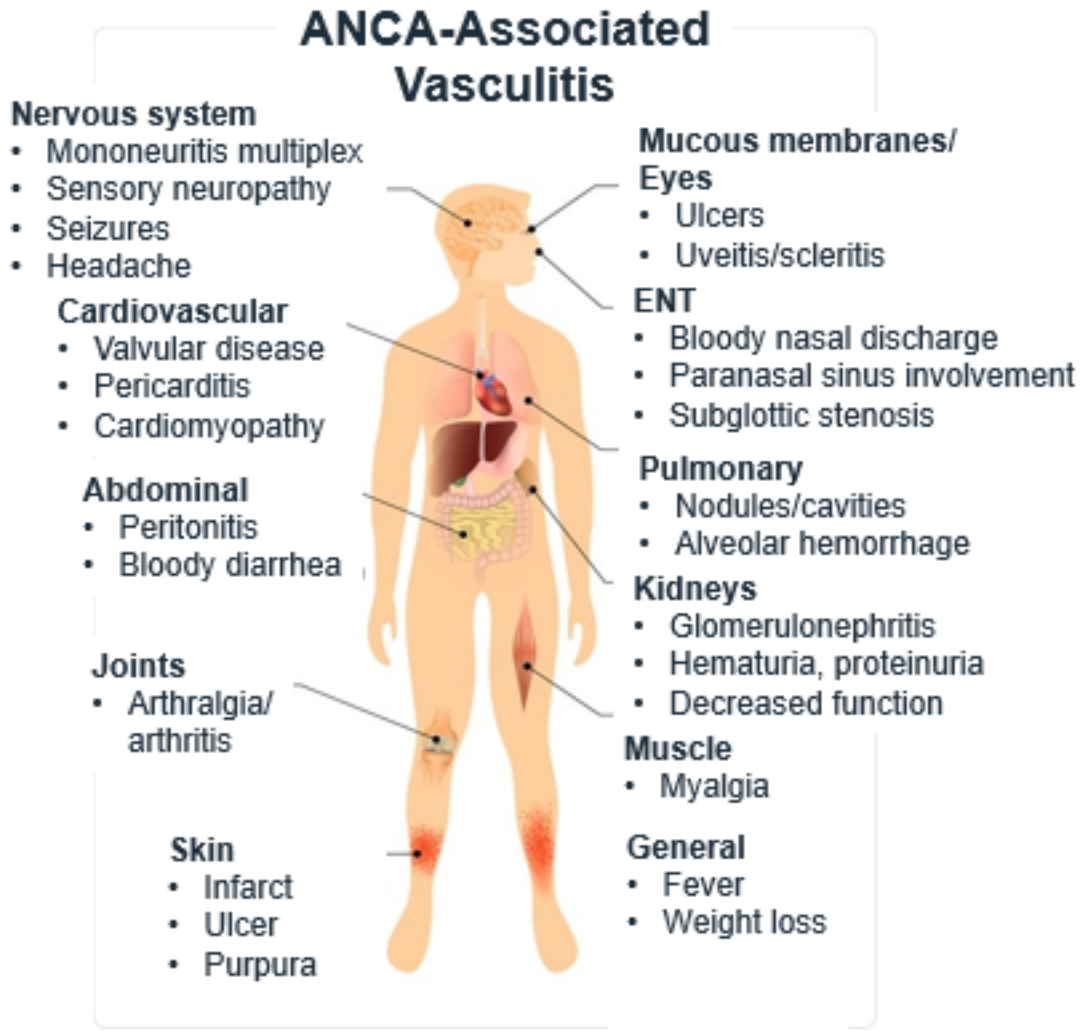
- Improvement of kidney function without daily scheduled oral prednisone
- Improvements in health-related quality of life

- Reduction in glucocorticoid-related toxicity (GTI and adverse events)
- Favorable safety profile

- Observations support the targeted mechanism of action of C5aR inhibition with avacopan

How Should Avacopan be Used in ANCA-Associated Vasculitis?

- Consistent with how avacopan was studied in ADVOCATE
- Give avacopan instead of daily oral glucocorticoids in newly diagnosed or relapsing GPA or MPA
- Continue avacopan to sustain remission and protect renal function
- Avacopan does not need to be interrupted during relapses, consistent with ADVOCATE study



