FDA Arthritis Advisory Committee Meeting

Overview of the Clinical Program

NDA 214487: avacopan for treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA) vasculitis

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U.S. Food and Drug Administration
May 6, 2021

Outline of FDA Presentations

- Overview of the Clinical Program
  - Suzette Peng, MD
  - Medical Officer: DRTM, OII, OND, CDER, FDA
- Statistical Review of Efficacy
  - Yura Kim, PhD
  - Biometrics Reviewer: DB3, OTS, CDER, FDA
- Clinical Review of Efficacy, Safety, and the Benefit-Risk Assessment
  - Suzette Peng, MD
  - Medical Officer: DRTM, OII, OND, CDER, FDA
- Charge to the Committee
  - Rachel Glaser, MD
  - Cross-Discipline Team Leader: DRTM, OII, OND, CDER, FDA

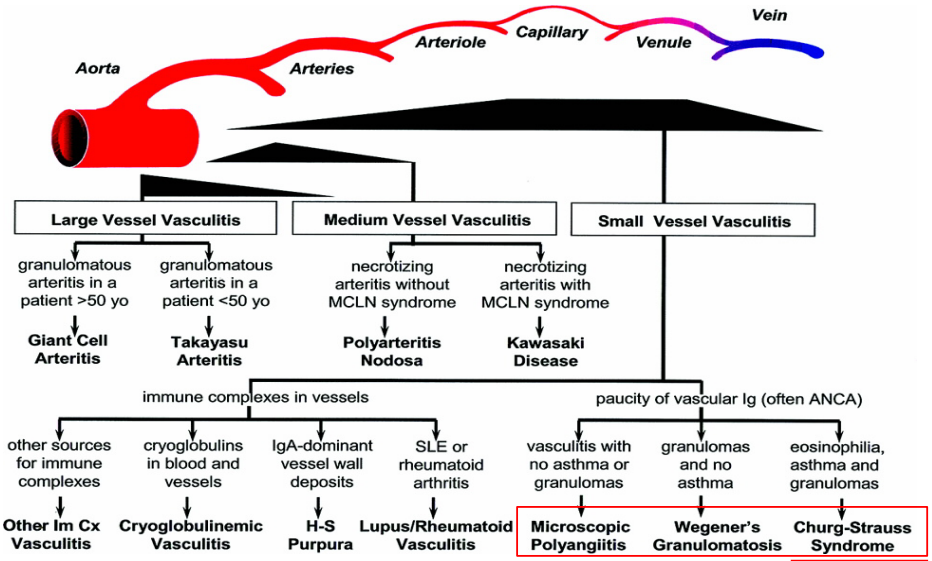
Outline

- Overview
- ANCA-associated vasculitis and current therapy
- Pertinent regulatory history
- Clinical program of avacopan for AAV
- Summary of clinical pharmacology

Overview

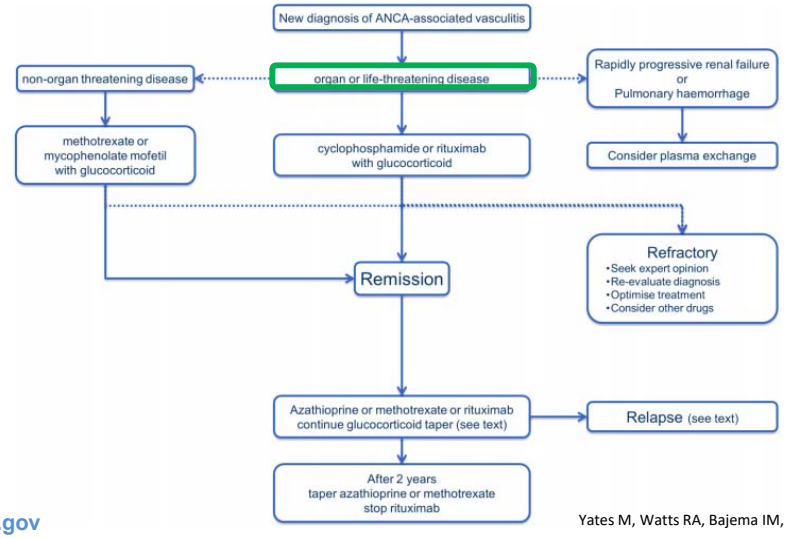
- **Product:** Avacopan
- **Applicant:** ChemoCentryx, Inc.
- **Mechanism of action:** C5a-receptor antagonist
- **Proposed indication:** Treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis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

ANCA-associated Vasculitis (AAV)



Jennette JC and Falk RJ. *Pathol Case Rev*. 2007;12:200-204.

ANCA-associated Vasculitis: Treatment of Severe Systemic Disease



Yates M, Watts RA, Bajema IM, et al. *Ann Rheum Dis.* 2016;75:1583-1594.

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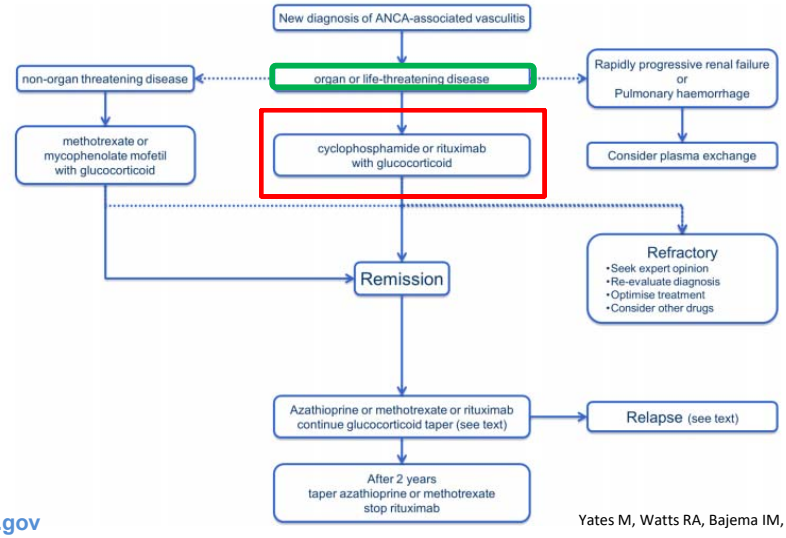

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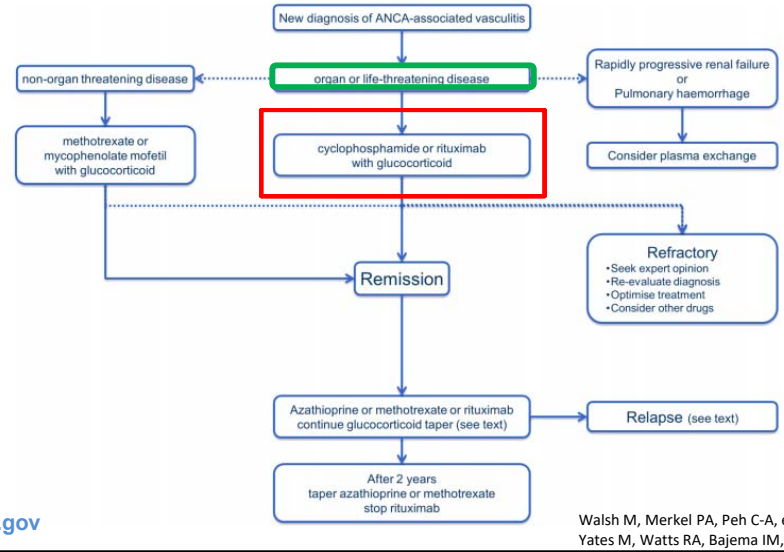

Glucocorticoids

- ↓ mortality
- No consensus on optimal dose, route, or duration
- Multiple toxicities
- Reduced dose regimen?

www.fda.gov

Walsh M, Merkel PA, Peh C-A, et al. *N Engl J Med.* 2020; 832:622-631.
Yates M, Watts RA, Bajema IM, et al. *Ann Rheum Dis.* 2016;75:1583-1594.

