Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Arthritis Advisory Committee Meeting
November 16, 2010

Location: **Marriott Inn & Conference Center, University of Maryland University College (UMUC), 3501 University Blvd., Adelphi, Maryland**

Issue: **The committee discussed biologic license application (BLA) 125370, belimumab, proposed trade name BENLYSTA, sponsored by Human Genome Sciences, for the proposed indication of reducing disease activity in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE).**

These summary minutes for November 16, 2010 Arthritis Advisory Committee Meeting were approved on November 19, 2010.

I certify that I attended the November 16, 2010, Arthritis Advisory Committee Meeting and that these minutes accurately reflect what transpired.

_____/s/_____
Yvette Waples, Pharm.D.
Acting Designated Federal Official, AAC

_____/s/_____
Kathleen O'Neil, M.D.
Committee Chair

Summary Minutes of the Arthritis Advisory Committee Meeting
November 16, 2010

The following is the final report of the Arthritis Advisory Committee meeting held on November 16, 2010. 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: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/ucm203434.htm

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

The Arthritis Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on November 16, 2010 at the Marriott Inn & Conference Center, University of Maryland University College (UMUC), 3501 University Blvd., Adelphi, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and Human Genome Sciences, Inc. The meeting was called to order by Kathleen O'Neil, M.D. (Chairman); the conflict of interest statement was read into the record by Yvette Waples, Pharm.D. (Acting Designated Federal Official). There were approximately 375 people in attendance. There were 30 Open Public Hearing (OPH) speakers.

Issue: The committee discussed biologic license application (BLA) 125370, belimumab, proposed trade name BENLYSTA, sponsored by Human Genome Sciences, for the proposed indication of reducing disease activity in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE).

Attendance:
Arthritis Advisory Committee members present:
David Blumenthal, M.D.; Lenore Buckley, M.D., M.P.H.; Robert Kerns, Ph.D.; Kathleen O'Neil, M.D. *(Chairman);* Mark Fletcher, M.D.*(non-voting industry representative)*

Arthritis Advisory Committee members not present:
Ted R. Mikuls, M.D., M.S.P.H.; Nancy J. Olsen, M.D.

Temporary Voting Members:
Kathleen Arntsen *(Patient Representative)*; Diane Aronson *(Consumer Representative)*; Dennis Dixon, Ph.D.; Gabor Illei, M.D., Ph.D., M.H.S.; Matthew Liang, M.D., M.P.H., FACP, FACR; R. John Looney, M.D.; David Pisetsky, M.D., Ph.D.; Christy Sandborg, M.D.; Maria E. Suarez-Almazor, M.D.; Mark Woods, Pharm.D., FASHP, BCPS; Daniel Zelterman, Ph.D.

FDA Participants:
Curtis Rosebraugh, M.D.; Badrul Chowdhury, M.D., Ph.D.; Sarah Okada, M.D.; Rosemarie Neuner, M.D., M.P.H.; Ruthanna Davi, Ph.D.; Thomas Permutt, Ph.D.

Open Public Hearing Speakers:
Margaret Dowd (President/CEO, Lupus Research Institute); Kate Kelly; Benjamin Schwartz, M.D., Ph.D. (Principal and Co-Founder, The Camden Group); Lisa Williams; Sabrina Nixon; Karen Britt; Janice Fitzgibbon; Brenda Blackmon; Angie Hudnell; Juliette Hale; Brian Kaplan; Christine Belcher; Donna Flenory; Sandra C. Raymond (President and CEO, Lupus Foundation of America); Wendy Rodgers ("Could

Open Public Hearing Speakers continued…
I Have Lupus Ad Campaign" National Spokesperson); Cindy Coney (Chair, LFA Board of Directors); Diana Lai; Erica Corcoran; Seth Ginsberg (GHLF President); Nancy Hey; Evanne Graté; Benjamin Pruitt; minor (name withheld); Elizabeth Gallagher; Penelope C. Fletcher (President and CEO, Lupus Foundation of America, DC / MD / VA Chapter); Valerie F. Hunt, Ph.D.; Elizabeth Murphy (Chairman, Lupus Foundation of America, DC / MD / VA Chapter); Kelly Drury; Virginia T. Ladd (President/Executive Director, American Autoimmune Related Diseases Association); Petra Harvey

The agenda was as follows:

Call to Order Introduction of Committee	**Kathleen O'Neil, M.D.** Chair, Arthritis Advisory Committee
Conflict of Interest Statement	**Yvette Waples, Pharm.D.** Acting Designated Federal Official
Opening Remarks	**Badrul Chowdhury, M.D., Ph.D.** Director, Division of Pulmonary, Allergy and Rheumatology Products (DPARP), Office of Drug Evaluation (ODE) II, Office of New Drugs (OND) CDER, FDA
SPONSOR PRESENTATIONS	
Introduction	**Diana Daly, RN, BSN** Executive Director, Regulatory Affairs Human Genome Sciences
Systemic Lupus Erythematosus: Unmet Medical Need	**Murray Urowitz, M.D., FACP, FRCPC** Professor of Medicine University of Toronto
Mechanism of Action: BLyS and Belimumab	**Thi Migone, Ph.D.** Executive Director, Clinical Immunology Human Genome Sciences
Efficacy	**William Freimuth, M.D., Ph.D.** Vice President, Clinical Research Human Genome Sciences
Safety	**Simon Cooper, M.D.** Director, Clinical Research Human Genome Sciences
Clinical Perspective	**Dr. Michelle Petri** Professor, Division of Rheumatology Johns Hopkins University Director, The Hopkins Lupus Cohort Co-Director, The Hopkins Lupus Pregnancy Center
Clarifying Questions for Sponsor Presenters	

