FDA Arthritis Advisory Committee Meeting
FDA Opening Remarks

NDA 214487: Avacopan for the treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA])

Rachel L. Glaser, MD
Clinical Team Leader
Division of Rheumatology and Transplant Medicine
US Food and Drug Administration
May 6, 2021

Overview

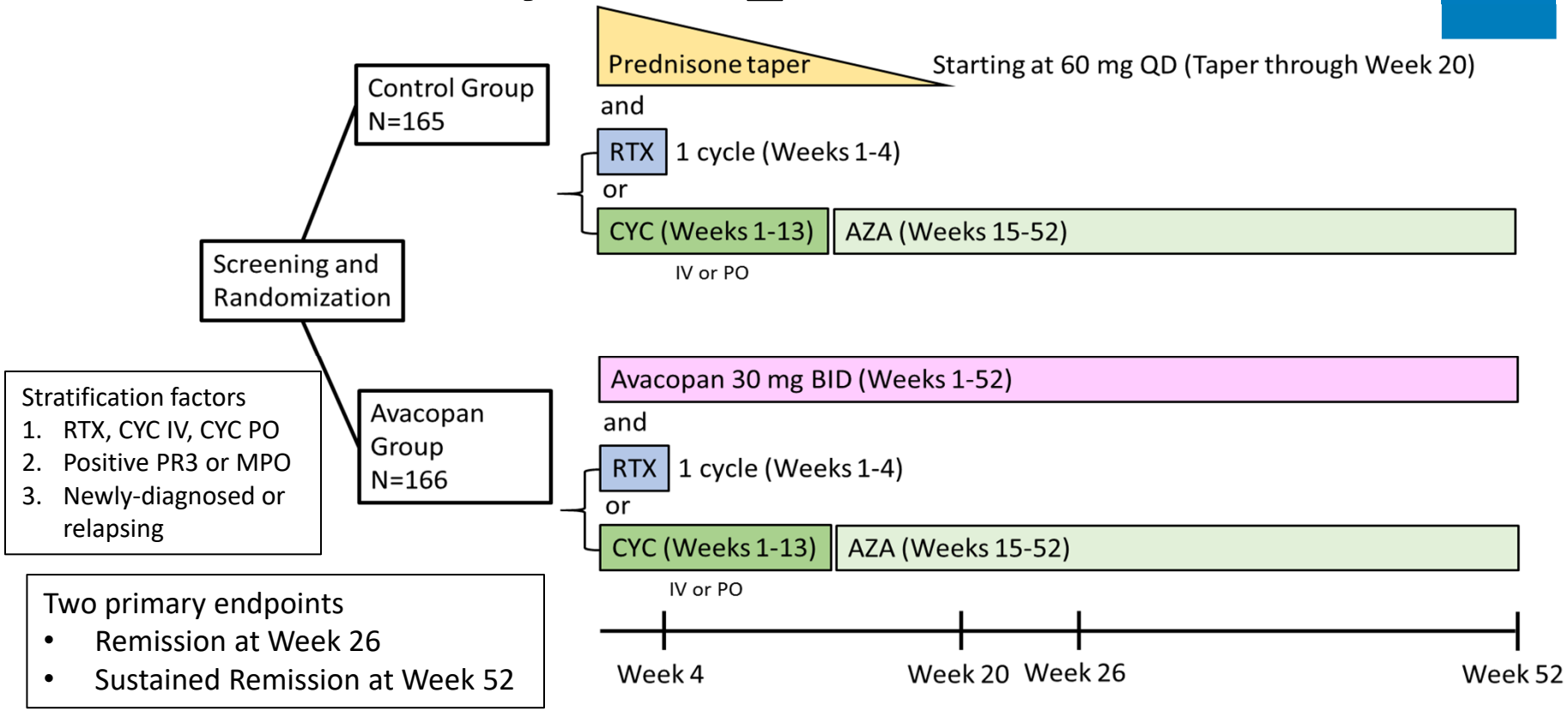
- **Product:** Avacopan
- **Applicant:** ChemoCentryx, Inc.
- **Mechanism of action:** C5a-receptor antagonist
- **Proposed indication:** Treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA])
- **Proposed dosing:** 30 mg by mouth twice daily, with food

Clinical Program: Phase 3 Study CL010_168

Design	Population	Treatment Regimens	Primary Efficacy
52-week, R, DB, active-control study	Newly diagnosed or relapsed AAV	• Prednisone taper (n=164) • Avacopan 30 mg BID (n=166) Background therapy: • RTX single cycle, no maintenance • CYC (PO or IV), AZA maintenance	• BVAS Remission at Week 26, and • Sustained BVAS Remission at Week 52

Abbreviations: AZA = azathioprine, BVAS = Birmingham Vasculitis Activity Score, CYC = cyclophosphamide, DB = double-blind, R = randomized, RTX = rituximab

Study CL010_168 Schematic

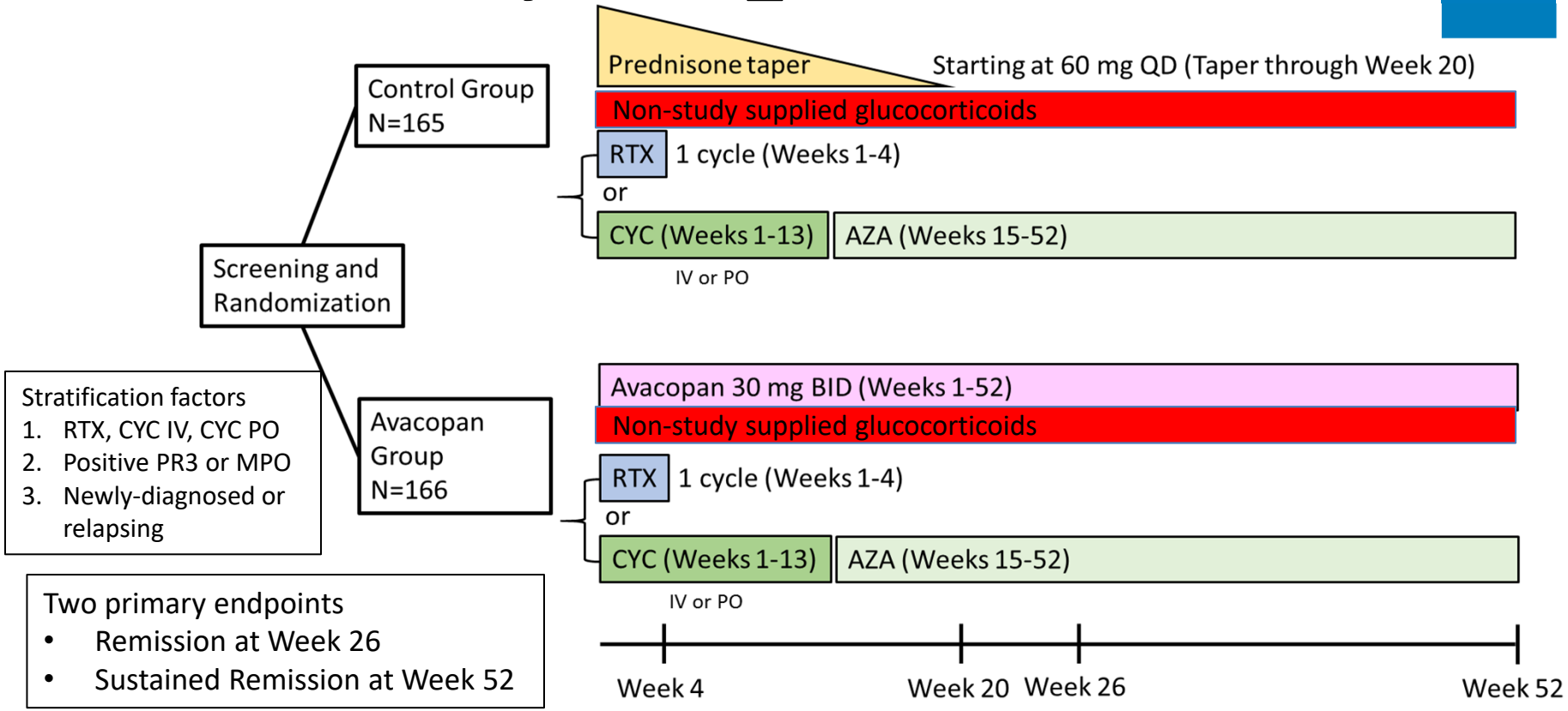


Stratification factors
1. RTX, CYC IV, CYC PO
2. Positive PR3 or MPO
3. Newly-diagnosed or relapsing

Two primary endpoints
- Remission at Week 26
- Sustained Remission at Week 52

Abbreviations: RTX=Rituximab, CYC = Cyclophosphamide, IV=intravenous, PO=orally, AZA=azathioprine, BID=twice per day, PR3 = proteinase-3, MPO=myeloperoxidase

