Summary Minutes of the Arthritis Advisory Committee Meeting
July 23, 2013
Location: FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center
(Rm. 1503), Silver Spring, MD

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

These summary minutes for July 23, 2013 Meeting of the Arthritis Advisory Committee of the Food and Drug Administration were approved on _8/30/13.

I certify that I attended the July 23, 2013 meeting of the Arthritis Advisory Committee and that these minutes accurately reflect what transpired.

_____/s/_____
Cindy Hong, Pharm.D.
Acting Designated Federal Officer
Arthritis Advisory Committee (AAC)

_____/s/_____
Tuhina Neogi, MD
Acting Chairperson, AAC

The Arthritis Advisory Committee (AAC) of the Center for Drug Evaluation and Research met on July 23, 2013 from 8 a.m. to 12:15 p.m. at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, MD.
Prior to the meeting, members and temporary voting members were provided copies of the background material from the FDA and the Sponsor, AbbVie, Inc. The meeting was called to order by Tuhina Neogi, MD (Acting Committee Chairperson); the conflict of interest statement was read into the record by Cindy Hong, PharmD (Acting Designated Federal Officer). There were approximately 150 persons in attendance. There were 2 (two) speakers for the Open Public Hearing session.

Issue: During the morning session, the committee met to discuss supplemental biologics license application (sBLA) 125057, HUMIRA (adalimumab) injection, by AbbVie Inc. for the proposed indication of reducing signs and symptoms in adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation by elevated CRP or MRI, who have had an inadequate response to, or are intolerant to, nonsteroidal anti-inflammatory drugs.

Attendance:

Arthritis Advisory Committee Members Present (Voting):
Lisa Gualtieri, PhD (Consumer Representative), Robert Lahita, MD, PhD, Tuhina Neogi MD, PhD (Acting Chairperson), Peter Peduzzi, PhD, Irwin Russell, MD, PhD

Arthritis Advisory Committee Members Present (Non-Voting):
Brian Kotzin, MD (Industry Representative)

Temporary Members (Voting):
G. Caleb Alexander, MD, MS, David Felson, MD, MPH, James Katz, MD, Nancy Lane, MD, Donald Miller, PharmD Jodi Segal, MD, MPH, Michael Smith (Patient Representative), Daniel H. Solomon, MD, MPH Michael Ward, MD

FDA Participants (Non-Voting):
Curtis Rosebraugh, MD, MPH, Badrul Chowdhury, MD, PhD, Sarah Yim, MD, Joan Buenconsejo, PhD, Janet Maynard, MD, MHS

Arthritis Advisory Committee Members Not Present:
None

Acting Designated Federal Officer:
Cindy Hong, PharmD

Open Public Hearing Speakers:
Max Hamburger, MD, President, New York State Rheumatology Society
Martha Dyer

The agenda was as follows:

Call to Order Introduction of Committee	**Tuhina Neogi, MD, PhD** Acting Chairperson, AAC
Conflict of Interest Statement	**Cindy Hong, PharmD** Acting Designated Federal Officer
Opening Remarks	**Sarah Yim, MD** Associate Director, Division of Pulmonary, Allergy & Rheumatology Products (DPARP), Office of Drug Evaluation II (ODE-II), Office of New Drugs (OND), CDER, FDA
Sponsor Presentations Introduction	**AbbVie, Inc** **John Medich, PhD** Divisional Vice President Immunology Clinical Development, AbbVie
Unmet Need	**Philip Mease, MD** Director of Rheumatology Research Swedish Medical Center/University of Washington
Study Design & Efficacy Results	**Aileen Pangan, MD** Senior Medical Director Immunology Clinical Development AbbVie
X-ray Challenges with Axial Spondyloarthritis	**Desiree van der Heijde, MD, PhD** Clinical Professor of Rheumatology Leiden University Medical Center Leiden, Netherlands
Physician and Patient Perspective	**Pendleton Wickersham, MD** Rheumatologist Arthritis Associates, PA San Antonio, Texas
Clarifying Questions for Sponsor	
FDA Presentations	
Efficacy and Safety Considerations	**Janet Maynard, MD, MHS** Clinical Reviewer DPARP, ODE-II, OND, CDER, FDA
Clarifying Questions to the FDA	

