



## **Summary Minutes of the Arthritis Advisory Committee Meeting April 23, 2018**

The Arthritis Advisory Committee (AAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on April 23, 2018, at the 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 Eli Lilly & Company. The meeting was called to order by Jose Scher, MD (Acting Chairperson). The conflict of interest statement was read into the record by Yinghua Wang, PharmD, MPH (Designated Federal Officer). There were approximately 200 people in attendance. There were six 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 the new drug application (NDA) 207924, for baricitinib tablets, submitted by Eli Lilly and Company, for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. The discussion included the following: efficacy, safety, including the risk of thromboembolic adverse events, dose selection, and overall risk benefit considerations.

### **Attendance:**

**Arthritis Advisory Committee Members Present (Voting):** Jennifer Horonjeff, PhD (Consumer Representative); Alyce M. Oliver, MD, PhD; Jose U. Scher, MD (Acting Chairperson)

**Arthritis Advisory Committee Members Not Present (Voting):** Daniel H. Solomon, MD, MPH (Chairperson); Mara L. Becker, MD, MSCE; Jeffrey Curtis, MD, MS, MPH; John M. Davis III, MD, MS; Aryeh Fischer, MD; Veena K. Ranganath, MD, MS; J. Steuart Richards, MD; Eric J. Tchetgen Tchetgen, BS, PhD

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

**Temporary Members (Voting):** Diane Aronson (Patient Representative); Warren Bilker, PhD; Denise M. Boudreau, PhD, RPh; Erica Brittain, PhD; Liron Caplan, MD, PhD; Beth L. Jonas, MD; James Katz, MD; Seoyoung Kim, MD, ScD, MSCE; Donald R. Miller, PharmD; Thomas Ortel, MD, PhD; I. Jon Russell, MD, PhD, ACR Master; Soko Setoguchi, MD, DrPH

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

**FDA Participants (Non-Voting):** Mary T. Thanh Hai, MD; Sally Seymour, MD; Nikolay Nikolov, MD; Raj Nair, MD

**Designated Federal Officer (Non-Voting):** Yinghua S. Wang, PharmD, MPH

**Open Public Hearing Speakers:** Oscar Soto-Raices, MD; Michael Carome, MD (Public Citizen); Christine DiPeri; Elizabeth Perkins, MD; Sarah Aoanan (Global Healthy Living Foundation); Denise Marksberry

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*The agenda was as follows:*

Call to Order and Introduction of Committee	<b>Jose U. Scher, MD</b> Acting Chairperson, AAC
Conflict of Interest Statement	<b>Yinghua Wang, PharmD, MPH</b> Designated Federal Officer, AAC
FDA Opening Remarks	<b>Nikolay Nikolov, MD</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>Eli Lilly and Company</b>
Introduction	<b>Robin Wojcieszek, RPh</b> Senior Director, Global Regulatory Affairs Eli Lilly & Company, USA
Unmet Need for Patients with Rheumatoid Arthritis	<b>Mark Genovese, MD</b> Director of the Rheumatology Clinic in the Division of Immunology & Rheumatology Stanford University Medical Center, USA
Clinical Design and Efficacy of Baricitinib	<b>Terence Rooney, MD</b> Senior Medical Director, Immunology Eli Lilly & Company, USA
Safety of Baricitinib	<b>Melissa Veenhuizen, DVM, MS</b> Senior Medical Director, Global Patient Safety Eli Lilly & Company, USA
Clinical Perspective	<b>Josef Smolen, MD</b> Professor of Medicine & Chairman of the Department of Medicine III & Division of Rheumatology Medical University of Vienna, Austria
Conclusion	<b>James McGill, MD</b> Global Development Leader, Immunology Eli Lilly & Company, USA

**FDA PRESENTATIONS**

Efficacy of Baricitinib

**Robert Abugov, PhD**  
Acting Biostatistics Team Leader  
Division of Biometrics II  
Office of Biostatistics (OB)  
Office of Translational Sciences (OTS)  
CDER, FDA