Study CL010_168 Schematic



Abbreviations: RTX=Rituximab, CYC = Cyclophosphamide, IV=intravenous, PO=orally, AZA=azathioprine, BID=twice per day, PR3 = proteinase-3, MPO=myeloperoxidase

Benefit-Risk Considerations

Benefits

- Non-inferiority for remission at Week 26
  - NI margin not adequately justified
  - Use of glucocorticoids (GCs) in both arms
  - Treatment effect of avacopan and magnitude of effect
- Sustained remission at Week 52
  - Superiority observed in RTX subgroup
- Reduced mean GC use
  - Specified based on study design
  - Potential drug-drug interaction
  - Clinical meaningfulness of differences
- Limited support from secondary endpoints or phase 2 studies

Risks

- Hepatotoxicity
- Angioedema
- CPK elevations
- Similar TEAEs, SAEs, AEs leading to discontinuation, infections between treatment groups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FDA Arthritis Advisory Committee Meeting Summary Presentation

NDA 214487: Avacopan for the treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA])

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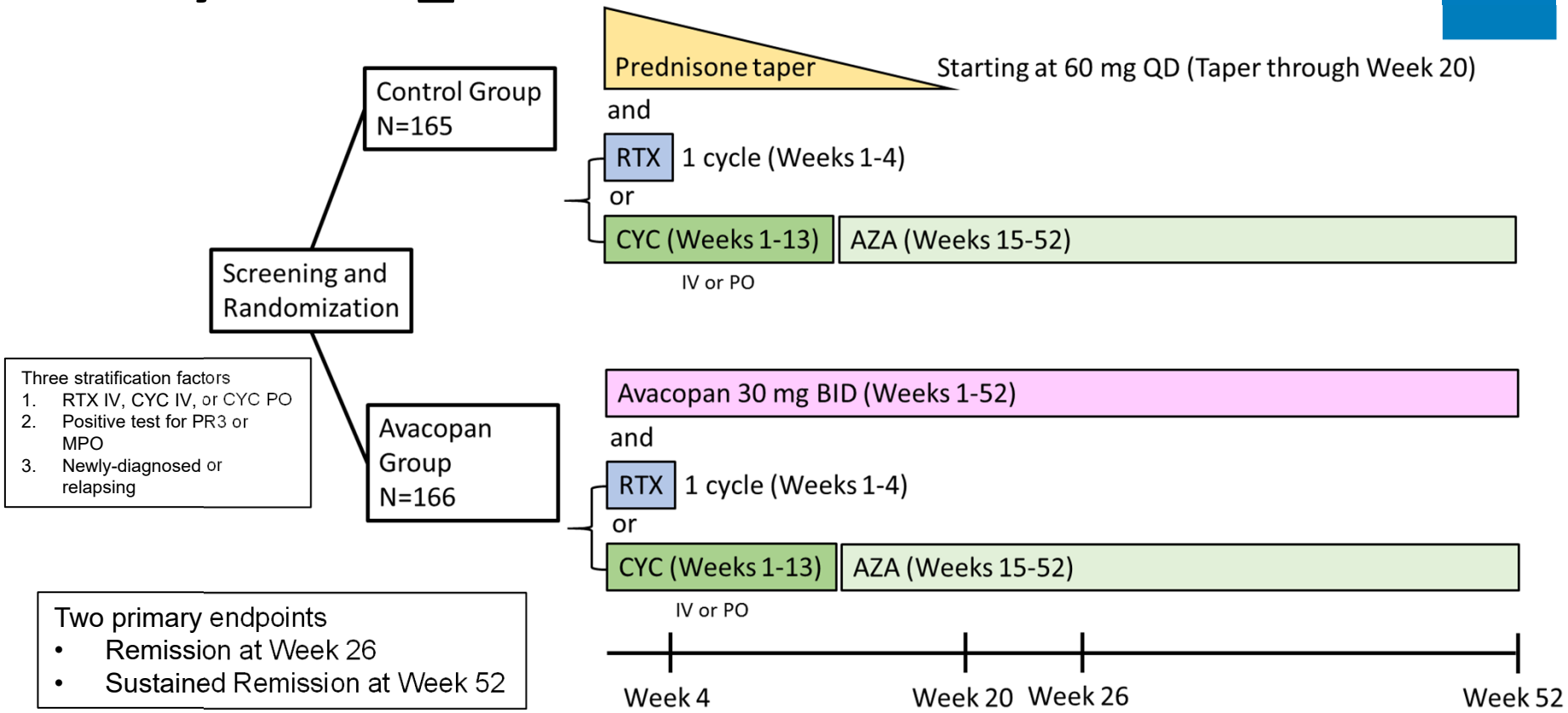
Clinical Program

Study	Study Design	Patient Population	Regimen/Schedule/Route	Treatment Duration/ Follow-up
CL010_168	R, DB, active-controlled efficacy and safety study in AAV	331 patients with AAV on background RTX or CYC/AZA	• PBO + prednisone taper (n=164) • Avacopan 30 mg BID (n=166) All patients received CYC or RTX for induction. Patients induced with CYC received AZA for maintenance.	Total 60 weeks Treatment: 52 weeks Follow-up: 8 weeks
Phase 2				
CL002_168	R, DB, PC safety and efficacy study	67 patients with AAV on background RTX or CYC/AZA	• PBO + prednisone 60 mg taper + CYC/RTX • Avacopan 30 mg BID + prednisone 20 mg taper + CYC/RTX • Avacopan 30 mg BID + NO prednisone + CYC/RTX All patients received CYC or RTX for induction.	Total 24 weeks Treatment: 12 weeks Follow-up: 12 weeks
CL003_168	Randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of avacopan in AAV on background CYC or RTX	42 patients with AAV	• Avacopan 10 mg BID + prednisone 60 mg taper (n=13) • Avacopan 30 mg BID + prednisone 60 mg taper (n=16) • PBO + prednisone 60 mg taper (n=13) All patients received CYC or RTX for induction.	Total 24 weeks Treatment: 12 weeks Follow-up: 12 weeks

Clinical Program

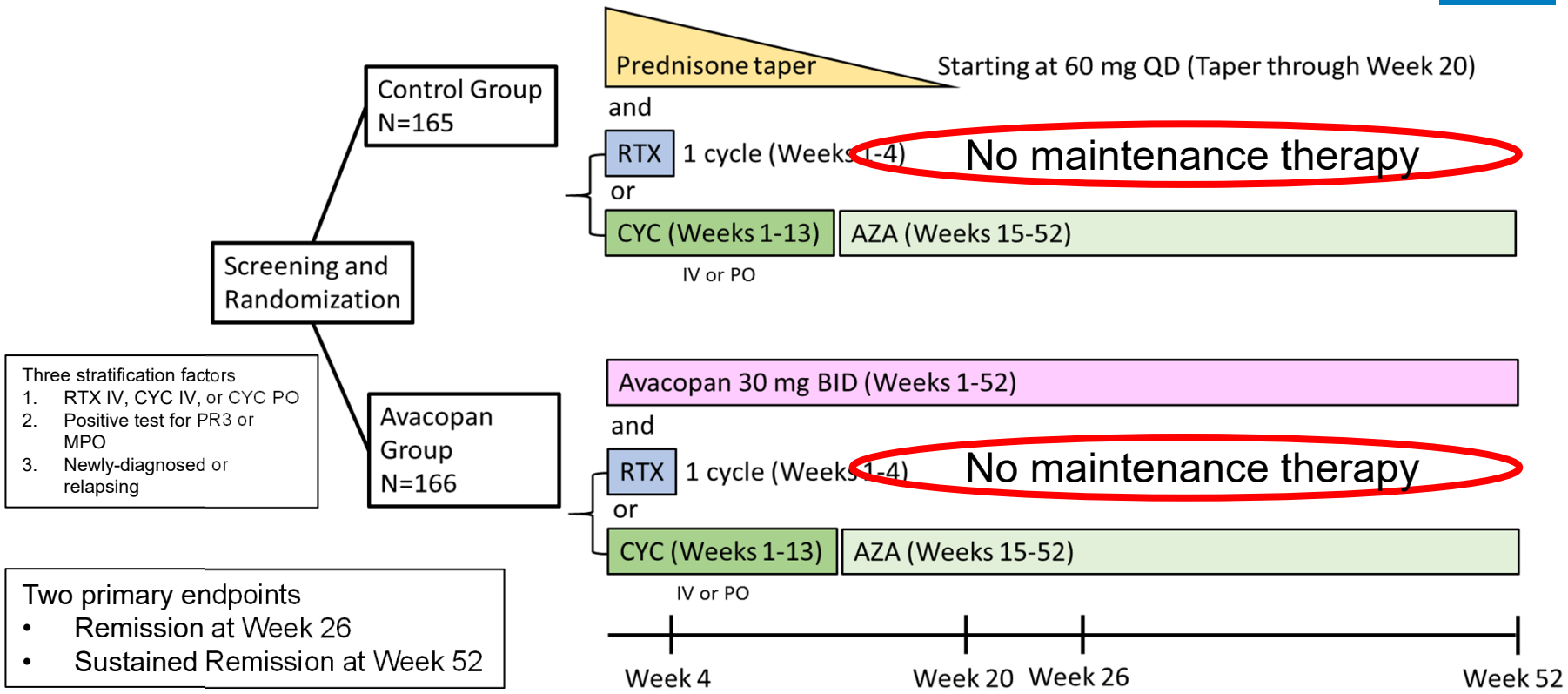
Study	Study Design	Patient Population	Regimen/Schedule/Route	Treatment Duration/ Follow-up
CL010_168	R, DB, active-controlled efficacy and safety study in AAV	331 patients with AAV on background RTX or CYC/AZA	• PBO + prednisone taper (n=164) • Avacopan 30 mg BID (n=166) All patients received CYC or RTX for induction. Patients induced with CYC received AZA for maintenance.	Total 60 weeks Treatment: 52 weeks Follow-up: 8 weeks
Phase 2				
CL002_168	R, DB, PC safety and efficacy study	67 patients with AAV on background RTX or CYC/AZA	• PBO + prednisone 60 mg taper + CYC/RTX • Avacopan 30 mg BID + prednisone 20 mg taper + CYC/RTX • Avacopan 30 mg BID + NO prednisone + CYC/RTX All patients received CYC or RTX for induction.	Total 24 weeks Treatment: 12 weeks Follow-up: 12 weeks
CL003_168	Randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of avacopan in AAV on background CYC or RTX	42 patients with AAV	• Avacopan 10 mg BID + prednisone 60 mg taper (n=13) • Avacopan 30 mg BID + prednisone 60 mg taper (n=16) • PBO + prednisone 60 mg taper (n=13) All patients received CYC or RTX for induction.	Total 24 weeks Treatment: 12 weeks Follow-up: 12 weeks