Open Public Hearing

Charge to the Committee **Sarah Yim, MD**

Committee Discussion and Voting

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Questions to the Committee:

1. **DISCUSSION:** Discuss the efficacy data for adalimumab.
   a) Discuss the treatment effect of adalimumab for ankylosing spondylitis (AS) patients versus non-radiographic axial spondyloarthritis (nr-axSpA) patients.
   b) Discuss whether the data for the subpopulation with "objective signs of inflammation by elevated c-reactive protein (CRP) or magnetic resonance imaging (MRI)" supports specifying this population in the proposed indication.

   The panel expressed frustration with the difficulty in interpreting the efficacy results given the differences in x-ray classification based on local versus central evaluation. The panel acknowledged that based on central readings the trial appeared to include patients with ankylosing spondylitis in addition to nr-axSpA. Thus, the treatment effects in the nr-axSpA group were unclear and it was difficult to know exactly which patients were included in the trials.

   Some members commented that MRI evidence of inflammation should focus only on the sacroiliac joints and not the spine. The panel expressed concerns regarding whether adequate data were provided to support efficacy in the subpopulation of patients with elevated CRP or abnormal MRI.

2. **DISCUSSION:** Discuss the safety data for adalimumab.
   a) Discuss whether nr-axSpA may include disease entities that are not chronic and progressive. In light of your position, discuss whether the currently available safety data are adequate or whether additional data are needed. If the latter, please explain what additional data should be required.

   One member commented that there is no information that nr-axSpA patients will have different outcomes in terms of safety than patients that have a long history with adalimumab. The panel concurred that the data presented did not highlight additional concerns.

3. **VOTE:** Overall, do the data provide substantial evidence that adalimumab provides a clinically meaningful beneficial effect in the treatment of active non-radiographic axial spondyloarthritis in adults with objective signs of inflammation by elevated CRP or MRI, who have had inadequate response or are intolerant to nonsteroidal anti-inflammatory drugs?

   a) If no, what additional data are necessary?

YES: 1 **NO: 12** **ABSTAIN: 1**

Those voting "No" commented that while efficacy was noted, additional data useful would be a trial with multiple arms that better defines the subpopulation and more closely matches the expanded indication. It was expressed that CRP and MRI should be included in defining this group of patients with clarification that MRI of sacroiliac joints rather than spinal MRI should be specified and other reasons for CRP elevation should be excluded.

The member voting "Yes" commented that in those defined by elevated CRP or MRI, there were notable improvement in signs and symptom.

One member who abstained commented that the overall trial including the target population showed positive results which are meaningful, but was concerned with the possibility of patients being classified into this group of disease when they do not have the disease and do not require the treatment.

4. **VOTE:** Is the safety profile of adalimumab adequate to support approval of adalimumab for the treatment of active non-radiographic axial spondyloarthritis in adults with objective signs of inflammation by elevated CRP or MRI, who have had inadequate response or are intolerant to nonsteroidal anti-inflammatory drugs?

a) If no, what additional data are necessary?

YES: 10 NO: 4 ABSTAIN: 0

The members voting "Yes" commented that they expect this group of patients to respond similarly to patients already using adalimumab for other indications and did not see significant safety signals.

Those voting "No" commented on the possibility of use by inappropriate patients who do not have nr-axSpA and the need for longer studies.

5. **VOTE:** Does the Committee recommend approval of adalimumab for the proposed indication of active non-radiographic axial spondyloarthritis in adults with objective signs of inflammation by elevated CRP or MRI, who have had inadequate response or are intolerant to nonsteroidal anti-inflammatory drugs?

a) If no, what additional data are necessary?

YES: 1 NO: 12 ABSTAIN: 1

The member voting "Yes" commented that he could see the value in patients that could get some benefit with the drug.