Safety of Baricitinib

**Raj Nair, MD**  
Clinical Reviewer  
DPARP, ODE-II, OND, CDER, FDA

Potential Biological Mechanisms for Baricitinib-induced Increase in Platelets

**Matthew Whittaker, PhD**  
Non-Clinical Reviewer  
DPARP, ODE-II, OND, CDER, FDA

Epidemiology Safety Study Review

**Veronica Sansing-Foster, PhD, MS**  
Epidemiologist  
Division of Epidemiology II (DEPI-II)  
Office of Pharmacovigilance and Epidemiology  
Office of Surveillance and Epidemiology (OSE)  
CDER, FDA

Benefit Risk Considerations

**Raj Nair, MD**

Clarifying Questions

**LUNCH**

**OPEN PUBLIC HEARING**

Charge to the Committee

**Nikolay Nikolov, MD**

Questions to the Committee/Committee Discussion

**BREAK**

Questions to the Committee/Committee Discussion (cont.)

**ADJOURNMENT**

***Questions to the Committee:***

1. **DISCUSSION:** Discuss the efficacy data for baricitinib for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate (MTX). Include a discussion of the 2 mg and 4 mg doses of baricitinib and whether available data support a benefit of one dose over the other.

**Committee Discussion:** *The committee agreed that the efficacy data show that both the 2 mg and 4 mg doses are superior to placebo. The committee also generally agreed that it is unclear whether there are significant differences, either clinically or statistically, between the two doses. It was noted that depending on how the data were interpreted, some aspect of the data point to a difference between the two doses for some treatment goals at times, but whether this difference was clinically meaningful is not certain. Some committee members noted that the 4 mg reduced radiographic progression but there was no sufficient evidence that the 2 mg would do the same. The disconnect between clinical efficacy with radiographic progression was discussed, and it was noted that radiographic data, although relevant and meaningful to patients, are not required in order to demonstrate efficacy for approval. Please see the transcript for details of the committee discussion.*

2. **VOTE:** Do the data provide substantial evidence of the efficacy of baricitinib 2 mg once daily for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate (MTX)?
- If no, what data are needed?

**Vote Result:      Yes: 14                      No: 1                      Abstain: 0**

**Committee Discussion:** *The majority of committee members voted “Yes”, that the data provide substantial evidence of the efficacy of baricitinib 2 mg once daily for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate. These members noted the robust efficacy of baricitinib versus placebo. The committee member who voted “No” noted that there was no adequate data to support radiographic improvement despite clinical improvement for the 2 mg dose. Please see the transcript for details of the committee discussion.*

3. **VOTE:** Do the data provide substantial evidence of the efficacy of baricitinib 4 mg once daily for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate (MTX)?
- If no, what data are needed?

**Vote Result:      Yes: 15                      No: 0                      Abstain: 0**

**Committee Discussion:** *The committee unanimously agreed that the data provide substantial evidence of the efficacy of baricitinib 4 mg once daily for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate. The committee noted that the data for the 4 mg dose supported efficacy clinically and radiographically. Please see the transcript for details of the committee discussion.*

4. **DISCUSSION:** Discuss the safety data for baricitinib for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate (MTX). Include a discussion of the following issues:
- a) Adequacy of safety database for the 2 mg dose of baricitinib

- b) Safety issues of interest and whether data suggest a dose response
  - Thromboembolic events
  - Malignancy
  - Serious infections, opportunistic infections, herpes zoster, tuberculosis
  - Abnormal laboratory parameters, specifically platelet count elevations
- c) Overall safety profile of the 2 mg dose and the 4 mg dose, and whether the data are more favorable for one dose versus the other

**Committee Discussion on 4a:** *Overall, the committee agreed the data for the 2 mg dose are not sufficient to answer the safety question.*