BREAK

FDA PRESENTATIONS

Efficacy and Safety Considerations	**Rosemarie Neuner, M.D.** Clinical Reviewer DPARP, ODE II, OND CDER, FDA
Statistical Considerations	**Ruthanna Davi, Ph.D.** Statistical Reviewer Division of Biometrics II, Office of Biostatistics Office of Translational Science CDER, FDA
Clarifying Questions for FDA Presenters	

LUNCH

Open Public Hearing

Charge to the Committee	**Badrul Chowdhury, M.D., Ph.D.** Director, DPARP, ODE II, OND CDER, FDA

Committee Discussion

Questions to the Committee

ADJOURNMENT

Questions to the Committee:

1. Discuss the efficacy data of belimumab considering the following:
   - **a.** Efficacy driven by contribution of musculoskeletal and mucocutaneous organ systems results
   - **b.** Lack of demonstrated efficacy in organ systems associated with poor outcome and mortality in systemic lupus erythematosus
   - **c.** Lack of demonstrated efficacy in patients of African American or African heritage
   - **d.** Numerically smaller efficacy results for patients from United States and Canada compared to some other regions

   Committee Discussion: *Overall, the committee had concerns with the efficacy data of belimumab. Some of the comments include:*
   - The study design excluded patients with severe lupus renal or central nervous system disease.
   - There is good evidence from BLISS 52 clinical trial that belimumab did meet its primary and secondary endpoints. The data from BLISS 72 clinical trial is less convincing in that there are concerns with the efficacy of belimumab over placebo.
   - The BLISS 52 trial does not closely reflect the demographics of the lupus population in the U.S.
   - Belimumab may have mild efficacy in patients who experience toxicity and intolerance to other regimens used to treat the symptoms of lupus.
   - Data showed lack of demonstrated efficacy in patients of African American or African heritage.

- The labeling needs revision to indicate the drug has not been tested in the segment of the U.S. lupus population that has severe renal or central nervous system disease.

Note: Questions #2 and #3 were discussed together

2. Discuss the overall safety profile of belimumab considering the following:
   a. Safety signals of infection, malignancy, suicidality, and mortality
   b. Potential risk of using belimumab when combined with other immunosuppressive agents, which may be needed to treat more serious manifestations of systemic lupus erythematosus that are associated with poor outcome and mortality

3. Discuss the suicidality data and provide recommendations for further evaluation, if necessary.

   Committee Discussion: *Overall, the committee felt although belimumab has safety signals, there are relatively small compared to other medications lupus patients are currently prescribed.*
   Some of the comments include:
   - The sponsor has recognized a number of issues and has identified plans for post marketing studies to further address these.
   - Drugs have side effects and one would expect belimumab to have side effects.
   - Safety profile appears to be favorable compared to the other medicines that are currently used.
   - If approved, more studies are needed to determine the potential risk of using belimumab when combined with other immunosuppressive agents.
   - Depression is common among people with chronic autoimmune diseases so it would be difficult to determine whether belimumab use was directly related to the suicides, but post-marketing surveillance of depression and suicidality is needed.

4. Considering the totality of the data, has belimumab at a dose of 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter demonstrated substantial evidence of <u>efficacy</u> for reducing disease activity in adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy? **(Voting Question; YES/NO/ABSTAIN)**

   YES: 10 NO: 5 ABSTAIN: 0

   a. If not, what further efficacy data should be obtained?

   Committee Discussion: *The majority of the committee felt the data demonstrated efficacy. For those who voted 'no' have concerns that the study was not representative of all U.S. patients and patients with severe renal or central nervous system disease were excluded. In addition, lack of demonstrated efficacy in African Americans was also a concern.*

   There was consensus that the label should clearly state patients with severe renal and central nervous system disease were not evaluated.

5. Is the <u>safety</u> profile of belimumab sufficient for approval for reducing disease activity in adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy? **(Voting Question; YES/NO/ABSTAIN)**

   a. If not, what further safety data should be obtained?

   YES: 14 NO: 1 ABSTAIN: 0

Committee Discussion: *The majority of the committee agreed that the safety profile of belimumab is acceptable.*

6. Do the efficacy and safety data provide substantial evidence to support approval of belimumab at a dose of 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter for reducing disease activity in adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy? **(Voting Question; YES/NO/ABSTAIN)**

   YES: 13 NO: 2 ABSTAIN: 0

   Committee Discussion: *The majority of the committee members agreed that the efficacy and safety data provide evidence to support approval of belimumab. The committee members voting 'no' felt although the data demonstrated safety, it lacked demonstrated efficacy in specific lupus populations.*

   There was consensus that the language in the labeling should clearly state patients with severe renal and central nervous system disease were not evaluated.

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The meeting was adjourned at approximately 4:55 p.m.