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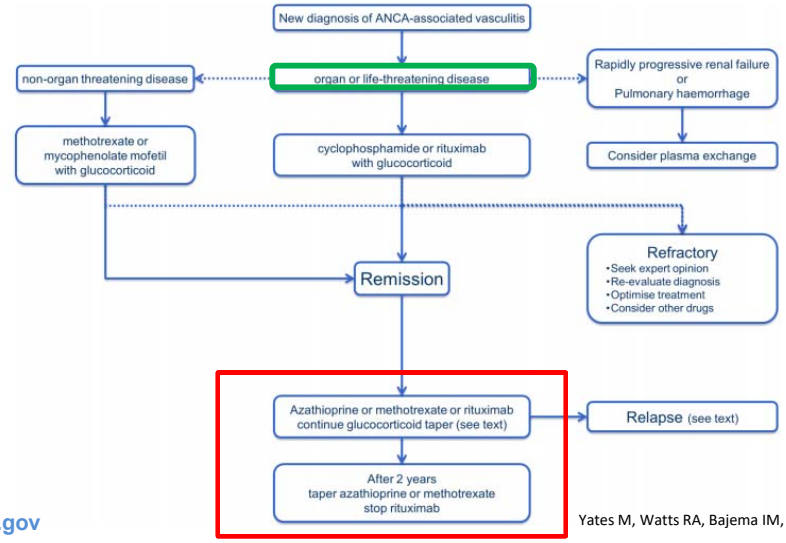

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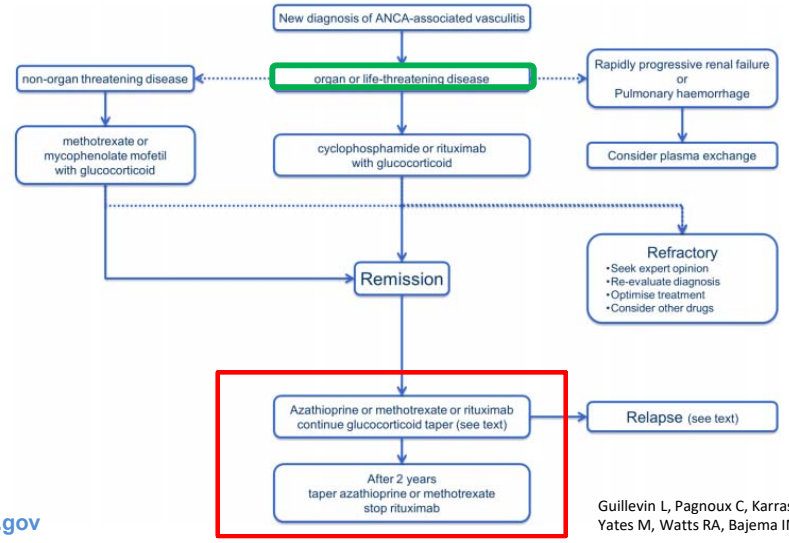

Rituximab

- FDA-approved for **treatment** in 2011
- FDA-approved for **follow-up treatment** in 2018

www.fda.gov

Guillevin L, Pagnoux C, Karras A. *N Engl J Med*. 2014; 371: 1771-80.
Yates M, Watts RA, Bajema IM, et al. *Ann Rheum Dis.* 2016;75:1583-1594.

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Pertinent Regulatory History

- Complicated study design with multiple variables
  - Removing SOC glucocorticoids and replacing with avacopan
  - Comparison of prednisone over 20-26 weeks and avacopan over 52 weeks
- Non-inferiority study design
- Alternate study designs to address concerns
  - Third treatment arm with no steroids or rapid steroid taper
  - Efficacy assessment at Week 52
- Secondary endpoints

* Discussions at the EOP2 meeting, post-EOP2 meeting, and pre-NDA meeting

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

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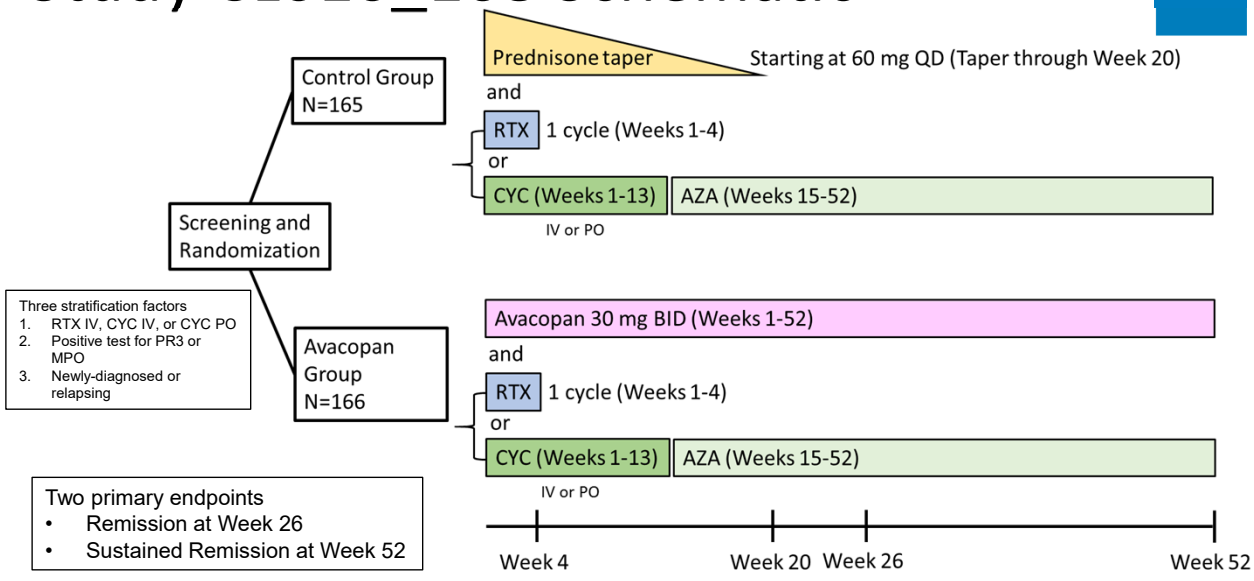
Study CL010_168 Schematic



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

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

- 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


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FDA Arthritis Advisory Committee Meeting

Statistical Review of Efficacy

NDA 214487: avacopan for treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA) vasculitis

Yura Kim, PhD
Statistical Reviewer
Division of Biometrics III, Office of Biostatistics
Office of Translational Sciences, CDER
U.S. Food and Drug Administration
May 6, 2021