**Committee Discussion on 4b:** *It was noted that the incidences of these adverse events were small and that the clinical trials were not powered to detect rare events, nor were they designed to do so. Some members voiced their concern that the number of thrombotic events was higher in treatment arms than those in the placebo arm; however, one committee member noted that the increase was modest and comparable to other marketed drugs such as oral contraceptives. The same committee member noted that the platelet increase was an interesting laboratory phenomenon but not linked to clinical outcome, thus, it should not be used to predict thromboembolic risk. The committee also acknowledged that the mechanism of action for thromboembolic events is not well understood.*

**Committee Discussion on 4c:** *The committee noted that it is not clear whether the 2 mg dose is safer than the 4 mg dose due to limitations in the comparison between doses, even though the 2 mg dose had less incidences of adverse reactions. The committee further noted that the difference in incidences of adverse reactions between the two doses is not statistically significant. However, one committee member commented that an assumption could be made that the risk estimates of safety of the 4 mg dose could be used as an upper bound of risk of adverse events for the 2 mg dose to help account for the limited exposure to the 2 mg dose in the baricitinib clinical trials. Another committee member noted that patients need options and a range of doses, so patients could review their risks with their healthcare providers. Please see the transcript for details of the committee discussion.*

5. **VOTE:** Are the safety data adequate to support approval of baricitinib 2 mg once daily for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate (MTX)?
- If no, what data are needed?

**Vote Result:      Yes: 9                      No: 6                      Abstain: 0**

**Committee Discussion:** *The majority of the committee voted “Yes”, that the safety data are adequate to support approval of baricitinib 2 mg once daily for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate. However, these members indicated that it was a very difficult vote and that they would like to see more safety data through post-marketing studies. The committee members who voted “No” noted the potential serious risk of thrombosis and that the sample size was small and the clinical trials were not powered to*

*detect differences in rare adverse events or answer some of the safety question, therefore the safety database was not adequate. Please see the transcript for details of the committee discussion.*

6. **VOTE:** Are the safety data adequate to support approval of baricitinib 4 mg once daily for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate (MTX)?
- If no, what data are needed?

**Vote Result:      Yes: 5                      No: 10                      Abstain: 0**

***Committee Discussion:** The majority of the committee voted “No”, that the safety data are not adequate to support approval of baricitinib 4 mg once daily for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate. These members agreed that although the study is not powered to answer the safety question, there was a clear signal for thromboembolic events since more patients were enrolled in the 4 mg trial. One committee member recommended a comparative trial between the two doses to look at safety in particular. The members who voted “Yes” noted that although there was a safety signal, the 4 mg dose would could be used in refractory population such as patients who failed biologic disease-modifying anti-rheumatic drugs (bDMARDs). Please see the transcript for details of the committee discussion.*

7. **VOTE:** Is the benefit-risk profile adequate to support approval of baricitinib 2 mg once daily 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 methotrexate (MTX)?
- If no, what data are needed?

**Vote Result:      Yes: 10                      No: 5                      Abstain: 0**

***Committee Discussion:** The majority of the committee voted “Yes”, that the benefit-risk profile is adequate to support approval of baricitinib 2 mg once daily 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 methotrexate. These members indicated that they would like to see more data through a mandatory post-marketing safety study. It was also recommended that if baricitinib 2 mg once daily was approved, it should be indicated for refractory patients who failed biologics. The members who voted “No” noted that there is not enough data to analyze for safety or that the baricitinib 2 mg dose should not be used in patients who were methotrexate inadequate responders but in a more refractory patient group. Please see the transcript for details of the committee discussion.*

8. **VOTE:** Is the benefit-risk profile adequate to support approval of baricitinib 4 mg once daily 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 methotrexate (MTX)?

- If no, what data are needed?

**Vote Result:      Yes: 5                      No: 10                      Abstain: 0**

***Committee Discussion:** The majority of the committee voted “No”, that the benefit-risk profile is not adequate to support approval of baricitinib 4 mg once daily 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 methotrexate. These members noted that safety was their main concern, and that more controlled data (potentially another randomized trial) are needed to understand the safety signal and determine whether the thromboembolic events seen in the trials were caused by baricitinib. The members who voted “Yes” indicated that they want refractory patients to have more options, and also noted that more data is warranted. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:57 PM.