Study CL010_168 Schematic



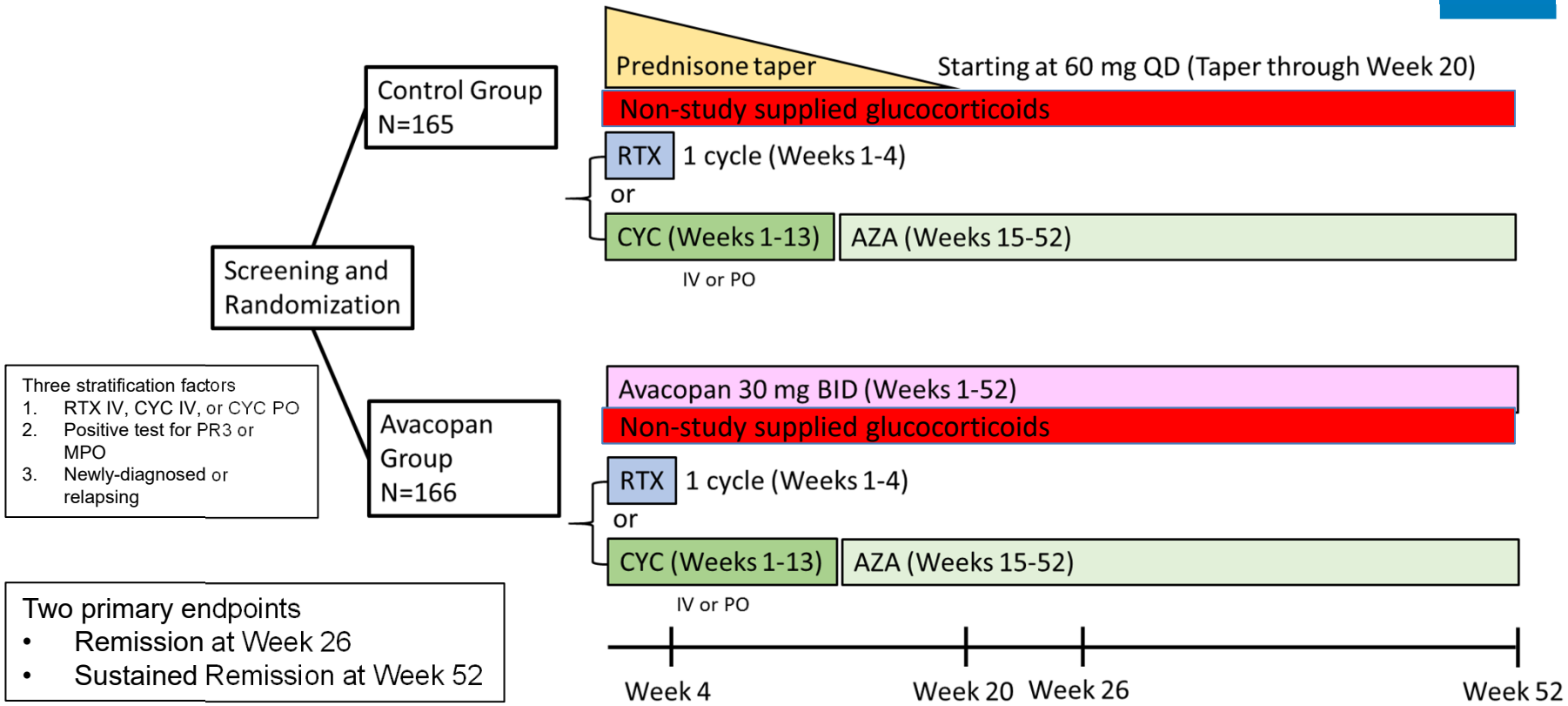
Abbreviations: RTX=Rituximab, CYC = Cyclophosphamide, IV=intravenous, PO=orally, AZA=azathioprine, BID=twice per day, PR3 = proteinase-3, MPO=myeloperoxidase

Maintenance Therapy



Abbreviations: RTX=Rituximab, CYC = Cyclophosphamide, IV=intravenous, PO=orally, AZA=azathioprine, QD=once a day, BID=twice per day, PR3 = proteinase-3, MPO=myeloperoxidase

Non-study Supplied Steroid Use



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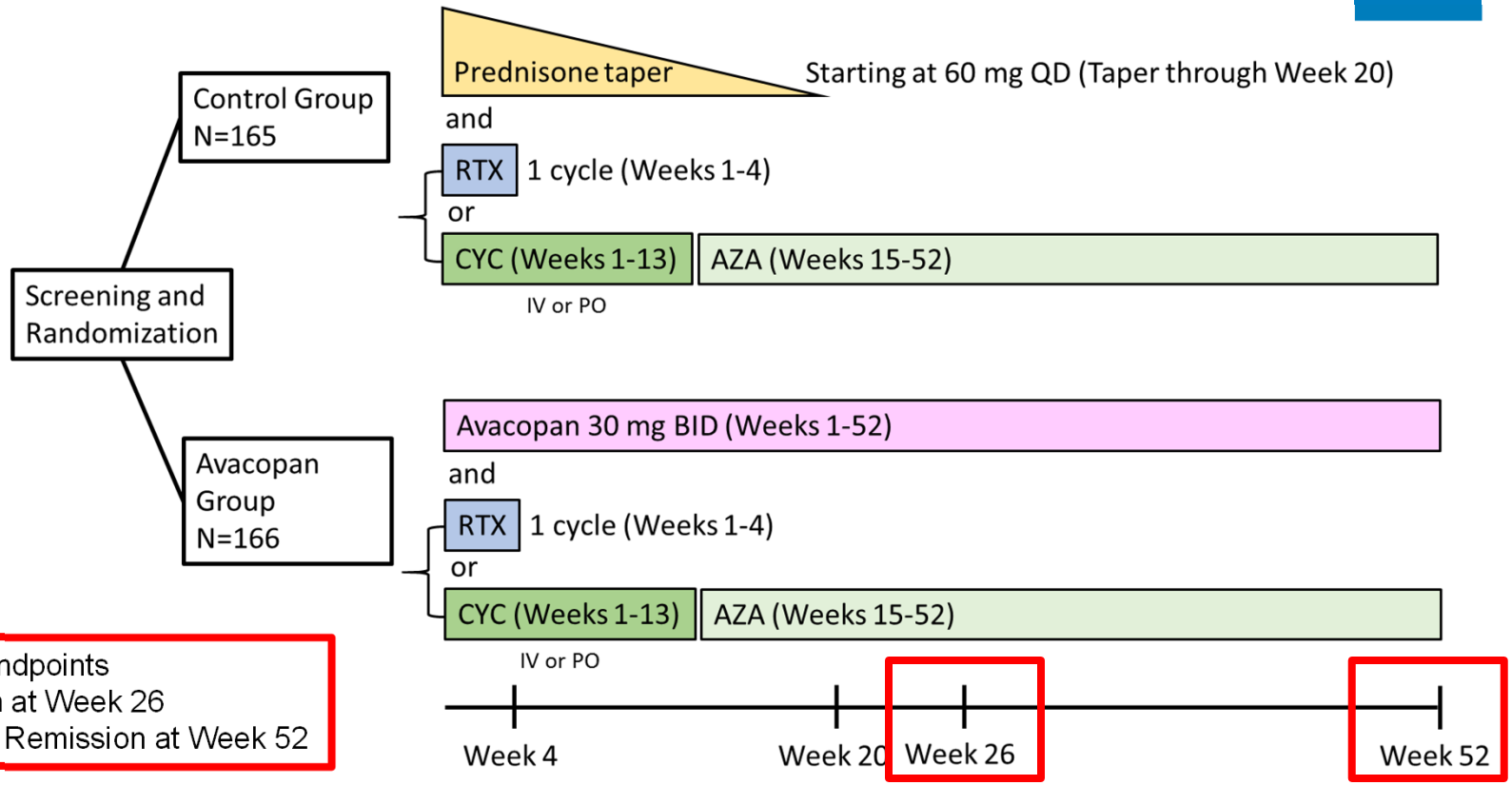
Primary Endpoints