Outline

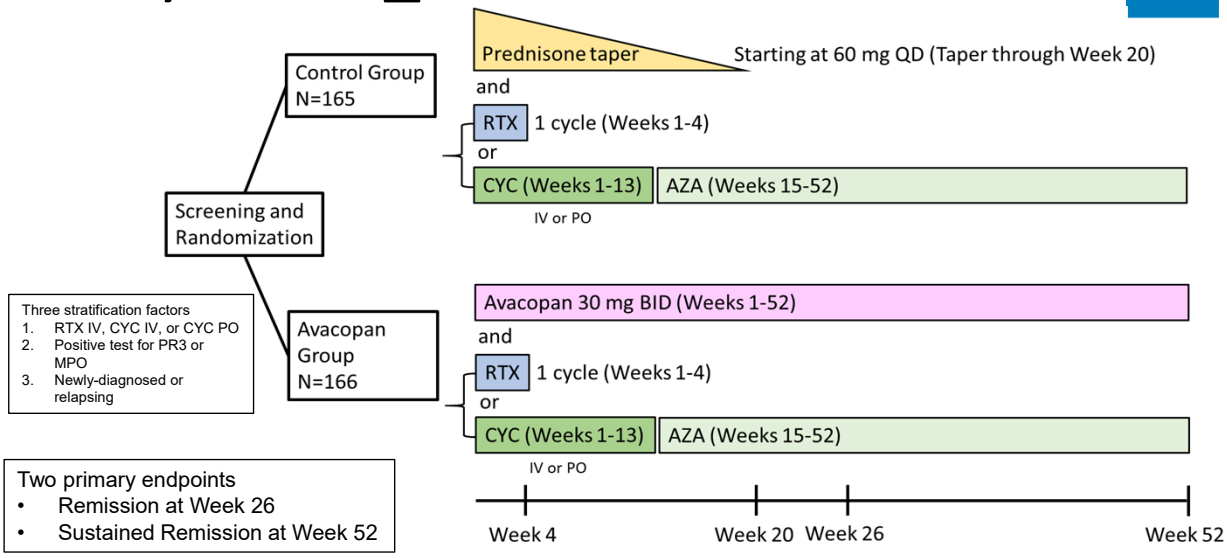
- Phase 3 Trial Design
- Primary Endpoints
- Analysis Methods
- Efficacy Analysis Results
  - Analysis of BVAS remission
  - Analysis of relapse
- Supplemental Analysis Results
  - Subgroup Analyses
  - Analysis based on Investigator assessments

PHASE 3 TRIAL DESIGN

Single Phase 3 Trial: CL010_168

- Multi-center, randomized, double-blind, parallel-group, active-controlled study
- Population: patients with newly diagnosed or relapsing ANCA-vasculitis (AAV)
- Key inclusion criteria: granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)
- Study duration: 52-week of treatment period + 8-week of follow-up period

Study CL010_168 Schematic



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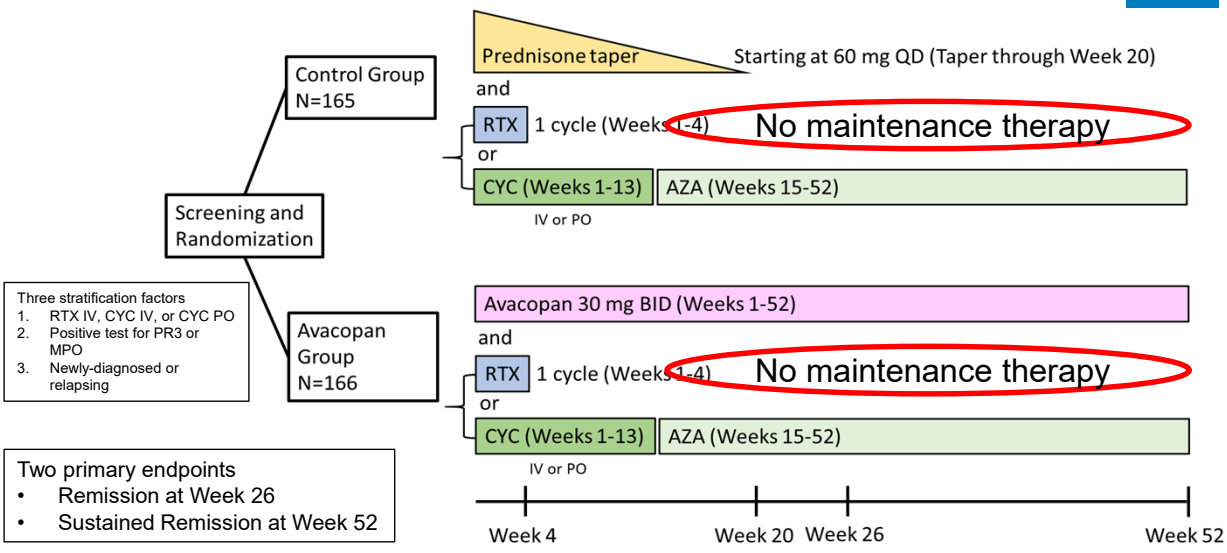
Lack of Maintenance Therapy



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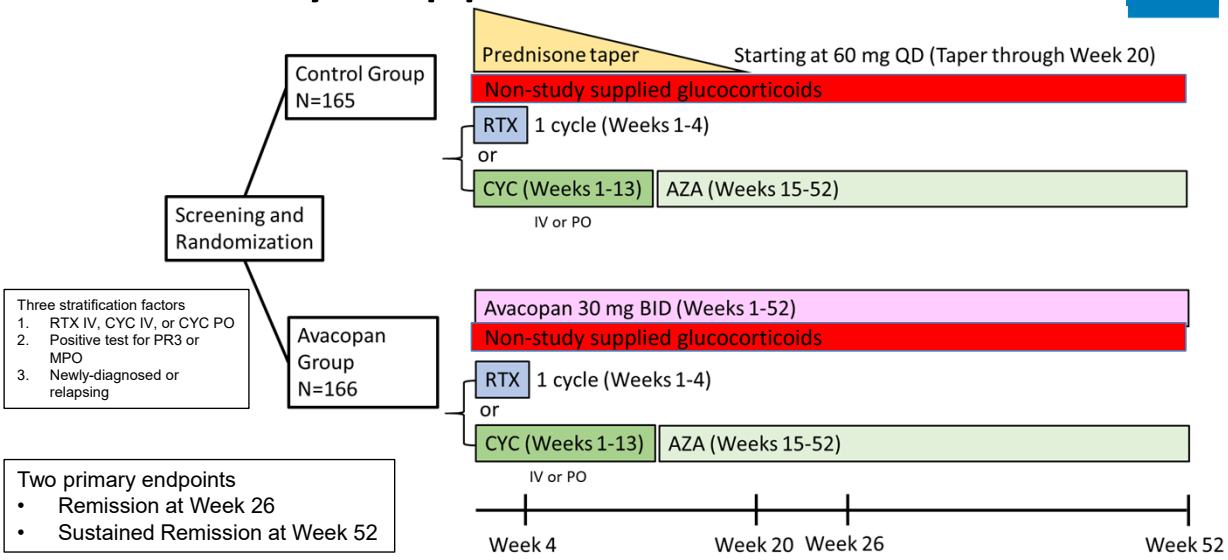
Non-study Supplied Steroid Use



