Food and Drug Administration
Center for Drug Evaluation and Research
ACS Conference Room, Rockville, MD

Summary Minutes of the Arthritis Advisory Committee Meeting for September 6, 2005.

On September 6, 2005, the committee discussed BLA 125118/0 Abatacept, Bristol Myers Squibb, proposed trade name Orencia, proposed inidcation for the treatment of moderately to severely active rheumatoid arthritis.

These summary minutes for the September 6, 2005 meeting of the Arthritis Advisory Committee Meeting were approved on September 29, 2005.

I certify that I attended the September 6, 2005 meeting of the Arthritis Advisory Committee and that these minutes accurately reflect what transpired.

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Johanna M. Clifford, M.S., RN
Executive Secretary

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Allan Gibofsky, M.D., J.D.
Chair, AAC

Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and from the sponsors. The meeting was called to order by Allan Gibofsky, M.D, J.D., AAC Chair; the conflict of interest statement was read into the record by Johanna Clifford (Executive Secretary). There were approximately 100 persons in attendance. There were no speakers for the Open Public Hearing session.

Attendance:
Arthritis Advisory Committee Members Present (voting)
J. Michael Finley, D.O., Allan Gibofsky, M.D., J.D., Chair, Norman Illowite, M.D.

Arthritis Advisory Committee Consultants (voting):
Janet Elashoff, Ph.D., David Felson, M.D., M.P.H., V. Michael Holers, M.D., Leona Malone (Patient Representative)

Acting Industry Representative (non-voting):
Roger Porter, M.D.

Arthritis Advisory Committee Members Absent:
Joan Bathon, M.D, Dennis Boulware, M.D., John J. Cush, M.D., Steven Geis, M.D., Ph.D., Gary Stuart Hoffman, M.D., Susan Manzi, M.D., M.P.H.

FDA Participants:
Bob Rappaport, M.D., Karen Weiss, M.D., Jeffrey Siegel, M.D., Keith Hull, M.D., Ph.D., Marc Walton, MD, PhD

Issue:
BLA 125118/0, Abatacept, Bristol-Myers Squibb, proposed trade name Orencia, proposed indication for the treatment of moderately to severely active Rheumatoid Arthritis.

The agenda proceeded as follows:

Opening Remarks	Karen Weiss, M.D., Director Office of Drug Evaluation VI, FDA
Abatacept (CTLA4-Ig) for the Treatment Of Rheumatoid Arthritis: Product Attributes And Mechanism of Action	Joy Williams, Ph.D. Division of Therapeutic Proteins, FDA

Sponsor Presentation	**Bristol Myers Squibb**
Introduction	Brian Daniels, M.D. Senior Vice President, Global Clinical Development
Introduction to the Product & Session Moderator	Anthony Waclawski, Ph.D. Executive Director, Global Regulatory Science
Efficacy Presentation	George Vratsanos, M.D. Director, Clinical Research
Safety Presentation	Daniel MacNeil, M.D. Executive Director, Clinical Safety
Closing	Brian Daniels, M.D.

FDA Presentation	
BLA 125118	Keith Hull, M.D., Ph.D., Medical Officer Division of Therapeutic Biological Internal Medicine Products, FD

Questions to the Committee:

1. There are 3 randomized placebo controlled studies of Abatacept in rheumatoid arthritis patients that evaluated the proposed weight-tiered dosing regimen and two studies which evaluated a regimen of 10 mg/kg. One study examined monotherapy with Abatacept, and 4 studies examined Abatacept as an add-on to other products.

Three of these studies followed the FDA Guidance on Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis as it relates to the duration of the placebo controlled period and the nature of the endpoints. Compared to placebo, Abatacept treatment showed effects on signs and symptoms (e.g., as evaluated by the ACR criteria), radiographic progression (as evaluated by the total Sharp Score) and physical function (as evaluated by the HAQ-DI) have been observed

Please discuss the strength of evidence regarding the demonstration of efficacy of Abatacept in the treatment of patients with rheumatoid arthritis.

Discussion: The committee noted that the data presented for physical function, signs and symptoms, and major clinical response were sufficient. However, the committee noted some concern as to the strength of the evidence presented for the inhibition of radiographic progression as it was based on a single study using abatacept and concomitant methotrexate in 391 individuals.

Several potential safety concerns have been identified for Abatacept:

For each of the following (Topics 2-6) please discuss the safety profile of Abatacept, and the major concerns you believe may be present. Please identify the areas of concern for which further safety assessment is warranted, and the types of studies that should be conducted to further characterize these concerns.

2) More serious infections have been observed in the Abatacept-treated groups than in the control comparison groups. This was particularly notable for, but not limited to, patients who received concomitant TNF-antagonist agents.

