Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Arthritis Advisory Committee Meeting
May 6, 2021

Location: Please note that due to the impact of this COVID-19 pandemic, all meeting participants joined this advisory committee meeting via an online teleconferencing platform.

Topic: The committee discussed new drug application (NDA) 214487, for avacopan oral capsules, submitted by ChemoCentryx, Inc., for the treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis.

These summary minutes for the May 6, 2021 meeting of the Arthritis Advisory Committee were approved on July 1, 2021.

I certify that I attended the May 6, 2021 meeting of the Arthritis Advisory Committee (AAC) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Moon Hee V. Choi, PharmD	Mara L. Becker, MD, MSCE
Acting Designated Federal Officer, AAC	Chairperson, AAC

Final Minutes of the Arthritis Advisory Committee Meeting
May 6, 2021

The Arthritis Advisory Committee (AAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on May 6, 2021. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials and pre-recorded presentations from the FDA and ChemoCentryx, Inc. The meeting was called to order by Mara L. Becker, MD, MSCE (Chairperson). The conflict of interest statement was read into the record by Moon Hee V. Choi, PharmD (Acting Designated Federal Officer). There were approximately 643 people online. There were a total of 15 Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The committee discussed new drug application (NDA) 214487, for avacopan oral capsules, submitted by ChemoCentryx, Inc., for the treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis.

Attendance:

Arthritis Advisory Committee Members Present (Voting): Mara L. Becker, MD, MSCE *(Chairperson);* Paul F. Dellaripa, MD**;** Hetlena J. Johnson, EdS (*Consumer Representative*); Martha C. Nason, PhD; Alyce M. Oliver, MD, PhD; David S. Pisetsky, MD, PhD; J. Steuart Richards, MD; Jasvinder Singh, MD, MPH; Margrit Wiesendanger, MD, PhD

Arthritis Advisory Committee Members Not Present (Voting): John M. Davis III, MD, MS**;** Michael H. Weisman, MD

Arthritis Advisory Committee Member Not Present (Non-Voting): Marek J. Honczarenko, MD, PhD (*Industry Representative*)

Acting Industry Representative to the Committee (Non-Voting): Sean P. Curtis, MD, MPH (*Acting Industry Representative*)

Temporary Members (Voting): Elizabeth J. Brant, MD *(Patient Representative);* Sharon A. Chung, MD, MAS; Seoyoung C. Kim, MD, ScD, MSCE; Walter K. Kraft, MD; Julia Lewis, MD; Susanne May, PhD; Pamela Shaw, MS, PhD; C. John Sperati, MD, MHS; Ravi I. Thadhani, MD, MPH

FDA Participants (Non-Voting): Julie Beitz, MD; Nikolay Nikolov, MD; Rachel L. Glaser, MD; Suzette Peng, MD; Yura Kim, PhD

Acting Designated Federal Officer (Non-Voting): Moon Hee V. Choi, PharmD

Open Public Hearing Speakers Present: Kathy Olevsky; Leonard Calabrese, MD; John Stadler; Dianne Shaw; Duvuru Geetha, MD; Jason Wadler; Trena Anderson; Joyce Kullman (The Vasculitis Foundation); Sean Downes; Michael Germain, MD; Frank B. Cortazar, MD; Tom Sharretts; Meg Seymour, PhD (National Center for Health Research); Erwin Mark Taylor; Glen F. Massie

The agenda was as follows:

Call to Order	**Mara L. Becker, MD, MSCE** Chairperson, AAC
Introduction of Committee and Conflict of Interest Statement	**Moon Hee V. Choi, PharmD** Acting Designated Federal Officer, AAC
FDA Opening Remarks	**Rachel L. Glaser, MD** Clinical Team Leader Division of Rheumatology and Transplant Medicine Office of Immunology and Inflammation Office of New Drugs, CDER, FDA
APPLICANT PRESENTATIONS	**ChemoCentryx, Inc.**
Introduction	**Pirow Bekker, MD, PhD** Clinical Lead Avacopan Clinical Development Program ChemoCentryx, Inc.
Efficacy	**Peter Merkel, MD, MPH** Chief, Division of Rheumatology Director, Penn Vasculitis Center University of Pennsylvania **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)
Safety	**Pirow Bekker, MD, PhD**
Clarifying Questions for Applicant	