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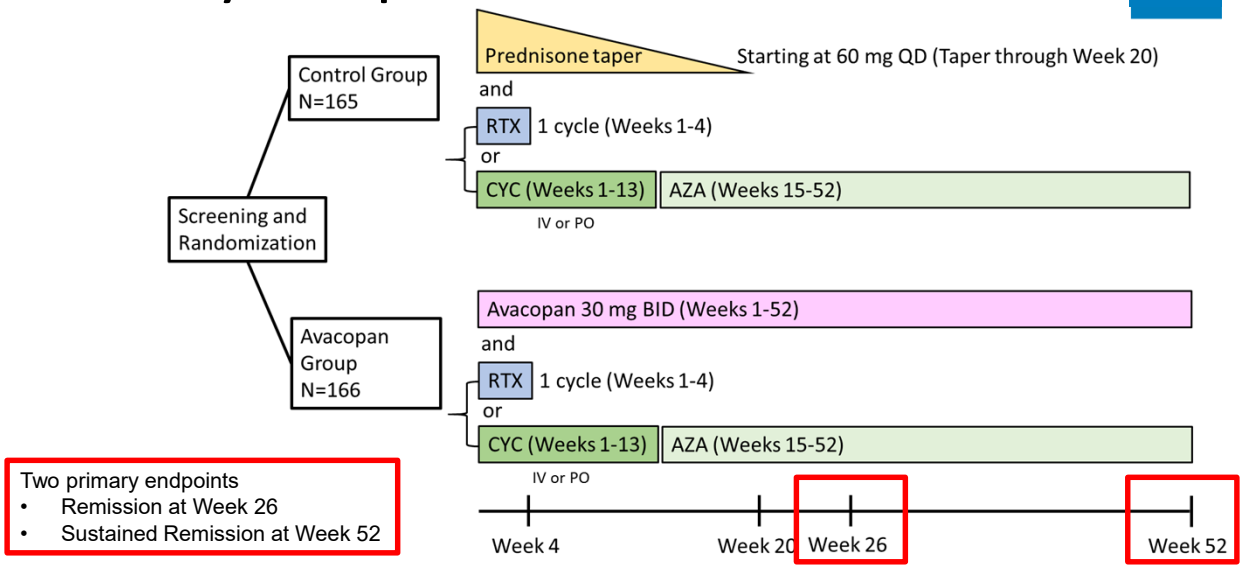
Considerations Regarding the Study Design

- Patients who received rituximab induction treatment did not receive maintenance therapy
  - May not represent standard-of-care
  - The comparisons at Week 52 may not be clinically meaningful
- Patients on both arms were allowed to receive 'non-study supplied' glucocorticoids
  - Impacts the interpretation of the comparison of the treatment arms

PRIMARY ENDPOINTS

Primary Endpoints



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

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Birmingham Vasculitis Activity Score (BVAS)

- A measure of disease activity. BVAS version 3 was used in this study
  - 57 clinical features, grouped into 9 organ systems plus an "other" category
  - Presence or absence of disease activity was assessed
    - The "persistent" disease aspect of the BVAS was not used in the determination of remission
    - Only items that were "new/worse" were considered active (i.e., presence of disease activity)
  - BVAS was assessed at Week 4, 10, 16, 26, 39, and 52
  - For all study visits (except Week 4), the disease activity present within the 28 days prior to the visit was to be recorded (e.g., Has a patient experienced weight loss >= 2kg within past 28 days?)

BVAS Adjudication

- The assessments performed by the study Investigators were adjudicated by an Adjudication Committee (AC)
- The members of the AC were blinded to individual subject treatment assignment

Disease Remission at Week 26

- Achieving a BVAS of 0 as determined by the Adjudication Committee

  AND

- No administration of glucocorticoids for the treatment of AAV within 4 weeks prior to Week 26

  AND

- No BVAS>0 during the 4 weeks prior to Week 26 (if collected at an unscheduled assessment)

Sustained Disease Remission at Week 52

- Disease remission at Week 26

  AND

- No disease relapse between Week 26 and Week 52 as determined by the AC
  - Relapse was defined using the BVAS as the occurrence of at least one major item at a single visit, at least 3 non-major items at a single visit, or 1 or 2 non-major items for at least 2 consecutive visits, after remission (BVAS=0) had been achieved

  AND

- Disease remission at Week 52 defined as a BVAS of 0 as determined by the AC and no administration of glucocorticoids for treatment of AAV within 4 weeks prior to Week 52

ANALYSIS METHODS

Statistical Analysis Plan

- Primary analysis set: all randomized subjects who received at least one dose of study drug
- Subjects who discontinued treatment were not automatically withdrawn from the study but were supposed to remain in the study for all regularly scheduled visits.
- The primary analysis was based on the stratified analyses adjusted for randomization strata.
  - Due to the low number of subjects in the oral cyclophosphamide randomization stratum, IV and oral cyclophosphamide strata were combined for the analyses.

Primary Endpoint Analysis

- Summary score test was used for both non-inferiority and superiority test of the stratified analysis at Weeks 26 and 52.
- For non-inferiority comparison at both weeks, margin of 20% was used.
- Missing data handling: For the primary endpoints, subjects with missing data were imputed as not achieving remission (Week 26) or sustained remission (Week 52)
  - Sensitivity analyses conducted to assess robustness of results to alternative missing data assumptions

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

Non-inferiority Margin Selection

- The Applicant proposed the non-inferiority (NI) margin of 20%
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  - Using these estimates, the Applicant estimated the contribution of glucocorticoids to the remission rate of the control arm as ~30%

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  - The lower bound of 95% CI for disease remission rate with glucocorticoids alone was estimated to be 28.7%
  - The Applicant estimated the contribution of glucocorticoids to the remission rate of the control arm as ~30%
  - By discounting this estimate by one-third to account for remaining uncertainties, the Applicant proposed 20% as the NI margin.

Considerations Regarding the Non-Inferiority Comparison

- In a non-inferiority (NI) study, the goal is to demonstrate that the test drug has an effect by showing that its effect is sufficiently close to the effect of an active control. As such, the study should be designed to detect differences between treatments, should such differences exist

- This study evaluated prednisone vs. avacopan on top of CYC or RTX
  - The benefit of glucocorticoids on top of CYC or RTX is not well-understood
  - As a result, it is difficult to assess if an observed similar treatment effect across arms can support a conclusion that avacopan is effective

Considerations Regarding the Proposed Margin

1. No literature that would isolate the effect of prednisone to inform the margin of the non-inferiority comparison
   - No historical placebo-controlled trials evaluating the efficacy of glucocorticoids as an add-on therapy to CYC or RTX
   - Applicant relied on single arm results from different studies

Considerations Regarding the Proposed Margin

2. The determination of the extent of the contribution of glucocorticoids to the historical estimated remission rate on glucocorticoids + CYC or RTX is based on key, implausible, and unverifiable assumptions
   - It is unlikely that the efficacy of glucocorticoids alone is similar to that of glucocorticoids when added on to CYC or RTX

Secondary Endpoint: Relapse

- Time to experiencing a relapse after achieving remission (BVAS=0) was a secondary endpoint
- Time to relapse were to be analyzed by Kaplan Meier methodology and log rank testing of the differences between treatment groups

Considerations Regarding Proposed Relapse Analysis

- Time-to-relapse analysis conditions on post-randomization variables, e.g., having first achieved remission, making it challenging to appropriately interpret these results
- Instead, FDA analyzed 'Proportion of Patients Who Did Not Achieve BVAS=0 or Relapse', which incorporates all patients