Discussion: *The committee felt that infection was a concern especially in the more vulnerable populations such as the pediatric and elderly. The Sponsor hopes to address these concerns and the concerns of adverse events when abatacept is used with other biologics in the pharmacovigilance plan and with recommendations to avoid use with other biologics.*

3) The Abatacept clinical development program incorporated an analysis of "Infections of Special Interest", which included fungal (e.g. aspergillosis), viral (e.g. herpes zoster) and bacterial infections (e.g. pneumonia and TB). Overall Infections of Special Interest were observed in 10% of Abatacept-treated patients compared to 7% of control group patients, with the majority of this difference in the Herpes and Pneumonia categories. However the total patient sample size and exposure duration (median 14 months) cannot rule out an Abatacept-associated increase in the rate of uncommon opportunistic infections.

Discussion: The committee felt the pharmacovigilance plan was sufficient and that the plan will provide the additional information both in the cohort studies from the insurance claims base and from the observational safety studies with registries. The committee was satisfied that there was a plan in place to continue to study the adverse events, recognizing that there are small numbers to date, stressing again, however, that the registries attempt to capture the data from each subpopulation, particularly the elderly, children, patients with co-morbidities, and patients with potential susceptibility to the adverse events as noted above.

4) Overall malignancy rates were not substantially different between Abatacept and placebo treated patients (1.5% and 1.1% respectively). However, more cases of lung cancer were observed in Abatacept treated patients than in the control group (4 versus 0). The rate of lymphomas was not increased in Abatacept-treated patients compared to placebo-treated patients, however for the complete safety dataset (controlled and uncontrolled periods) the rate of lymphoma in Abatacept-treated patients was higher than expected based on the general US population. In addition, an increase in the rate of lymphomas and mammary tumors was observed in the murine model, though not in non-human primates.

Discussion: The committee had concerns with abatacept, as it does with other biologic agents. The committee specifically noted the increased rate of lymphoma and agreed that this is a concern that needs to be actively assessed, specifically noting the sponsor's 5-year pharmacovigilance plan. The committee discussed the size of the post-marketing safety database that would be required to determine whether the rate of lymphoma is increased with abatacept. The committee concluded that the database should be large but did not reach consensus on a specific number.

5) Hypersensitivity reactions have been observed, including a case of anaphylaxis.

Discussion: The committee noted that hypersensitivity have been observed, however felt overall that this was not a major concern as this is an infusional drug and the risk of hypersensitivity with an infused product is known and accepted.

6) Patients with chronic obstructive pulmonary disease (COPD) treated with Abatacept had a higher incidence of adverse events and serious adverse events, particularly respiratory disorders.

Discussion: The committee noted that the product is indicated for patients who have failed at least one DMARD, possibly more, and that the patient receiving the product should be informed of the potential benefit with the full understanding and listing of safety concerns that have been presented in the data.

The committee had concerns, specifically with regard to the pediatric patients receiving the product off-label, and commended the sponsor on the ongoing, well designed trial in children, but there was some concern about the number of patients being enrolled in other countries. The committee suggested that the company might consider additional pharmacovigilance studies in children receiving the product off-label use and followed for longer periods of time.

7) Please discuss any other areas of safety concern that have not been specifically highlighted above.

The committee was particularly concerned with potential harmful effects of abatacept regarding the potential for the development of autoimmune disease in children exposed to abatacept while in utero.

8) <u>Overall Assessment</u>

In view of all the data available for the safety and efficacy of Abatacept, do the benefits outweigh the known and potential risks?

Please discuss and then vote.

Yes: 7 No: 0

Discussion: The committee unanimously felt that the data demonstrated evidence of abatacept being efficacious and that the benefits of the product as currently understood, outweigh the risks.

<u>Additional Advice</u>

In addition to assessing ACR 20, 50 and 70 responses, the sponsor collected data on the percentage of patients achieving low disease activity, as assessed by the DAS-defined remission (DAS < 2.6). Since DAS is a composite of tender joints, swollen joints, pain and acute phase reactants, it is possible to achieve a DAS below 2.6 but still have multiple tender and/or swollen joints.

a. Does assessing the proportion of patients achieving low disease activity provide important information of a nature that is not adequately assessed by analyzing the proportions of patients achieving high levels of improvement (e.g. ACR 70 or major clinical response). If so, please discuss the nature of difference in the information

b. If assessing the proportion of patients achieving low disease activity does provide important additional information, please comment on which measures are suitable or optimal to identify low disease activity. Please consider in particular:

   i. DAS-defined remission (DAS < 2.6);

   ii. DAS < 2.6 plus no more than 1 tender joint;

   iii. DAS < 2.6 plus no more than 1 tender or 1 swollen joint

Discussion: The committee noted that the traditional measures of ACR response should be maintained as the primary endpoints for clinical trials and reported in product labels. The committee suggested that there would be value in also assessing and reporting the proportion of patients attaining low disease activity. However the committee did not endorse any of the specific measures mentioned under i, ii or iii above. Rather the committee suggested that an effort underway by the American College of Rheumatology would soon publish guidelines for assessing low disease activity that could be considered. Additionally, the committee suggested that future studies may want to consider identifying different thresholds for low disease activity for patients with different levels of disease duration.

The meeting adjourned at approximately 3:00 p.m.