Two primary endpoints
- Remission at Week 26
- Sustained Remission at Week 52

Abbreviations: RTX=Rituximab, CYC = Cyclophosphamide, IV=intravenous, PO=orally, AZA=azathioprine, QD=once a day, BID=twice per day, PR3 = proteinase-3, MPO=myeloperoxidase

Multiple Testing Hierarchy

1. Remission at Week 26 (Non-inferiority)
2. Sustained remission at Week 52 (Non-inferiority)
3. Sustained remission at Week 52 (Superiority)
4. Remission at Week 26 (Superiority)

- No secondary endpoints were controlled for multiplicity

Primary Efficacy Analysis Results

	Avacopan (N=166)	Prednisone (N=164)	Avacopan vs. Prednisone
	Count (%)	Count (%)	Difference (95% CI)
Remission at Wk26	120 (72.3%)	115 (70.1%)	3.4% (-6.0, 12.8)
Sustained Remission at Wk52	109 (65.7%)	90 (54.9%)	12.5% (2.6, 22.3)

Abbreviations: NI=non-inferiority, Sup=superiority, CI=confidence interval.

Patients with missing data at week of evaluation were imputed as non-responders. Nominal p-value was constructed using summary score test adjusted for randomization strata. For non-inferiority test, margin of 20% is used.

1. Remission at Week 26 (Non-inferiority): p-value < 0.0001
2. Sustained remission at Week 52 (Non-inferiority): p-value < 0.0001
3. Sustained remission at Week 52 (Superiority): p-value=0.0132
4. Remission at Week 26 (Superiority): p-value=0.48

- Tipping point analyses showed the robustness of the treatment effect to missing data assumptions

Subgroup Analyses by Background Induction Therapy

Endpoint	Background Induction Therapy	Treatment	N	Responder Count (%)	Response Rate Difference 95% CI
Remission at Week 26	RTX	Avacopan	107	83 (77.6)	1.9% (-9.5%, 13.2%)
		Prednisone	107	81 (75.7)	
	CYC	Avacopan	59	37 (62.7)	3.1% (-14.7%, 20.8%)
		Prednisone	57	34 (59.6)	
Sustained Remission at Week 52	RTX	Avacopan	107	76 (71.0)	15.0% (2.2%, 27.7%)
		Prednisone	107	60 (56.1)	
	CYC	Avacopan	59	33 (55.9)	3.3% (-14.8%, 21.4%)
		Prednisone	57	30 (52.6)	

Counts and percentages relative to N. Point estimate and 95% confidence interval using normal approximation were reported.

Abbreviations: CI=confidence interval, N=number of patients in the primary analysis set, RTX=rituximab, CYC=cyclophosphamide

Analysis Based on Investigator Assessments

	Avacopan (N=166)	Prednisone (N=164)	Difference	NI p-value	Sup p-value
Remission at Wk26	104 (62.7%)	102 (62.2%)	1.3%	<0.0001	0.79
95% CI	(54.8, 70.0)	(54.3, 69.6)	(-8.7, 11.4)		
Sustained Remission at Wk52	91 (54.8%)	77 (47.0%)	8.5%	<0.0001	0.10
95% CI	(46.9, 62.5)	(39.1, 54.9)	(-1.7, 18.6)		

Abbreviations: NI=non-inferiority, Sup=superiority, CI=confidence interval, N=number of patients in the primary analysis set. Patients with missing data at week of evaluation were imputed as non-responders. Nominal p-value was constructed using summary score test adjusted for randomization strata. For non-inferiority test, margin of 20% is used.

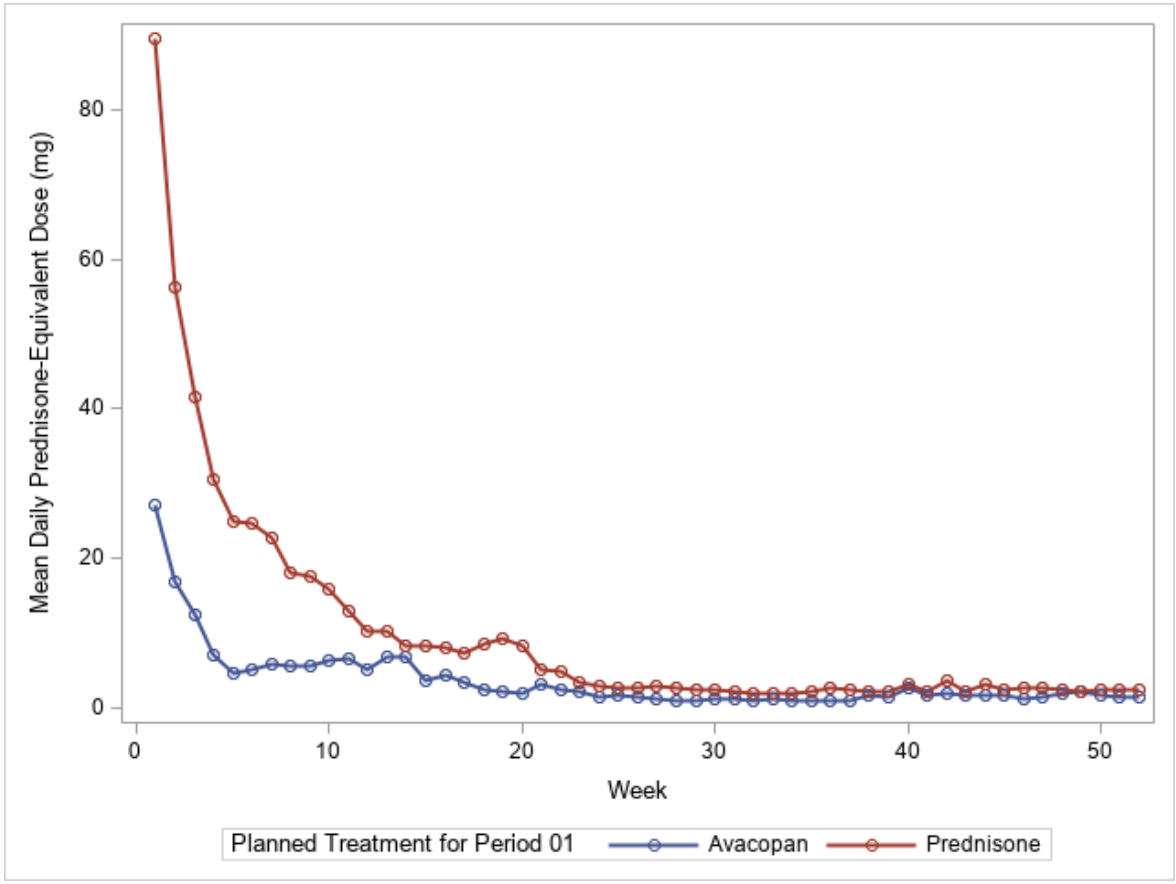
Efficacy Considerations (1)

- Remission at Week 26 – ***Noninferiority but not superiority***
  - Noninferiority (NI) margin not adequately justified
  - Both treatment groups received glucocorticoids (GC)
    - 86% of patients in avacopan arm received non-study supplied GC
  - Treatment effect of avacopan and magnitude of effect are unclear

Efficacy Considerations (1)

- Remission at Week 26 – ***Noninferiority but not superiority***
  - Noninferiority (NI) margin not adequately justified
  - Both treatment groups received glucocorticoids (GC)
    - 86% of patients in avacopan arm received non-study supplied GC
  - Treatment effect of avacopan and magnitude of effect are unclear
- Sustained remission at Week 52 – ***Noninferiority and superiority***
  - Treatment effect observed in rituximab (RTX) subgroup that did not receive maintenance treatment
  - No treatment effect in cyclophosphamide/azathioprine subgroup
  - Superiority not achieved based on Investigator assessment

Cumulative Total Glucocorticoid Use



Secondary Endpoint: Glucocorticoid Toxicity Index (GTI)

GTI-CWS

Cumulative glucocorticoid toxicity, regardless of whether the toxicity has lasting effects or is transient

Treatment Arm	Change from Baseline	
	LS Mean[1] (95% CI)	Diff (95% CI)
Week 13		
Prednisone	36.9 (31.3, 42.6)	
Avacopan	26.0 (20.4, 31.6)	-10.9 (-18.2, -3.7)
Week 26		
Prednisone	57.0 (49.4, 64.6)	
Avacopan	40.2 (32.7, 47.8)	-16.8 (-27.0, -6.5)

GTI-AIS

Assess whether therapy is effective at diminishing glucocorticoid toxicity over time

Treatment Arm	Change from Baseline	
	LS Mean[1] (95% CI)	Diff (95% CI)
Week 13		
Prednisone	23.3 (16.7, 29.9)	
Avacopan	10.0 (3.4, 16.5)	-13.3 (-21.8, -4.8)
Week 26		
Prednisone	23.5 (16.4, 30.6)	
Avacopan	11.4 (4.3, 18.5)	-12.1 (-21.5, -2.7)

1. Derived from a mixed effects model for repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction as factors, and baseline as covariate. An unstructured covariance matrix was used to model the within-subject variance-covariance structure for the model errors.