EFFICACY ANALYSIS RESULTS

Patient Disposition

	Avacopan (N=166)	Prednisone (N=164)
Completed Week 26 Study	155 (93.4%)	154 (93.9%)
Discontinued Study prior to Week 26	11 (6.6%)	10 (6.1%)
Withdrawal by subject	4 (2.4%)	2 (1.2%)
Withdrawal by guardian	1 (0.6%)	-
Lost to follow-up	1 (0.6%)	-
Adverse event	2 (1.2%)	5 (3.0%)
Physician decision	2 (1.2%)	3 (1.8%)
Other	1 (0.6%)	-

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Other	1 (0.6%)	-
Completed Week 52 Study	151 (91.0%)	152 (92.7%)
Discontinued Study prior to Week 52	15 (9.0%)	12 (7.3%)
Withdrawal by subject	6 (3.6%)	3 (1.8%)
Withdrawal by guardian	1 (0.6%)	-
Lost to follow-up	1 (0.6%)	-
Adverse event	3 (1.8%)	6 (3.7%)
Physician decision	3 (1.8%)	3 (1.8%)
Other	1 (0.6%)	-

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

Evaluation of Relapse Rates

- Proportion of Patients Who Did Not Achieve BVAS=0 or Relapse after achieving BVAS=0

	Avacopan (N=166)	Prednisone (N=164)
Did not achieve BVAS=0	8 (4.8%)	7 (4.3%)
Achieved BVAS=0	158 (95.2%)	157 (95.7%)
Relapse after achieving BVAS=0	16 (9.6%)	33 (20.1%)
Between Week 0-Week 26	3 (1.8%)	16 (9.8%)
Between Week 27-Week 52	13 (7.8%)	17 (10.4%)
Did not achieve BVAS=0 OR relapse after achieving BVAS=0	24/166 (14.5%)	40/164 (24.4%)
	Diff (95% CI): -9.9% (-18.4%, -1.5%)	

Abbreviations: Diff=difference, CI=confidence interval. Point estimate and 95% confidence interval using normal approximation were reported. N=number of patients in the primary analysis set.

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Between Week 0-Week 26	3 (1.8%)	16 (9.8%)
Between Week 27-Week 52	13 (7.8%)	17 (10.4%)
Did not achieve BVAS=0 OR relapse after achieving BVAS=0	24/166 (14.5%)	40/164 (24.4%)
	Diff (95% CI): -9.9% (-18.4%, -1.5%)	

Abbreviations: Diff=difference, CI=confidence interval. Point estimate and 95% confidence interval using normal approximation were reported. N=number of patients in the primary analysis set.

SUPPLEMENTAL ANALYSIS RESULTS

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.

Investigator Assessment

- Discrepancy between investigator score vs. adjudicated score
  - Most frequently related to the attribution of persistent vasculitis which was not captured in the version of the BVAS administered in the study
  - The investigators considered persistent vasculitis as active vasculitis when scoring the BVAS
  - The assessment based on the Investigators may better reflect real-world use

STATISTICAL REVIEW SUMMARY

Remission at Week 26

- Superiority not achieved
- Non-inferiority comparison not sufficient to determine whether avacopan is effective given the contribution of glucocorticoids on top of RTX/CYC is not well understood
- Interpretation of NI comparison limited as avacopan patients also received glucocorticoids

Sustained Remission at Week 52

- Two complementary subgroups:
  1. Treatment comparison in RTX subgroup may not be an informative comparison as maintenance therapy was not administered during weeks 26-52
  2. For CYC subgroup, there is not enough evidence of presence of clinically meaningful treatment effect
  3. Data shows noticeable disparity of estimated treatment effect
- Analysis based on Investigator assessments do not support sustained remission at Week 52

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FDA Arthritis Advisory Committee Meeting

Clinical Review of Efficacy, Safety, and Benefit-Risk Assessment

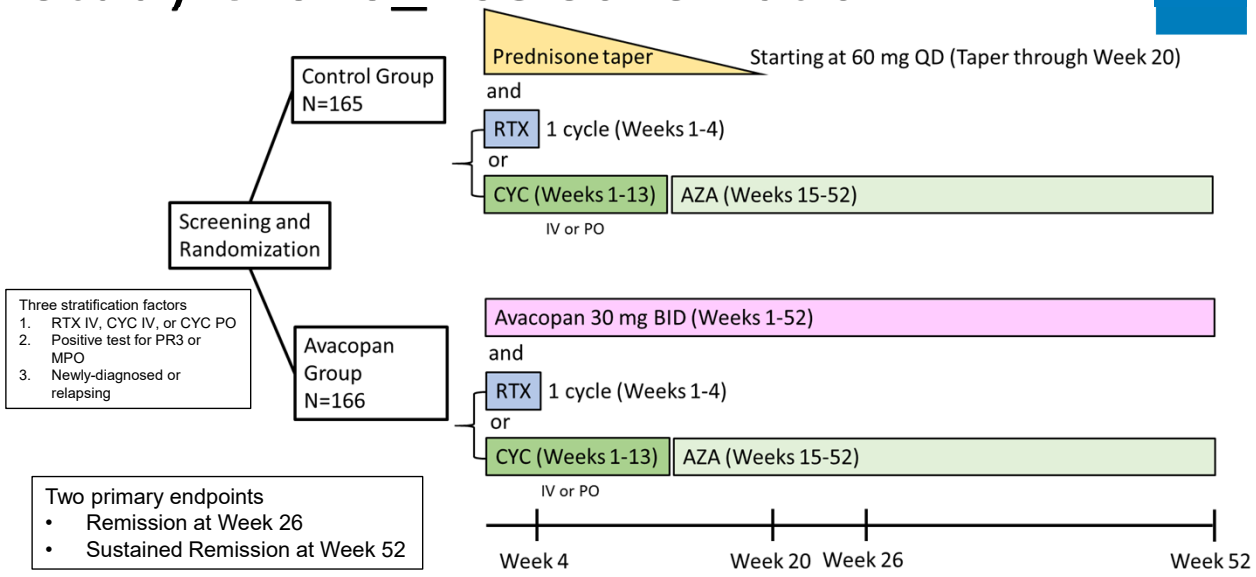
NDA 214487: avacopan for treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA) vasculitis

Suzette Peng, MD
Clinical Reviewer
Division of Rheumatology and Transplant Medicine
Office of New Drug/Office of Immunology and Inflammation
U.S. Food and Drug Administration
May 6, 2021

Outline

- **Phase 3 study CL010_168**
  - Glucocorticoid use
    - Use in both treatment arms
    - Reasons for use
    - Glucocorticoid Toxicity Index
  - Other secondary endpoints
    - Vasculitis Damage Index (VDI)
    - Renal assessments
    - Quality of Life (QoL) measures
  - Clinical considerations on efficacy
  - Summary of safety
    - Hepatotoxicity, infections, hypersensitivity
  - Clinical considerations on safety
- **Phase 2 studies CL002_168 and CL003_168**
  - Summary of efficacy
  - Summary of safety
- **Overall benefit-risk considerations**