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

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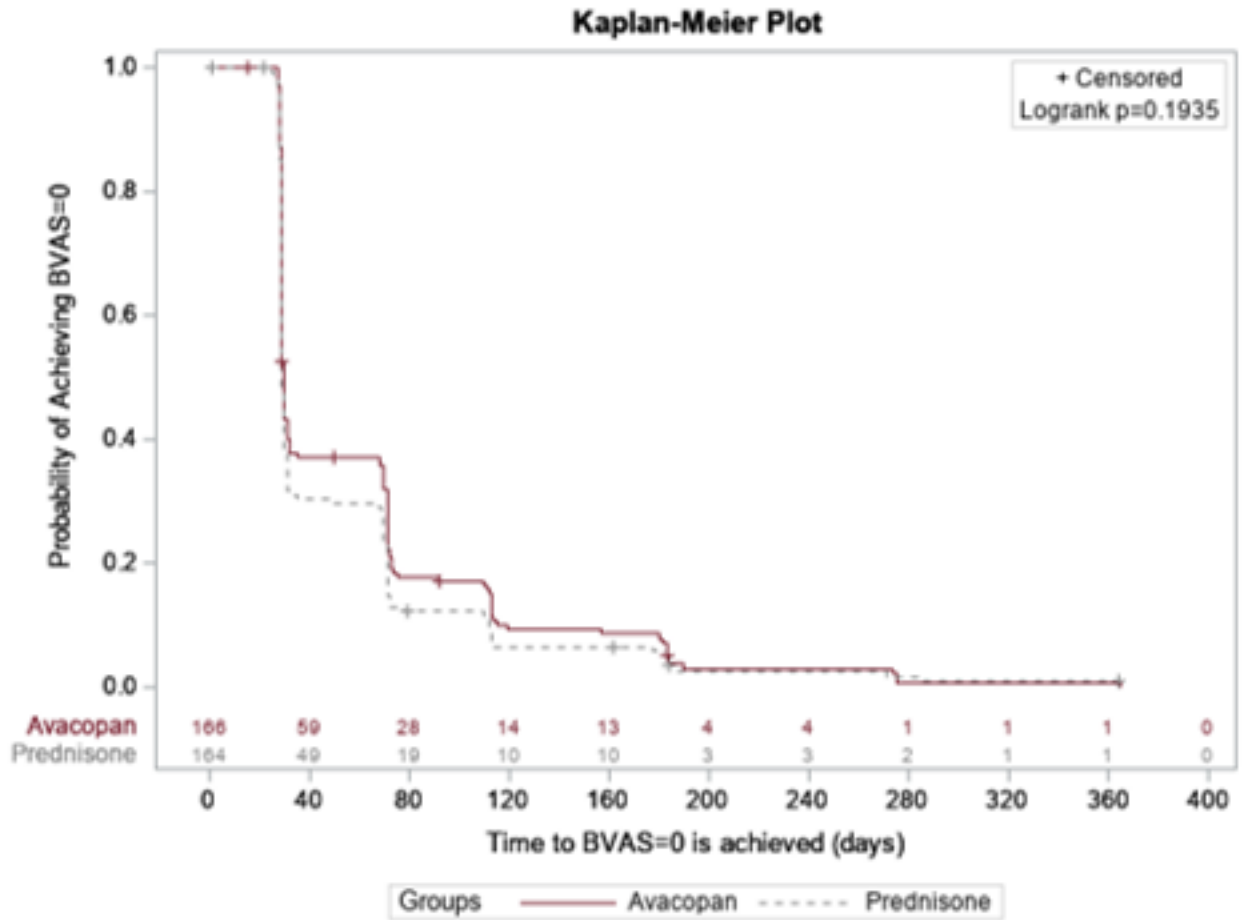
Back-up Slides

Examples of Inappropriate Investigator BVAS Assessments at Week 52

Patient	Investigator BVAS	Adjudicator BVAS	Adjudicator Comments
1	4 – Hypertension	0	GFR improved, no hematuria, proteinuria did not reflect activity. In this setting hypertension related to chronic kidney disease not disease activity.
2	1 – Headache	0	Explained by recent diagnosis of hypertension. Not previously associated with disease activity and no other features of activity at headache onset.
3	4 – Hypertension	0	Isolated hypertension is not a BVAS item in ANCA vasculitis. GFR normal, no hematuria or proteinuria
4	1 – Arthritis/arthralgia	0	Sole constitutional item, no supporting evidence of vasculitis activity
5	1 – Arthritis/arthralgia	0	Queried with PI, arthritis not attributable to active vasculitis
6	4 – Endobronchial involvement	0	Endobronchial disease queried with PI and had not worsened, moved from activity to damage

Time to BVAS = 0 is Achieved is Similar in Avacopan and Prednisone Groups (ITT)



	Number of Responders
Avacopan	158
Prednisone	157
LogRank P-value	0.1935

Time to BVAS = 0 is achieved is defined as the time from randomization to when BVAS = 0 first achieved

Phase 3 Study: Remission at Week 26 Defining High GC Users* as Non-Remitters

Treatment	N	n	(%)	95% CI	Diff. in %	Estimate of Common Diff. in %	Two-sided 95% CI for Common Diff.	Non-inferior p-value	Superior p-value
Avacopan	166	110	66.3	58.5, 73.4	-2.6	-0.9	-10.5, 8.6	<0.0001	0.5766
Prednisone	164	113	68.9	61.2, 75.9					

* Patients who used > 1460 mg prednisone equivalent within first 26 weeks of study considered not to have achieved BVAS remission at Week 26 endpoint

Phase 3 Study: Sustained Remission at Week 52 Defining High GC Users* as Non-Remitters

Treatment	N	n	(%)	95% CI	Diff. in %	Estimate of Common Diff. in %	Two-sided 95% CI for Common Diff.	Non-inferior p-value	Superior p-value
Avacopan	166	104	62.7	54.8, 70.0	10.2	12.0	2.1, 22.0	<0.0001	0.0087
Prednisone	164	86	52.4	44.5, 60.3					

* Patients who used > 560 mg prednisone equivalent from Week 26 through Week 52 considered not to have achieved BVAS sustained remission at Week 52 endpoint