FDA PRESENTATION

	Rachel L. Glaser, MD
FDA Summary Presentation	
Clarifying Questions for FDA	

LUNCH BREAK

OPEN PUBLIC HEARING

Charge to the Committee	**Rachel L. Glaser, MD**
Questions to the Committee/Committee Discussion	

ADJOURNMENT

Questions to the Committees:

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

    Committee Discussion*: The committee did not come to an agreement regarding the appropriateness of a primary non-inferiority (NI) comparison. Some committee members stated that they did not have concerns with an NI study design and agreed that there were enough data supporting a clinically meaningful benefit of avacopan at Week 26. The committee members who disagreed expressed concerns that there were not adequate available data to determine an appropriate NI margin in order to draw conclusions based on the NI comparison. Other committee members added that there are too many uncertainties in the NI comparison and, thus, did not find the NI at Week 26 compelling.*

    b. Use of additional non-study supplied glucocorticoids (GCs) in the avacopan group

    Committee Discussion*: The committee expressed difficulty interpreting the data regarding the use of additional non-study supplied glucocorticoids (GCs) in the avacopan group. Committee members noted that the use of GC in the avacopan arm makes the interpretation of the non-inferiority assessment at Week 26 difficult; concerns were raised that participants who received significant amounts of GC may be counted as responders, resulting in difficulty determining the true effects of avacopan vs. prednisone.*

    c. Lack of statistically significant superiority at Week 26

    Committee Discussion*: Several committee members expressed that the lack of statistically significant superiority of avacopan vs. the comparator group at Week 26 was*

not concerning or unexpected due to the fact that patients in both groups received background treatment with GCs and cyclophosphamide/azathioprine or RTX and the outcomes at week 26 are likely representing the effects of induction treatment.

Please see the transcript for details of the Committee's discussion.

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 (RTX) subgroup

   ***Committee Discussion**: Overall, the committee members agreed that data from this single subgroup is difficult to interpret, as the trial was not designed to respond to this specific question. Committee members noted that there is ambiguity in how this drug should be used. Some committee members added that one would need a new trial where there is a separation in induction and maintenance therapy in order to evaluate if avacopan can be appropriately used as maintenance therapy as suggested by the effect observed in the RTX subgroup. Other committee members expressed challenges in differentiating the effects of treatment related to background medication, adding that the RTX subgroup was relatively small in sample size and use of CYC vs RTX as background therapy was not randomized.*

   b. Discrepancies in Birmingham Vasculitis Activity Score (BVAS) remission responses as determined by Adjudication Committee vs. Investigators

   ***Committee Discussion**: The committee members discussed the differences in how the site Investigators and Adjudication Committee may have scored the BVAS, how the Applicant provided data to the Adjudication Committee, and how the Adjudication Committee may have changed the scores. Some committee members noted that there was a loss of significance in the statistical analysis based on the Investigator assessment and that it may impact the strength of the evidence at Week 52. Other committee members noted difficulties in scoring the BVAS instrument including the determination of whether symptoms are due to persistent disease activity or damage. Several committee members noted that the Adjudication Committee BVAS assessment was a pre-specified analysis, thus is the analysis that should be used, and did not have specific concerns about the discrepancies.*

   Please see the transcript for details of the Committee's discussion.