Study CL010_168 Schematic



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

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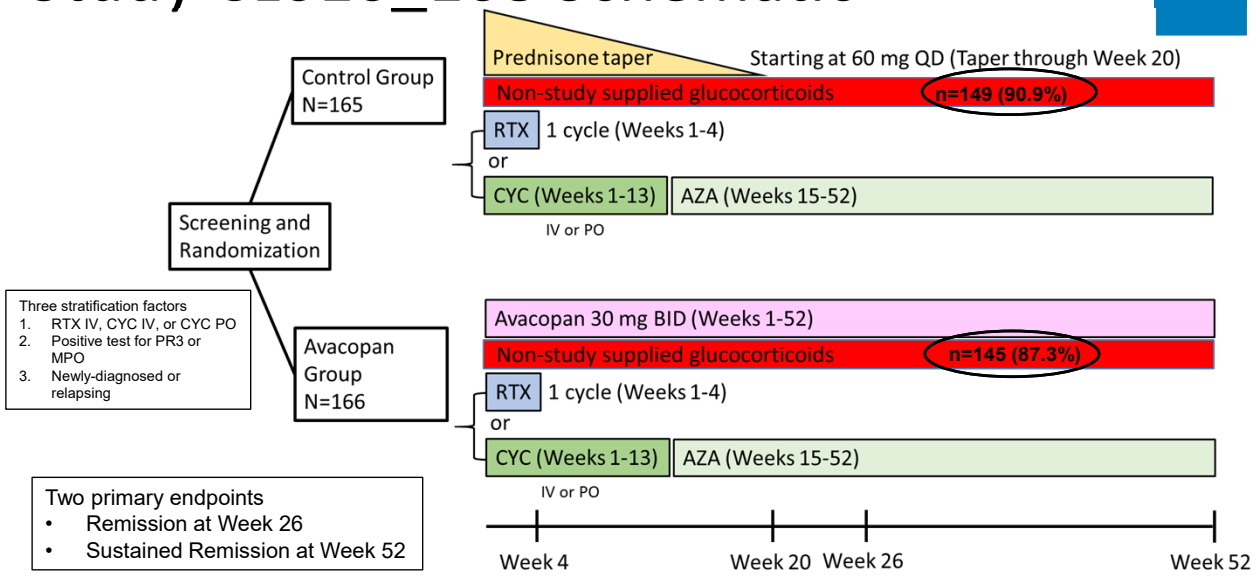
3

Study CL010_168 Schematic



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

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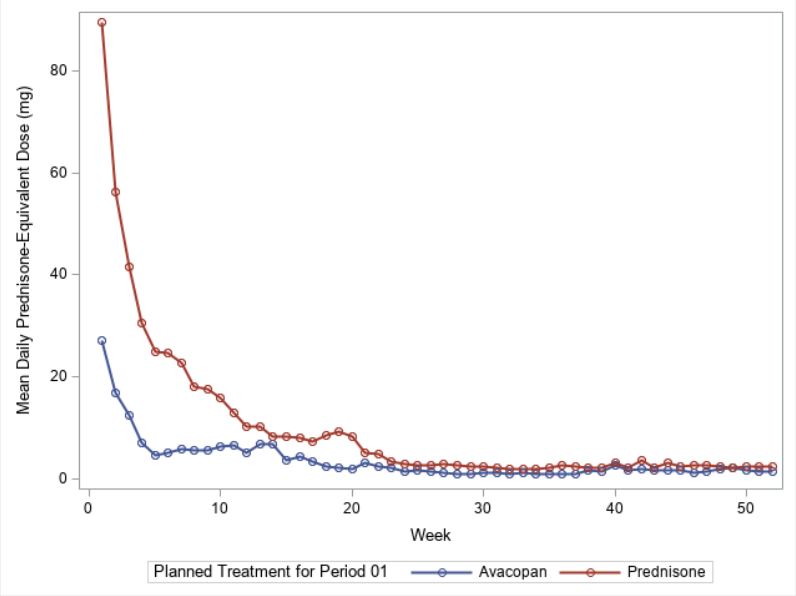
Cumulative Total Glucocorticoid Use



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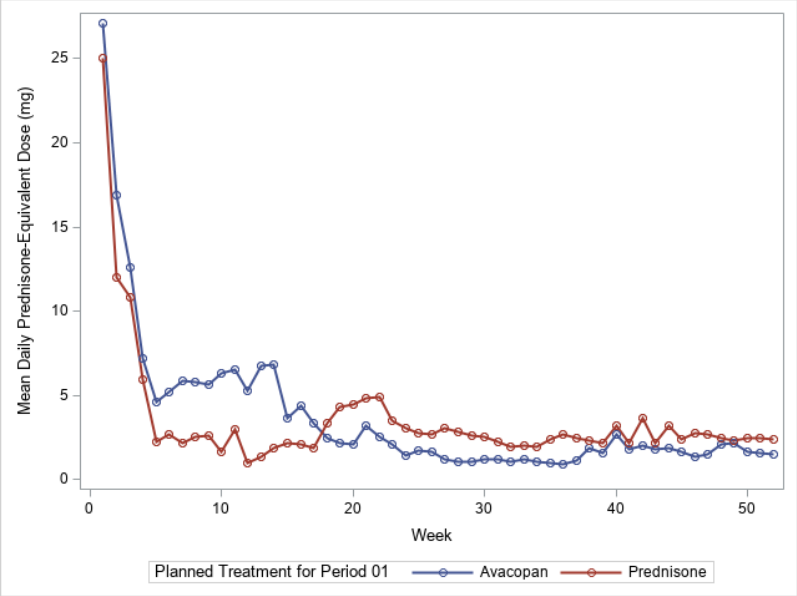
Cumulative Non-Study Supplied Glucocorticoid Use



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Cumulative Glucocorticoid Use

	Avacopan (N=166)	Prednisone (N=164)
Cumulative Total Glucocorticoid Use Weeks 0-52		
Number of subjects	145 (87.3%)	164 (100%)
Mean dose	1348.9	3654.4
Median dose	400	2939
Range of dose	0-9612	760-12033
Cumulative Total Non-Study Supplied Glucocorticoid Use Weeks 0-52		
Number of subjects	145 (87.3%)	149 (90.9%)
Mean dose	1348.9	1265.2
Median dose	400	483
Range of dose	0-9612	0-8488

7

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

- 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

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All non-study supplied glucocorticoids in Phase 3 Study CL010_168 are CYP3A4 substrates

Prednisone arm	Avacopan arm	CYP3A4 substrate (Yes or No)
Dexamethasone		Yes
Hydrocortisone		Yes
Hydrocortisone sodium succinate		Yes
Methylprednisolone		Yes
Methylprednisolone sodium succinate		Yes
Prednisolone		Yes
Prednisolone sodium succinate		Yes
Prednisone		Yes
--	Betamethasone	Yes
--	Betamethasone sodium phosphate	Yes
--	Cortisone	Yes
--	Hydrocortisone sodium phosphate	Yes

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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%)

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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%)
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Treatment of persistent vasculitis	10 (6.0%)	14 (8.5%)
Maintenance of remission	13 (7.8%)	16 (9.8%)

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Non-Study Supplied Glucocorticoid Use

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Treatment of persistent vasculitis	10 (6.0%)	14 (8.5%)
Maintenance of remission	13 (7.8%)	16 (9.8%)

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Secondary Endpoint: Glucocorticoid Toxicity Index (GTI)

GTI-CWS

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

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.

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.