Potential Drug-Drug Interaction Considerations

Avacopan is a CYP3A4 inhibitor and may increase the systemic exposure of CYP3A4 substrates such as glucocorticoids

- Avacopan capsules were administered with food in phase 2 and 3 studies
- Food effect
  - Avacopan: Cmax↔, AUC↑72%
  - M1: Cmax↓51%, AUC↔
- Drug-drug interactions
  - Avacopan and M1 inhibit CYP3A4
  - Study CL008_168: when co-administered with avacopan under fasted condition, midazolam (a sensitive CYP3A4 substrate) Cmax↑55%, AUC↑81%
  - The impact of avacopan on CYP3A4 substrates under fed condition could be higher but has not been studied
  - PK results of Phase 2 studies could not rule out the potential exposure increase of prednisone when co-administered with avacopan

Efficacy Considerations (2): GC Use

- Differences in cumulative GC use
  - Specified based on study design
  - Potential drug-drug interaction
  - Clinical meaningfulness of differences

Secondary Endpoints

- Glucocorticoid Toxicity Index (GTI) over first 26 weeks
  - Cumulative Worsening Score (CWS) and Aggregate Improvement Score (AIS)
- Proportion of patients and time to relapse after remission
- Change in Vasculitis Damage Index (VDI) over 52 weeks
- If renal disease at baseline
  - Change in estimated Glomerular Filtration Rate (eGFR) at Week 52
  - % change in urine albumin creatinine ratio (UACR) over 52 weeks
  - % change in urinary monocyte chemoattractant protein 1 (MCP-1) to creatinine ratio over 52 weeks
- Early Remission (BVAS 0 at Week 4)
- Change from baseline in health-related Quality of Life (hr-QOL) at Week 52
  - SF-36 v2 and EQ-5D-5L VAS

- **Not adjusted for multiplicity**
- **Secondary endpoints were assessed at multiple timepoints**

Efficacy Considerations (3): Supportive Evidence

- Secondary endpoints provide limited support of efficacy
  - Not adjusted for multiplicity
  - Fewer relapses in avacopan arm, but other measures of increased disease activity similar
    - Trial not designed to assess relapse and interpretability of analysis results is limited
  - Similar changes in Vasculitis Damage Index
  - Differences in renal endpoints small and not sustained
- Phase 2 studies provide limited and inconsistent evidence of efficacy

Safety Considerations

- Potential hepatotoxicity
  - More avacopan-treated patients with hepatobiliary adverse events (AEs), serious adverse events (SAEs), and hepatic AEs leading to discontinuation
- Angioedema
- Creatinine phosphokinase (CPK) elevations
- Infections, serious infections, opportunistic infections similar between treatment groups
- Treatment-emergent AEs, SAEs, AEs leading to discontinuation similar between treatment groups

Benefit-Risk Considerations

Benefits

- Non-inferiority for remission at Week 26
  - NI margin not adequately justified
  - Use of GCs in both arms
  - Treatment effect of avacopan and magnitude of effect
- Sustained remission at Week 52
  - Superiority observed in RTX subgroup
- Reduced mean GC use
  - Specified based on study design
  - Potential drug-drug interaction
  - Clinical meaningfulness of differences
- Limited support from secondary endpoints or phase 2 studies

Risks

- Hepatotoxicity
- Angioedema
- CPK elevations
- Similar TEAEs, SAEs, AEs leading to discontinuation, infections between treatment groups

FDA Arthritis Advisory Committee Meeting
Charge to the Committee

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May 6, 2021

Effectiveness Standard
21 CFR 314.125
Refusal to Approve an Application

- (b)(5) "…substantial evidence consisting of adequate and well-controlled investigations…that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."

Effectiveness Standards

- **Gold standard:** substantial evidence from 2 adequate, well-controlled studies

From: [1]Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products guidance, 1998
and [2]Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products draft guidance, 2019

Effectiveness Standards

- **Gold standard:** substantial evidence from 2 adequate, well-controlled studies
- Otherwise, "one adequate and well-controlled clinical investigation plus confirmatory evidence"[1,2]
  - Key factors include "persuasiveness of evidence from a single study" and "robustness of confirmatory evidence" [1]

From: [1]Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products guidance, 1998
and [2]Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products draft guidance, 2019

Effectiveness Standards

- **Gold standard:** substantial evidence from 2 adequate, well-controlled studies
- Otherwise, "one adequate and well-controlled clinical investigation plus confirmatory evidence"[1,2]
  - Key factors include "persuasiveness of evidence from a single study" and "robustness of confirmatory evidence" [1]
  - A single study should "be limited to situations in which the trial has demonstrated a clinically meaningful and statistically *very persuasive effect* on mortality…" [2]

From: [1]Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products guidance, 1998
and [2]Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products draft guidance, 2019

Safety Standard
21 CFR 314.125
Refusal to Approve an Application

- (b)(2) "…do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling"
- (b)(3) "The results of the test show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions."
- (b)(4) "There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

Discussion Points and Voting Questions (1)

1. **DISCUSSION:** Discuss whether the results at Week 26 support a clinically meaningful benefit of avacopan.
   Include discussion of the following:
   a. Appropriateness of a primary non-inferiority (NI) comparison
   b. Use of additional non-study supplied GC in the avacopan group
   c. Lack of statistically significant superiority at Week 26

Discussion Points and Voting Questions (2)

2. **DISCUSSION:** Discuss whether the results at Week 52 support a clinically meaningful benefit of avacopan.
   Include discussion of the following:
   a. Impact of the lack of maintenance therapy in the rituximab subgroup
   b. Discrepancies in BVAS remission responses as determined by Adjudication Committee vs. Investigators

BVAS = Birmingham Vasculitis Assessment Score

Discussion Points and Voting Questions (3)

3. **DISCUSSION:** Discuss whether the data support the use of avacopan as a steroid-sparing agent in AAV.
   Include discussion of the following:
   a. Use of additional non-study supplied GCs in the avacopan group
   b. Impact of a potential increase in GC exposures due to CYP3A4 inhibition by avacopan

Discussion Points and Voting Questions (4)

4. **DISCUSSION:** Based on the data from the clinical program, discuss how avacopan, if approved, should be used in the treatment of AAV.

Discussion Points and Voting Questions (5)

5. **VOTE:** Do the efficacy data support approval of avacopan for the treatment of adult patients with AAV (GPA and MPA)?
   - If no, what data are needed?

Discussion Points and Voting Questions (6)

6. **VOTE:** Is the safety profile of avacopan adequate to support approval of avacopan for the treatment of adult patients with AAV (GPA and MPA)?
   - If no, what data are needed?

Discussion Points and Voting Questions (7)

7. **VOTE:** Is the benefit-risk profile adequate to support approval of avacopan at the proposed dose of 30 mg twice daily for the treatment of adult patients with AAV (GPA and MPA)?
   - If no, what further data are needed?


