

**Food and Drug Administration  
Center for Drug Evaluation and Research**

**Summary Minutes of the Arthritis Advisory Committee Meeting  
August 2, 2017**

Location: The FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland.

Topic: The committee discussed biologics license application (BLA) 761057, for sirukumab injection (proposed trade name PLIVENSIA), submitted by Janssen Biotech, Inc., for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more disease modifying anti-rheumatic drugs. The discussion included dose selection, efficacy, radiographic progression study, and safety.

These summary minutes for the August 2, 2017, meeting of the Arthritis Advisory Committee of the Food and Drug Administration were approved on August 22, 2017.

I certify that I attended the August 2, 2017, meeting of the Arthritis Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

\_\_\_\_\_  
*/s/*  
Philip A. Bautista, PharmD  
Acting Designated Federal Officer, AAC

\_\_\_\_\_  
*/s/*  
Daniel H. Solomon, MD, MPH  
Chairperson, AAC

## Summary Minutes of the Arthritis Advisory Committee Meeting August 2, 2017

The following is the final report of the Arthritis Advisory Committee meeting, held on August 2, 2017. A verbatim transcript will be available in approximately six weeks, sent to the Division of Pulmonary, Allergy, and Rheumatology Products, and posted on the FDA website at: <https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm564748.htm>

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

---

The Arthritis Advisory Committee met on August 2, 2017, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Janssen Biotech, Inc. The meeting was called to order by Daniel H. Solomon, MD, MPH (Chairperson). The conflict of interest statement was read into the record by Philip A. Bautista, PharmD (Acting Designated Federal Officer). There were approximately 190 people in attendance. There were three Open Public Hearing (OPH) speaker presentations.

**Issue:** The committee discussed biologics license application (BLA) 761057, for sirukumab injection (proposed trade name PLIVENSIA), submitted by Janssen Biotech, Inc., for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more disease modifying anti-rheumatic drugs. The discussion included dose selection, efficacy, radiographic progression study, and safety.

### **Attendance:**

**Arthritis Advisory Committee Members Present (Voting):** Mara L. Becker, MD, MSCE; Jennifer Horonjeff, PhD (Consumer Representative); Beth L. Jonas, MD; Alyce M. Oliver, PhD, MD; Daniel H. Solomon, MD, MPH (Chairperson)

**Arthritis Advisory Committee Members Not Present (Voting):** Liron Caplan, MD, PhD; Jeffrey Curtis, MD, MS, MPH; Veena K. Ranganath, MD, MS; Andreas M. Reimold, MD; Jose U. Scher, MD; Eric J. Tchetgen Tchetgen, BS, PhD

**Arthritis Advisory Committee Members Not Present (Non-Voting):** James B. Chung, MD, PhD (Industry Representative)

**Temporary Members (Voting):** Diane Aronson (Patient Representative); Erica Brittain, PhD; David T. Felson, MD, MPH; James Katz, MD; Steven B. Meisel, PharmD; Maria E. Suarez-Almazor, MD, PhD; Scott A. Waldman, MD, PhD; Michael H. Weisman, MD

**Temporary Members (Non-Voting):** Sean P. Curtis, MD (Acting Industry Representative)

**FDA Participants (Non-Voting):** Curtis Rosebraugh, MD, MPH; Badrul Chowdhury, MD, PhD; Gregory Levin, PhD; Janet Maynard, MD, MHS; Mark Borigini, MD

**Acting Designated Federal Officer (Non-Voting):** Philip A. Bautista, PharmD

**OPH Speakers:** Stephen Marmaras (Global Health Living Foundation and Creaky Joints); Tiffany Westrich-Robertson (International Foundation for Autoimmune and Autoinflammatory Arthritis); Stephanie Mosely

*The agenda was as follows:*

Call to Order and Introduction of Committee	<b>Daniel H. Solomon, MD, MPH</b> Chairperson, AAC
Conflict of Interest Statement	<b>Philip A. Bautista, PharmD</b> Acting Designated Federal Officer, AAC
FDA Introductory Remarks	<b>Janet Maynard, MD, MHS</b> Clinical Team Leader Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) Office of Drug Evaluation II (ODE II) Office of New Drugs (OND), CDER, FDA
<b>APPLICANT PRESENTATIONS</b>	<b>Janssen Biotech, Inc.</b>
Introduction	<b>George Vratsanos, MD</b> Vice President Translational Medicine Janssen R&D
Unmet Medical Need	<b>Sergio Schwartzman, MD</b> Professor of Clinical Medicine Weill Cornell Medical College
Efficacy	<b>George Vratsanos, MD</b>
Safety	<b>Newman Yeilding, MD</b> Head of Immunology Development Clinical Development Janssen R&D
Conclusion	<b>George Vratsanos, MD</b>
Clarifying Questions	
<b>BREAK</b>	

**FDA PRESENTATIONS**

Introduction and Clinical Overview

**Mark Borigini, MD**  
Medical Officer  
DPARP, ODE II, OND, CDER, FDA

Dose Selection Considerations: Phase  
2 Study Results

**Dipak Pisal, PhD**  
Clinical Pharmacology Reviewer  
Division of Clinical Pharmacology II  
Office of Clinical Pharmacology  
Office of Translational Science (OTS), CDER, FDA

Review of Efficacy

**William Koh, PhD**  
Statistical Reviewer  
Division of Biometrics II  
Office of Biostatistics, OTS, CDER, FDA

Safety Assessment and Risk/Benefit  
Considerations

**Mark Borigini, MD**

Clarifying Questions

**LUNCH**

**OPEN PUBLIC HEARING**

Charge to the Committee

**Janet Maynard, MD, MHS**

Questions to the  
Committee/Committee Discussion

**BREAK**

Questions to the  
Committee/Committee Discussion  
(cont.)