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**

Secondary Endpoints

- Glucocorticoid Toxicity Index (GTI) over first 26 weeks
  - Cumulative Worsening Score (CWS) and Aggregate Improvement Score (AIS)
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- Change in Vasculitis Damage Index (VDI) over 52 weeks
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- 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**

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.

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Secondary Endpoint: Renal Assessments

BVAS criteria for renal disease at baseline		Avacopan N=166	Prednisone N=164
Renal disease at baseline based on the following BVAS criteria		134 (80.7%)	134 (81.7%)
Hypertension (HTN)	Diastolic blood pressure > 95 mm Hg Related to ANCA-associated vasculitis	21 (12.7%)	23 (14.0%)
Proteinuria	> 1+ on urinalysis or > 0.2 g/g creatinine on a urine sample	110 (66.3%)	107 (65.2%)
Hematuria	≥ 10 RBC per high power field on microscopy	77 (46.4%)	68 (41.5%)
Serum creatinine Elevation at first assessment	Serum creatinine 1.41-2.82 mg/dL	60 (36.1%)	61 (37.2%)
	Serum creatinine 2.83-5.64 mg/dL	26 (15.7%)	20 (12.2%)
	Serum creatinine ≥ 5.6 mg/dL	1 (0.6%)	0
Rise in Serum creatinine > 30% or fall in creatinine clearance >25%		17 (10.2%)	20 (12.2%)
Other	RBC casts and/or glomerulonephritis	60 (36.1%)	59 (36.0%)

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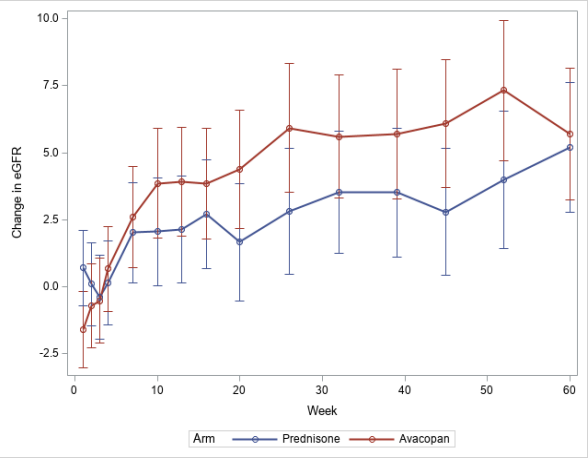
Renal Assessment

Change from Baseline in eGFR over 60-week Study Period in All Patients with Baseline Renal Disease



Least Squares (LS) means with 95% confidence intervals. 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.
* Study medication (avacopan or placebo) was discontinued at Week 52.

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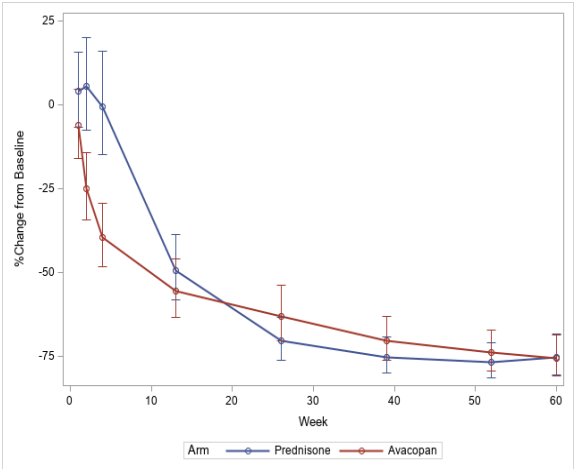
Renal Assessment

% Change from Baseline in UACR over 60-week Study Period



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* Study medication (avacopan or placebo was discontinued at Week 52.

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Secondary Endpoint: QoL

SF-36

Treatment Arm	Change from Baseline	
	LS Mean[1] (95% CI)	Diff (95% CI)
PCS		
Avacopan	5.2 (3.7, 6.8)	
Prednisone	2.7 (1.1, 4.3)	2.6 (0.5, 4.7)
MCS		
Avacopan	6.4 (4.8, 8.0)	
Prednisone	4.7 (3.1, 6.3)	1.7 (-0.4, 3.8)

EQ-5D-5L

Treatment Arm	Change from Baseline	
	LS Mean[1] (95% CI)	Diff (95% CI)
VAS		
Avacopan	13.1 (10.2, 15.9)	
Prednisone	7.0 (4.2, 9.9)	6.1 (2.3, 9.8)
Index		
Avacopan	0.05 (0.02, 0.08)	
Prednisone	-0.003 (-0.03, 0.03)	0.05 (0.01, 0.09)

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.

Clinical Consideration on Efficacy (1): Treatment of ANCA-associated Vasculitis

- Remission at Week 26
  - Noninferiority (NI) margin not adequately justified
  - Both treatment groups received glucocorticoids (GC)
  - Treatment effect of avacopan and magnitude of effect are unclear
- Sustained remission at Week 52
  - 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

Clinical Considerations on Efficacy (2): Steroid-Sparing Agent

- Glucocorticoid use in both treatment arms
- Protocol-specified prednisone taper in the control arm
- Potential drug-drug interaction
- Clinical meaningfulness of differences

Safety: Overall Summary

Number of patients with ≥ 1	Avacopan N=166 n (%)	Prednisone N=164 n (%)	Avacopan vs. Prednisone Diff (95% CI)
TEAEs	164 (98.8%)	161 (98.2%)	0.6% (-2.0, 3.3)
Deaths	2 (1.2%)	4 (2.4%)	-1.2% (-4.1, 1.7)
Serious TEAEs (SAEs)	70 (42.2%)	74 (45.1%)	-3.0% (-13.7, 7.7)
Severe TEAEs	39 (23.5%)	41 (25.0%)	-1.5% (-10.8, 7.7)
Life-Threatening TEAEs	8 (4.8%)	14 (8.5%)	-3.7% (-9.1, 1.7)
TEAEs Leading to Treatment Discontinuations	27 (16.3%)	28 (17.1%)	-0.8% (-8.9, 7.2)

Source: CL010_168 CSR, Table 22 and ISS

Safety: Liver Toxicity

- More liver-associated AEs in the avacopan arm
  - 22 patients (13.3%) in the avacopan arm vs. 19 patients (11.6%) in the prednisone arm
  - 9 patients (5.4%) in the avacopan arm vs. 6 patients (3.7%) in the prednisone arm with SAEs of increased blood liver tests
- 4 cases of potential Drug-Induced Liver Injury (DILI) secondary to avacopan
- 1 case of possible DILI meeting Hy's law laboratory criteria

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Safety: Liver Toxicity

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  - 22 patients (13.3%) in the avacopan arm vs. 19 patients (11.6%) in the prednisone arm
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- 1 case of possible DILI meeting Hy's law laboratory criteria

- Elevated aminotransferase >3x ULN
- Increase in bilirubin ≥ 2x ULN without evidence of cholestasis by ALP <2x ULN
- No other cause