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Back Up Slides Shown

Non-Study Supplied Glucocorticoid Use

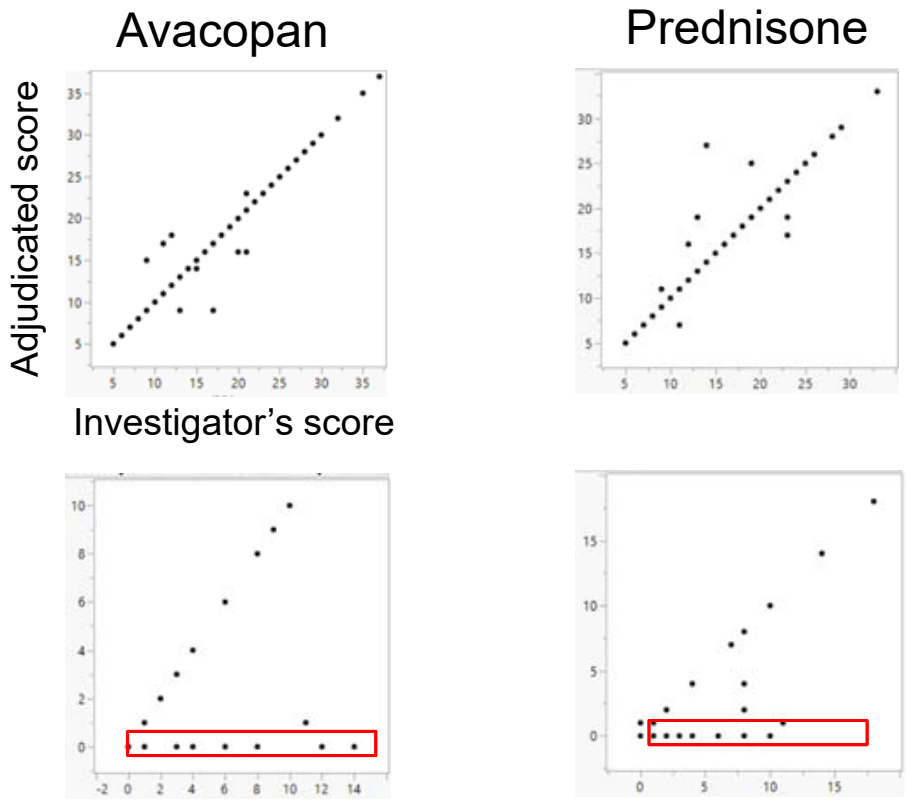
	Avacopan (N=166)	Prednisone (N=164)
Week 0 to 26		
Treatment of worsening vasculitis	27 (16.3%)	22 (13.4%)
Treatment of relapse	11 (6.7%)	29 (17.4%)
Treatment of persistent vasculitis	77 (46.4%)	83 (50.6%)
Maintenance of remission	27 (16.3%)	20 (12.2%)
Week 27 to 52		
Treatment of worsening vasculitis	10 (6.0%)	14 (8.5%)
Treatment of relapse	8 (4.8%)	25 (15.2%)
Treatment of persistent vasculitis	10 (6.0%)	14 (8.5%)
Maintenance of remission	13 (7.8%)	16 (9.8%)

Vasculitis Damage Index (VDI)

Treatment Arm	Change from Baseline	
	LS Mean[1] (95% CI)	Diff (95% CI)
Week 26		
Prednisone	0.95 (0.77, 1.13)	
Avacopan	1.04 (0.87, 1.22)	0.10 (-0.13, 0.33)
Week 52		
Prednisone	1.13 (0.94, 1.32)	
Avacopan	1.16 (0.97, 1.34)	0.03 (-0.21, 0.27)

1. Derived from a mixed effects model for repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction as factors, and baseline as covariate. An unstructured covariance matrix was used to model the within-subject variance-covariance structure for the model errors.

Investigator vs. Adjudicator Assessments



Specification in the Documents

- Protocol
  - Specified the use of BVAS version 3 and cited *Mukhtyar C, et al. 2009 Modification and validation of the Birmingham Vasculitis Activity Score (version 3) Ann Rheum Dis 68:1827–1832*
    - The BVAS version 2 generates two scores; BVAS1 reflects new or worse disease, and BVAS2 reflects persistent disease
    - "Ignoring BVAS2 (persistent disease) underestimates true disease activity"
    - For BVAS version 3, the "persistent" boxes for each item were replaced by a single "persistent" box for the whole form. This box was marked, only if every disease manifestation was attributable to "persistent" disease. All items were treated as "new/worse" if any of them were "new/worse"

- Adjudication Charter
  - BVAS adjudication form does not include this single "persistent" box

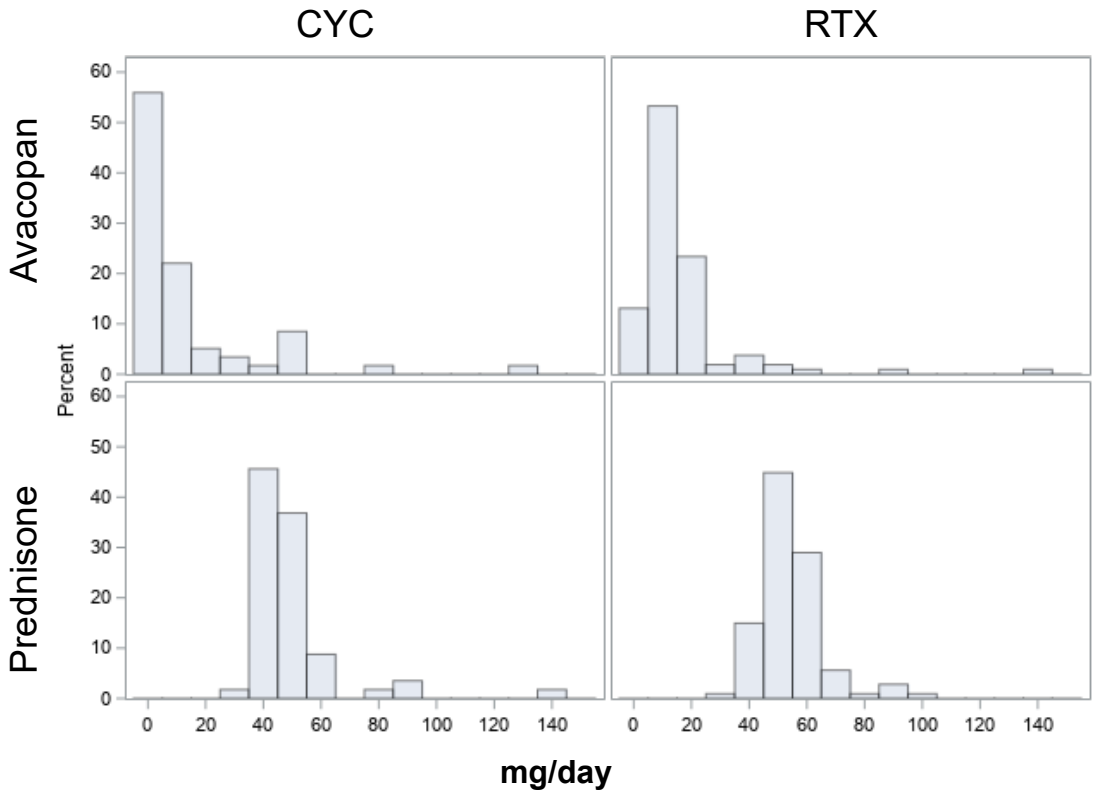
Non-study Supplied Glucocorticoid Use (Patients Who Used Steroid)

	Avacopan	Prednisone
Glucocorticoid Use Weeks 0-26		
Number of subjects	143 (86.1%)	149 (90.9%)
Mean dose (mg)	1245.5	884.0
Glucocorticoid Use Weeks 27-52		
Number of subjects	44 (26.5%)	63 (38.4%)
Mean dose (mg)	1041.2	1202.7
Glucocorticoid Use Weeks 0-52		
Number of subjects	145 (87.3%)	149 (90.9%)
Mean dose (mg)	1544.3	1392.5

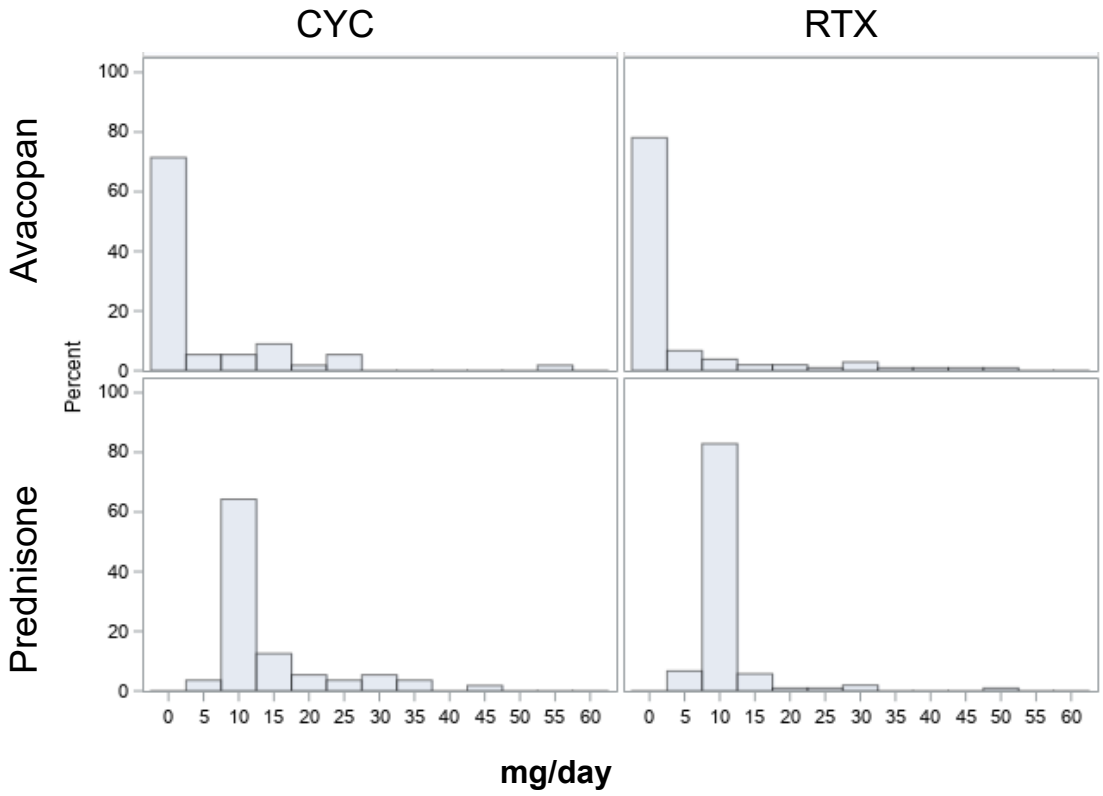
Non-study Supplied Glucocorticoid Use Adjusted for Time in Study