**ADJOURNMENT**

***Questions to the Committee:***

1. **DISCUSSION:** Discuss the efficacy of sirukumab for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs).

***Committee Discussion:*** *The committee agreed that results of the submitted studies demonstrated the efficacy of sirukumab for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). The committee noted that the efficacy of sirukumab was clear based on the percentage of study patients achieving*

*American College of Rheumatology response criteria (ACR 20, ACR 50, and ACR 70), the reduction in DAS28-CRP scores, the reduction in Health Assessment Questionnaire Disability Index (HAQ-DI) score, and the reduction in radiographic progression (van der Heijde modified Sharp score). One committee member noted that 5-10% of patients achieved remission in comparison to placebo in study ARA3002, which had minimal response. Please see the transcript for details of the committee discussion.*

2. **VOTE:** Overall, do the data provide substantial evidence of the efficacy of sirukumab for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more DMARDs?

- a. If not, what data are needed?

**Vote Result:** Yes: 13 No: 0 Abstain: 0

***Committee Discussion:** The committee unanimously (13 members) agreed that the data provide substantial evidence of the efficacy of sirukumab for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more disease modifying anti-rheumatic drugs (DMARDs). One committee member recommended that additional studies be conducted comparing sirukumab to other IL-6 inhibitors. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** Discuss the design of the 52-week placebo-controlled radiographic study, ARA3002.

***Committee Discussion:** Overall, the majority of the committee agreed that the 52-week placebo-controlled radiographic study ARA3002 was designed and conducted appropriately. Some of the members noted ethical concerns regarding the use of a 52-week placebo treatment arm in patients with active disease given the potential for subsequent disease progression. The members appreciated that the study design allowed for “early escape” at week 18 and “late escape” at week 40 from the placebo arm if patients did not achieve 20% improvement in swollen and tender joint count from baseline. One committee member added that achieving an ACR20 is not an appropriate reason to allow a patient to stay on placebo, especially given the safety data. Given the advances in imaging techniques, some committee members suggested that radiographic progression could have been measured more frequently rather than just at the end of the study. One of the members added that frequent measures of radiographic progression could have informed the decision on whether a patient was eligible for early escape or late escape from the placebo arm. One of the members noted that active-controlled trials should be considered instead of placebo-controlled trials. Please see the transcript for details of the committee discussion.*

4. **DISCUSSION:** Discuss the safety findings in the phase 3 program, with particular consideration of the imbalance in all-cause death between sirukumab and placebo.

**Committee Discussion:** *The committee agreed that there are concerns with regards to the safety findings in the phase 3 program. The committee noted that there were a high number of deaths in the sirukumab arms vs. placebo arms in studies ARA3002 and ARA3003. The committee members commented that it is unclear whether the imbalance in all-cause death between sirukumab and placebo is a result of study design or whether it is a real safety signal. Regarding study ARA3005, which compared sirukumab to an active comparator (adalimumab), one member added that the sirukumab arm had a higher rate of adverse events, including death, vs. adalimumab, and that this might indicate more safety issues with sirukumab. Please see the transcript for details of the committee discussion.*

5. **DISCUSSION:** Discuss the dose selection for the phase 3 program.

**Committee Discussion:** *The committee noted that there was a clear separation in treatment effect for ACR20, ACR50, Disease Activity Score 28, and Clinical Disease Activity Index score for the 100 mg every 2 week dosing during the phase 2 dose ranging study. The committee highlighted that this separation in treatment effect was not observed between the 100 mg every 2 weeks and 50 mg every 4 weeks dosing in the phase 3 studies. The committee agreed that based on the data, there was no clear dose treatment effect or a clear dose response for adverse events in the phase 3 program. The committee could not conclude whether reducing the dose would improve safety outcomes with sirukumab. Please see the transcript for details of the committee discussion.*

6. **VOTE:** Is the safety profile of sirukumab adequate to support approval of sirukumab for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more DMARDs?

a. If not, what data are needed?

**Vote Result:** Yes: 2 No: 11 Abstain: 0

**Committee Discussion:** *The majority of the committee (11 to 2) did not agree that the safety profile of sirukumab is adequate to support the approval of sirukumab for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more disease modifying anti-rheumatic drugs (DMARDs). The majority of the committee agreed that it is unclear whether the imbalance in all-cause mortality is a true safety signal or whether it is a result of bias due to the study design. The majority of the committee also agreed that additional studies should be conducted to further define the safety profile of sirukumab. One committee member proposed that the sponsor find alternative methods to reanalyzing the data in addition to conducting more studies. One of the members who voted "yes" stated that sirukumab is no less safe than the other approved biologics on the market. Please see the transcript for details of the committee discussion.*

7. **VOTE:** Do you recommend approval of sirukumab at the proposed dose of 50 mg subcutaneously every 4 weeks for the proposed indication of the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more DMARDs?

a. If not, what data are needed?

**Vote Result:** Yes: 1 No: 12 Abstain: 0

**Committee Discussion:** *The majority of the committee (12 to 1) did not recommend the approval of sirukumab at the proposed dose of 50 mg subcutaneously every 4 weeks for the proposed indication of the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more disease modifying anti-rheumatic drugs (DMARDs). The majority agreed that efficacy was clear but the safety data was lacking, and a few members emphasized that sirukumab would be more suitable for patients who have had an inadequate response or are intolerant to one or more biologic DMARDs. These members added that the benefit of this drug for this narrower indication might outweigh the unknown safety risks, especially for patients who have limited treatment options left. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 3:37 p.m.