Those voting "No" commented on the lack of sufficient efficacy data in the ideal intended patient population that may be required for FDA approval for a new indication. It was also noted that an unmet need was recognized, but the indication as worded was felt to be too broad. It was felt that there is a need for better definition of progression of the disease and a need for a better study with a larger sample size and central x-ray evaluation.

The member who "abstained" noted that the drug cannot be approved, but the risk-benefit profile almost suggests approval since AS patients will benefit and those who do not benefit can be instructed by the labeling to discontinue if ineffective.

(Please see official transcript for details.)

The morning session adjourned at approximately 11:45 am.

The Arthritis Advisory Committee (AAC) of the Center for Drug Evaluation and Research met on July 23, 2013 from 1 p.m. to 5:30 p.m. at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, MD.
Prior to the meeting, members and temporary voting members were provided copies of the background material from the FDA and the Sponsor, UCB, Inc. The meeting was called to order by Tuhina Neogi, MD (Acting Committee Chairperson); the conflict of interest statement was read into the record by Cindy Hong, PharmD (Acting Designated Federal Officer). There were approximately 100 persons in attendance. There were 2 (two) speakers for the Open Public Hearing session.

Issue: During the afternoon session, the committee met to discuss (sBLA) 125160, CIMZIA (certolizumab) injection, by UCB, Inc., for the proposed indication of treatment of adult patients with active axial spondyloarthritis, including patients with ankylosing spondylitis.

Attendance:

Arthritis Advisory Committee Members Present (Voting):
Lisa Gualtieri, PhD (Consumer Representative), Robert Lahita, MD, PhD, Tuhina Neogi, MD, PhD (Acting Chairperson), Peter Peduzzi, PhD, Irwin Russell, MD, PhD

Arthritis Advisory Committee Members Present (Non-Voting):
Brian Kotzin, MD (Industry Representative)

Temporary Members (Voting):
G. Caleb Alexander, MD, MS, David Felson, MD, MPH, James Katz, MD, Nancy Lane, MD, Donald Miller, PharmD Jodi Segal, MD, MPH, Michael Smith (Patient Representative), Daniel H. Solomon, MD, MPH Michael Ward, MD

FDA Participants (Non-Voting):
Curtis Rosebraugh, MD, MPH, Badrul Chowdhury, MD, PhD, Sarah Yim, MD, Joan Buenconsejo, PhD, Janet Maynard, MD, MHS

Arthritis Advisory Committee Members Not Present:
None

Acting Designated Federal Officer:
Cindy Hong, PharmD

Open Public Hearing Speakers:
Donald Biscoe, Michael Shrader

The agenda was as follows:

Call to Order Introduction of Committee	**Tuhina Neogi, MD, PhD** Acting Chairperson, AAC
Conflict of Interest Statement	**Cindy Hong, PharmD**

	Acting Designated Federal Officer
Opening Remarks	**Sarah Yim, MD** Associate Director, Division of Pulmonary, Allergy & Rheumatology Products (DPARP), Office of Drug Evaluation II (ODE-II), Office of New Drugs (OND), CDER, FDA
Sponsor Presentations	**UCB, Inc.**
Introduction	**Deborah Hogerman** Vice President Regulatory Affairs North America UCB, Inc
Disease Burden and Unmet Need	**Atul Deodhar, MD, FACP, FACR** Professor of Medicine Medical Director, Rheumatology Clinics Oregon Health & Science University Portland, OR
Design and Efficacy	**Victor S. Sloan, MD, FACP, FACR** VP and Head, Immunology Practice, UCB Clinical Associate Professor of Medicine Division of Rheumatology and Connective Tissue Diseases Rutgers Robert Wood Johnson Medical School
Safety	**Victor S. Sloan, MD, FACP, FACR**
Benefit-Risk Assessment	**Deborah Hogerman**
Clinical Perspective	**Megan Clowse, MD, MPH** Assistant Professor Department of Medicine, Rheumatology-Immunology Duke University
Clarifying Questions to the Sponsor	
FDA Presentations	
Efficacy and Safety Considerations	**Janet Maynard, MD, MHS**
Clarifying Questions to the FDA	
Open Public Hearing	