	Avacopan (N=166)	**Prednisone (N=164)**
Glucocorticoid Use Weeks 0-26		
Total dose (mg)	178105.14	131718.89
Patient day	29203	29228
Total/patient-day	6.1	4.5
Glucocorticoid Use Weeks 27-52		
Total dose (mg)	45812.3	75768.65
Patient day	27883	27966
Total/patient-day	1.6	2.7
Glucocorticoid Use Weeks 0-52		
Total dose (mg)	223917.44	207487.54
Patient day	57086	57194
Total/patient-day	3.9	3.6

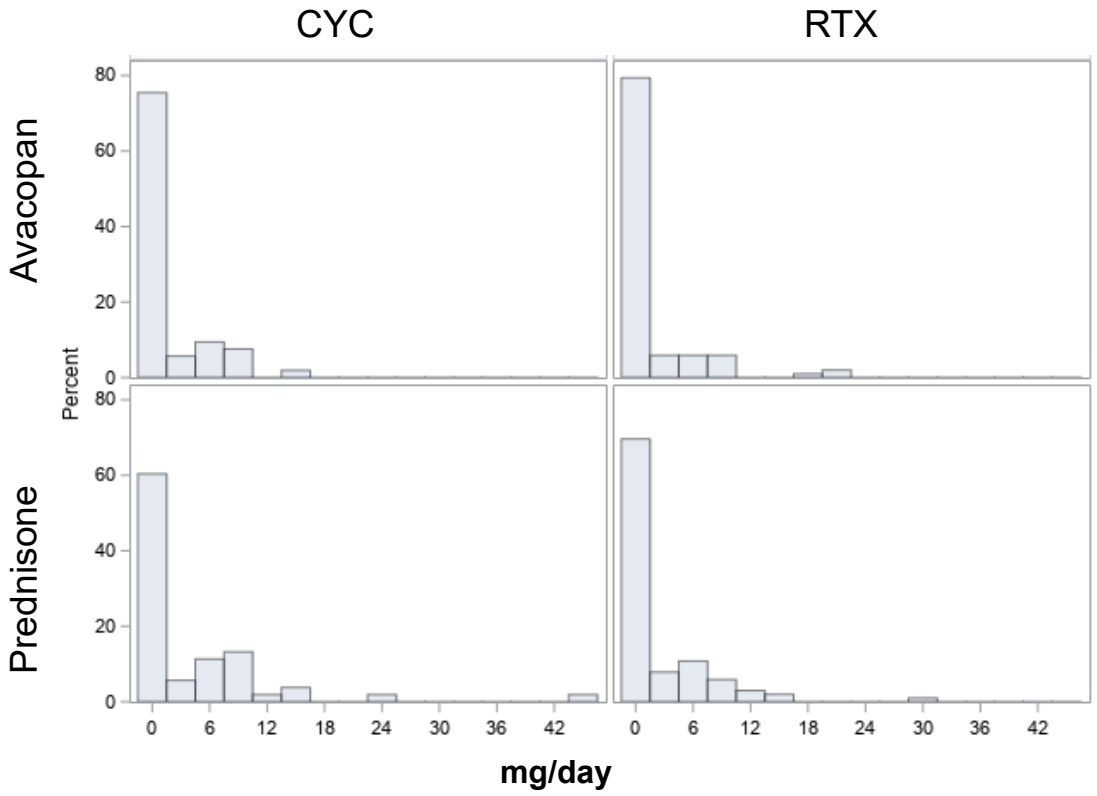
Cumulative Glucocorticoid Use (Day 1 – Week 4)



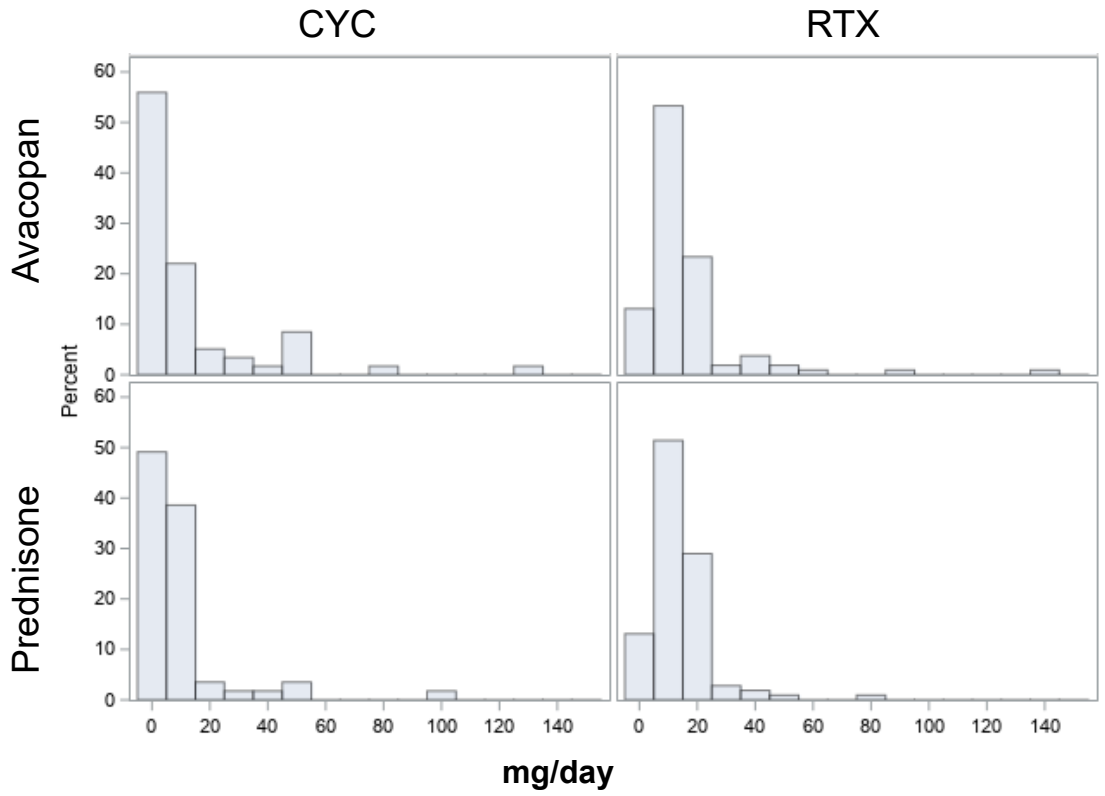
Cumulative Glucocorticoid Use (Week 5 – Week 26)



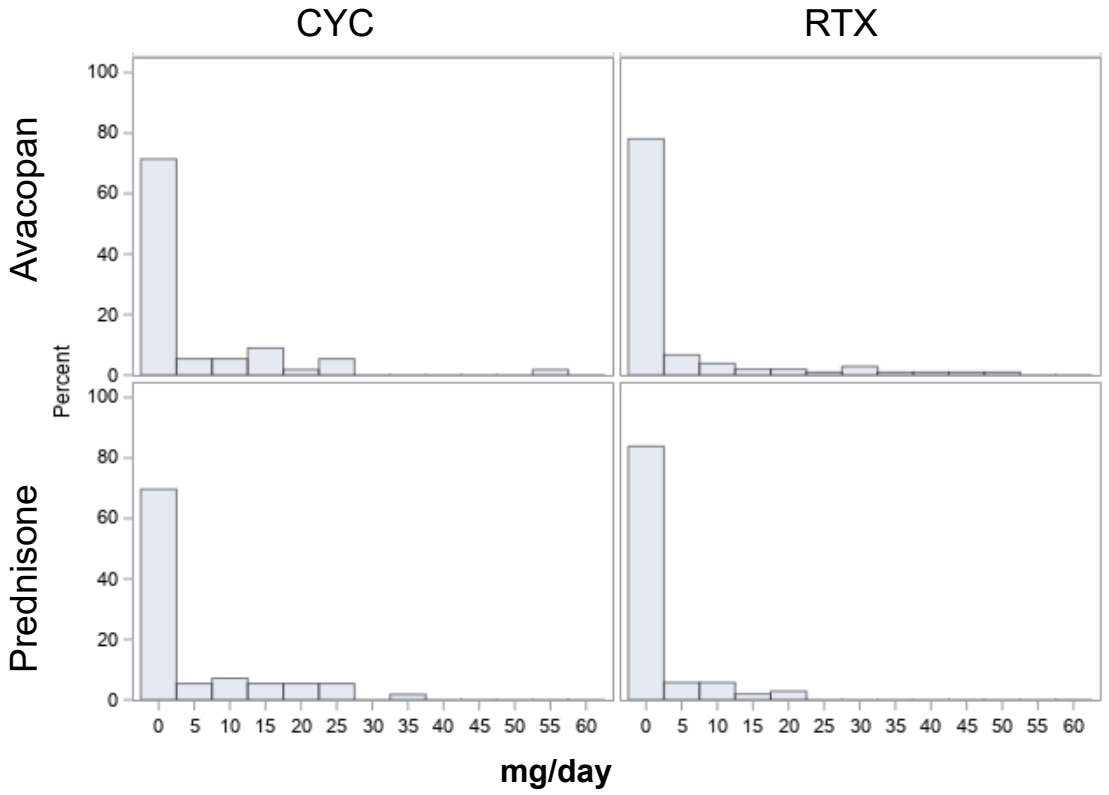
Cumulative Glucocorticoid Use (Week 27 – Week 52)