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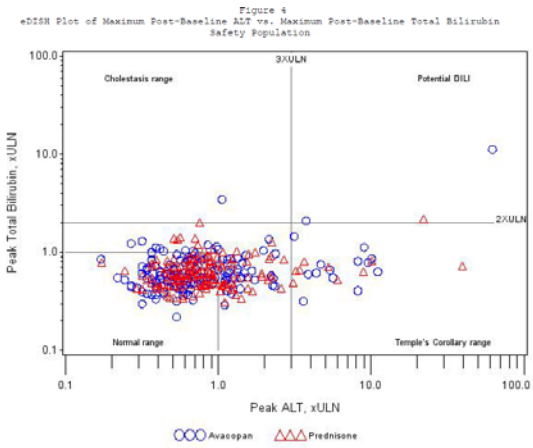
Safety: Liver Toxicity



Source: ChemoCentryx response to IR# 22

- 9 liver-related SAEs from the pivotal trial
  - 3 cases unlikely avacopan hepatotoxicity
  - 2 cases possible DILI due to competing diagnoses (cephalexin, simvastatin)
  - 3 cases probable DILI due to avacopan
  - 1 case highly likely DILI due to avacopan

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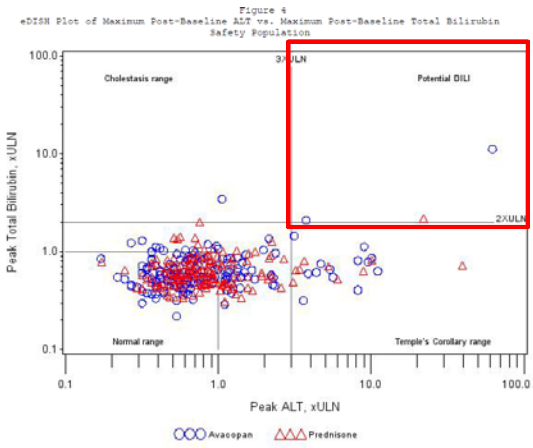
Safety: Liver Toxicity



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  - 2 cases possible DILI due to competing diagnoses (cephalexin, simvastatin)
  - 3 cases probable DILI due to avacopan
  - 1 case highly likely DILI due to avacopan

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Safety: Infections

Number of patients with ≥ 1	Avacopan N=166 n (%)	Prednisone N=164 n (%)	Avacopan vs. Prednisone Diff (95% CI)
Any Treatment-Emergent Infections	113 (68.1)	124 (75.6)	-7.5% (17.2, 2.1)
Any Serious Treatment-Emergent Infections	22 (13.3)	25 (15.2)	-2.0% (-9.5, 5.6)
Any Severe Treatment-Emergent Infections	12 (7.2)	10 (6.1)	1.1% (-4.2, 6.5)
Any Treatment-Emergent Infection Leading to Study Drug Discontinuation	4 (2.4)	5 (3.0)	-0.6% (-4.2, 2.9)
Any Treatment-Emergent Life-threatening Infection	1 (0.6)	2 (1.2)	-0.6% (-2.7, 1.4)
Any Treatment-Emergent Infection Leading to Death	1 (0.6)	2 (1.2)	-0.6% (-2.7, 1.4)

Source: CL010_168 CSR Tab le 27, pages 127-128.

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Safety: Other

Hypersensitivity

- Standardized MedDRA Query (SMQ) for hypersensitivity
- 68 patients (41.0%) in the avacopan arm vs. 70 patients (42.7%) in the prednisone arm
- 2 SAEs of hypersensitivity possibly related to avacopan
  - Angioedema
  - Rash and eosinophilia

Elevated CPK

- 6 patients in avacopan arm vs. 1 patient in the prednisone arm
  - 1 drug interruption
  - 1 drug discontinuation
- No SAEs of elevated CPK
- No differences in events of myalgias or myopathies

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Clinical Considerations on Safety

- Overall conclusions limited by small database
- No difference in infection risk
- Potential liver toxicity
- Potential cases of hypersensitivity
- Potential elevation in CPK

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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

CL002_168 Efficacy Endpoints

- BVAS 50% response at Week 12
  - BVAS reduction of at least 50% from baseline and no worsening in any body system component
- BVAS remission at Week 12
  - BVAS score of 0 or 1 plus no worsening in eGFR and urinary RBC count <10/hpf
- BVAS 0 at Week 12

	PBO + CYC/RTX + High Dose Prednisone (SOC Control) N=20	Avacopan 30 mg BID + CYC/RTX + Low Dose Prednisone N=22	Avacopan 30 mg BID + CYC/RTX + No Prednisone N=21
BVAS 50% Response, n (%)	14 (70.0%)	19 (86.4%)	17 (81.0%)
Difference in percentage vs. control	--	16.4%	11.0%
Two-sided 90% CI for difference, avacopan minus control	--	-4.3%, 37.1%	-11.0%, 32.9%
BVAS remission at Week 12, n (%)	7 (35.0%)	6 (27.3%)	4 (19.0%)
Difference in percentage vs. control	--	-7.7	-16.0
Two-sided 90% CI for difference, avacopan minus control	--	-31.2, 15.8	-38.5, 6.6
BVAS 0 at Week 12, n (%)	8 (40.0%)	10 (45.5%)	7 (33.3%)
Difference in percentage vs. control	--	5.5	-6.7
Two-sided 90% CI for difference, avacopan minus control	--	-19.6, 30.5	-31.4, 18.1

Source: CL002_168 CSR

CL003_168 Efficacy Endpoints

	PBO + CYC/RTX + Prednisone (SOC Control) N=13	Avacopan 10 mg BID + CYC/RTX + Prednisone N=12	Avacopan 30 mg BID + CYC/RTX + Prednisone N=12
BVAS 50% Response, n (%)	11 (84.6%)	11 (91.7%)	12 (80.0%)
Difference in percentage vs. control	--	7.1%	-4.6%
Two-sided 90% CI for difference, avacopan minus control	--	-14.0%, 28.1%	-28.3%, 19.0%
BVAS 0 at Day 85, n (%)	7 (53.8%)	8 (66.7%)	7 (46.7%)
Difference in percentage vs. control	--	12.8%	-7.2%
Two-sided 90% CI for difference, avacopan minus control	--	-19.1, 44.7	-38.3, 23.9
BVAS 0 at Days 29 and 85, n (%)	2 (15.4%)	1 (8.3%)	3 (20.0%)
Difference in percentage vs. control	--	-7.1	4.6
Two-sided 90% CI for difference, avacopan minus control	--	-28.1, 14.0	-19.0, 28.3

Source: CL003_168 CSR

Phase 2 Studies: Safety

CL002_168

- No deaths
- Few SAEs
  - n=3 in avacopan and low dose prednisone arm
  - n=8 in the avacopan and no prednisone arm
    - **Increased hepatic enzymes and pancreatic enzymes**
  - n=4 in the control arm

CL003_168

- No deaths
- Few SAEs, similar number in all arms
  - n=2 in the avacopan 10 mg arm
  - n=3 in the avacopan 30 mg arm
  - n=2 in the control arm

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Overall 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
Charge to the Committee

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

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

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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

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Efficacy Considerations (2): GC Use

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

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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

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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

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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

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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."

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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

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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

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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

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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."

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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:
   - Appropriateness of a primary non-inferiority (NI) comparison
   - Use of additional non-study supplied GC in the avacopan group
   - 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:
   - Impact of the lack of maintenance therapy in the rituximab subgroup
   - 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:
   - Use of additional non-study supplied GCs in the avacopan group
   - Impact of a potential increase in GC exposures due to CYP3A4 inhibition by avacopan

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Discussion Points and Voting Questions (4)

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

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

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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?

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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?

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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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