3. **DISCUSSION:** Discuss whether the data support the use of avacopan as a steroid-sparing agent in anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (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

Committee Discussion: *Regarding the use of additional non-study supplied GCs in the avacopan group, the committee noted that avacopan may not eliminate the use of steroids, but some members felt the data support decreased steroid use with avacopan treatment, while others stated differences in GC use observed in the first half of the study were a result of the nature of the design, and questioned the clinical relevance of the observed differences. The committee didn't express much concern on the impact of a potential increase in GC exposure due to CYP34A inhibition by avacopan based on prior experience with coadministration of GCs with known strong CYP3A4 inhibitors, as well as the results of the Glucocorticoid Toxicity Index which showed lower scores in the avacopan arm.*

Please see the transcript for details of the Committee's discussion.

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

Committee Discussion*: Some committee members agreed that this was a difficult question to answer, particularly because the study, as designed and conducted, doesn't directly assess the role of avacopan for induction vs. maintenance therapy. Other committee members noted avacopan treatment may be considered in the following: 1) use as induction therapy consistent with the pivotal study; 2) use in patients with the highest risk for harm due to complications from high dose steroids; and 3) use in patients at risk for relapse or patients not responding to current therapy. One committee member expressed additional concerns that, given the limited experience with avacopan, it would be more appropriate for use in relapsing or refractory patients. However, if approved, avacopan use may be more widespread in an attempt to decrease GC use and may rapidly become first line treatment rather than rescue therapy.*

Please see the transcript for details of the Committee's discussion.

5. **VOTE:** Do the efficacy data support approval of avacopan for the treatment of adult patients with AAV (granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA))?

    a. If you voted "No", what data are needed?

Vote Result: Yes: 9 No: 9 Abstain: 0

Committee Discussion*: The committee members were split on whether the efficacy data support approval of avacopan for the treatment of adult patients with AAV (granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)). The committee members who voted "No" agreed that there is not enough substantial clinical and statistical evidence from a single trial to support approval of avacopan for the proposed broad indication. Some committee members stated the need for confirmatory evidence from another study, and some suggested that the drug may be better positioned as a maintenance therapy and recommended a study designed to evaluate this. One committee member noted the acceptability for a noninferiority trial to be considered if an effect on lowering steroid doses and BVAS remission were confirmed. The committee members who voted "Yes" agreed that,*

although the results did not demonstrate complete replacement of steroids, the sparing effect was sufficient enough to warrant approval of this drug, and also cited the difficulty of conducting studies in this rare disease.

Please see the transcript for details of the Committee's discussion.

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)?

    a. If you voted "No", what data are needed?

Vote Result: Yes: 10 No: 8 Abstain: 0

***Committee Discussion**: The majority of the committee members agreed that the safety profile of avacopan is adequate to support approval of avacopan for the treatment of adult patients with AAV (GPA and MPA). The committee members who voted "Yes" also provided recommendations for post-marketing surveillance. The committee members who voted "No" expressed concerns with the following: 1) small sample size; 2) shorter term safety database (as compared to knowledge of long-term safety of steroids); 3) risks of angioedema and hepatotoxicity; and 4) lack of data in minority groups.*

Please see the transcript for details of the Committee's discussion.

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)?

    a. If you voted "No", what further data are needed?

Vote Result: Yes: 10 No: 8 Abstain: 0

***Committee Discussion**: A slight majority of the committee members voted that the benefit-risk profile is 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). One committee member who voted "Yes" explained how they interpreted this question in a hypothetical sense but stated that they do not think the data that is needed is available yet. Therefore, the committee members were evenly split on whether the benefit-risk profile based on the data currently available are adequate to support approval of avacopan. The committee members who voted "Yes" advised on the judicious use of avacopan and guidance regarding the appropriate patient group for whom this medication should be reserved. The committee members who voted "No" stated concerns about the issues with the efficacy trial design as well as concerns with the safety data. In terms of what further data are needed, one committee member noted that there were uncertainties about the effects of the GC and recommended a specified steroid taper in the experimental and comparator arms, and then a study evaluating efficacy in induction with re-randomization to evaluate maintenance of remission.*

Please see the transcript for details of the Committee's discussion.

The meeting was adjourned at approximately 5:10 p.m. ET.