Charge to the committee **Sarah Yim, MD**

Committee Discussion and Voting

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the efficacy data for certolizumab.
   a. Discuss the treatment effect of certolizumab for axial spondyloarthritis, with consideration of the subgroups of ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA).
   b. Discuss whether the submitted data are adequate to determine the treatment effect of certolizumab in AS and in nr-axSpA or whether additional data are needed. If the latter, please explain what additional data should be required.

Members of the panel commented that data on the AS population is compelling as well as those in MRI positive subgroups, but saw the need for more study in the nr-axSpA group. The panel agreed that they saw efficacy signals, but noted issues with implementation in the real practice setting, particularly with regards to accurately identifying nr-ax-SpA patients in the community.

2. **DISCUSSION:** Discuss the safety data for certolizumab.
   a. Discuss whether nr-axSpA may include disease entities that are not chronic and progressive. In light of your position, discuss whether the currently available safety data are adequate or whether additional data are needed. If the latter, please explain what additional data are needed.
   b. Discuss whether the safety data for the AS subgroup are adequate or whether additional data are needed. If the latter, please explain what additional data should be required.

The panel noted some signals in the trial data which were not the same as in rheumatoid arthritis or known for AS and expressed uncertainty as to whether this is worrisome. There was general consensus that there are no substantial safety concerns.

3. **VOTE:** Overall, do the data provide substantial evidence that certolizumab provides a clinically meaningful beneficial effect in the treatment of active axial spondyloarthritis, including patients with ankylosing spondylitis?

   a. If no, what additional data are necessary?

YES: 8 **NO: 5** **ABSTAIN: 1**

One member who "abstained" commented that although there is good efficacy data for a subgroup of patients with nr-axSpA, it's not entirely clear as to which group the data apply.

Members voting "Yes" commented that for the population in the study, the efficacy data were persuasive. One member noted concerns of categorization of AS vs. nr-axSpA in the studies. Few members commented that there were strong signals for both local and central radiographic

evaluations and that there were compelling data for ankylosing spondylitis group and for the subgroup of non-radiographic ankylosing spondylitis group.

Those members voting "No" commented that there is lack of a clear definition of "active" axial spondyloarthritis and it is unclear which patient population is captured by the indication "axial spondyloarthropathy." One member noted that data presented showed efficacy signals, but it is uncertain whether the small number of patients exposed is sufficient for FDA requirements for a new indication.

4. **VOTE:** Is the safety profile of certolizumab adequate to support approval of certolizumab for the treatment of active axial spondyloarthritis, including patients with ankylosing spondylitis?

a. If no, what additional data are necessary?

YES: 13 **NO: 1** **ABSTAIN: 0**

Members voting "Yes" expressed concerns with the risk of patients without nr-axSpA (e.g., those with mechanical low back pain) being inappropriately treated with the therapy and thereby subjected to risk of serious infection and concerns with CK elevations.

One member voting "No" commented on the same concern as those voting Yes.

5. **VOTE:** Does the Committee recommend approval of certolizumab for the proposed indication of active axial spondyloarthritis, including patients with ankylosing spondylitis?

a. If no, what additional data are necessary?

YES: 7 **NO: 6** **ABSTAIN: 1**

Members voting "Yes" expressed that the data were compelling and saw the potential for appropriate use in practice.

Members voting "No" commented on insecurity with accurately identifying the no-radiographic group and wanted to see data that this is the group that will respond. Few members noted that the number of patients studied was small and they wanted more data and clarity on the definition of active axial spondyloarthritis.

One member "abstained" from voting and noted that the data is compelling, but uncertainty about the indication and the broadness of the indication exist.

(Please see official transcript for details.)

The meeting adjourned at approximately 4:30 p.m.