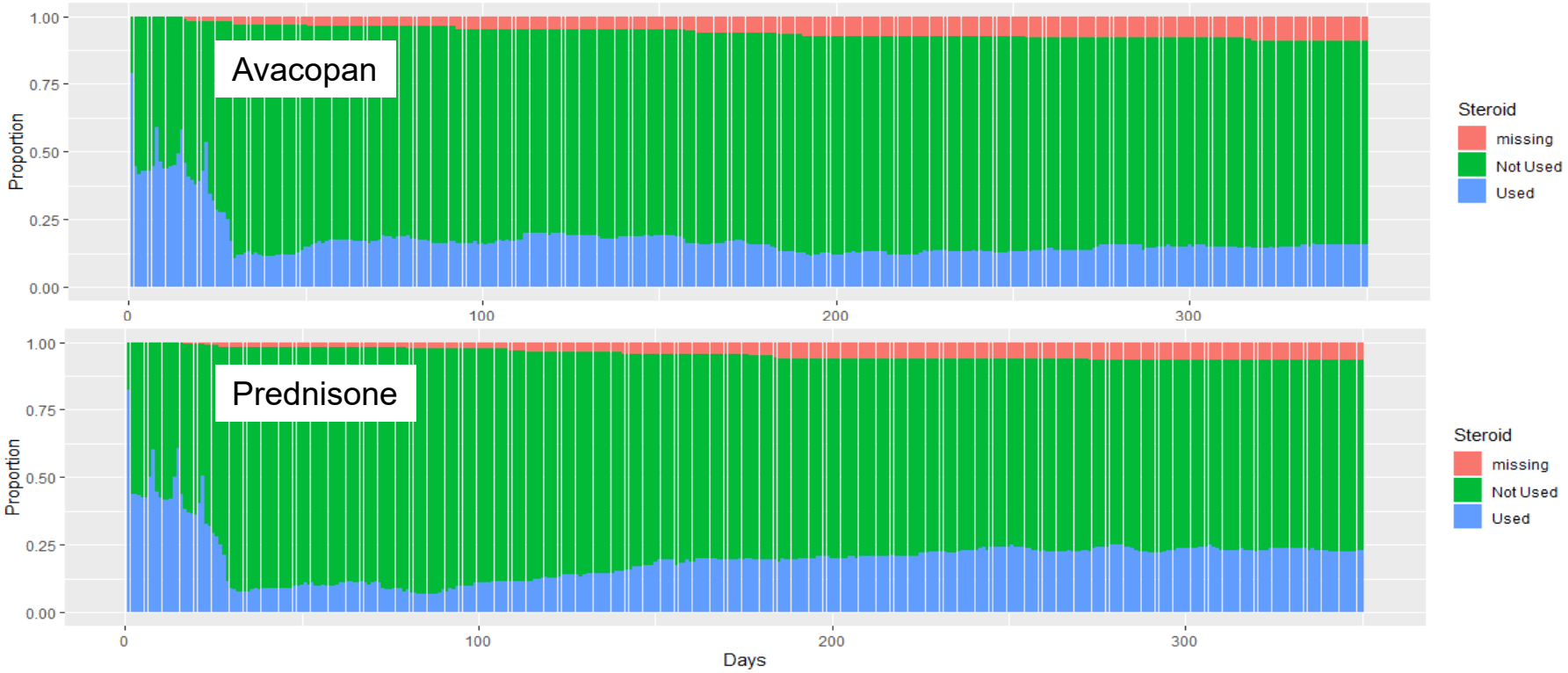
Cumulative Non-study Supplied Glucocorticoid Use (Day 1 – Week 4)



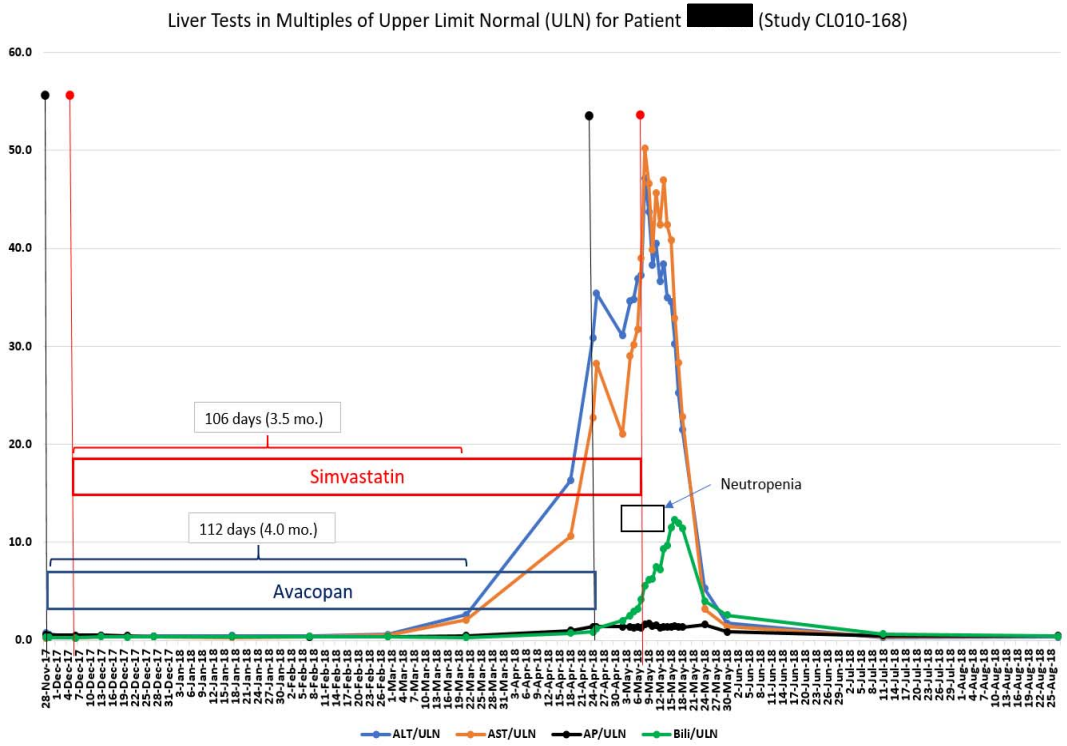
Cumulative Non-study Supplied Glucocorticoid Use (Week 5 – Week 26)



Non-study Supplied Glucocorticoid Use (Proportion of Patients Using Steroid)



Safety: Liver Toxicity (1)



Source: DHN DILI Team

- 62-year-old white woman
- Hy's law laboratory criteria
- Elevated transaminases 4 months after starting avacopan
- Concomitant medication of simvastatin
- Possible DILI due to avacopan

Investigator vs. Adjudicator (Week 52)

- 18 discrepancies in 17 patients
  - Avacopan: 8 patients
  - Prednisone: 9 patients

- BVAS organ systems

- Renal (n=10)	- Nervous (n=2)
- ENT (n=2)	- Abdominal (n=1)
- Chest (n=2)	- General (n=1)

Investigator vs. Adjudicator (Week 26)

- 45 discrepancies in 39 patients
  - Avacopan: 21 patients
  - Prednisone: 18 patients

- BVAS organ systems
  - Renal (n=25)
  - ENT (n=6)
  - Chest (n=4)
  - Nervous (n=3)
  - General (n=7)

Alternate Study Design Considerations

- Treatment arms
  - A = placebo plus 20-week prednisone taper
  - B = avacopan plus 20-week prednisone taper
  - C = avacopan plus no/low dose prednisone

- Primary analysis: superiority analysis of A vs. B
- Additional analysis: A vs. C