



**Summary Minutes of the Arthritis Advisory Committee Meeting  
June 21, 2011**

The following is the final report of the Arthritis Advisory Committee meeting held on June 21, 2011. A verbatim transcript will be available in approximately four 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/ucm256293.htm>

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

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The Arthritis Advisory Committee (AAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on June 21, 2011 at the Marriott Inn and Conference Center, University of Maryland University College (UMUC), Hyattsville, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and Novartis Pharmaceutical Corporation. The meeting was called to order by Kathleen O'Neil, M.D. (Chair). The conflict of interest statement was read into the record by Philip Bautista, Pharm.D. (Designated Federal Officer). There were approximately 150 people in attendance. There were five Open Public Hearing speakers.

**Issue:** The committee discussed the supplemental biologics license application 125319 for Ilaris (canakinumab) by Novartis Pharmaceuticals for the "treatment of gouty arthritis attacks in patients who cannot obtain adequate response with NSAIDS or colchicine. Ilaris has also been shown to extend the time to next attack and reduce the frequency of subsequent attacks."

**Attendance:**

**AAC Members Present (Voting):** David Blumenthal, M.D.; Lenore Buckley, M.D., M.P.H.; Ted Mikuls, M.D., M.S.P.H.; Kathleen O'Neil, M.D. (Chair)

**AAC Members Not Present (Voting):** Robert Kerns, Ph.D.; Nancy Olsen, M.D.

**AAC Members Present (Non-Voting):** Mark Fletcher, M.D. (Industry Representative)

**Temporary Members (Voting):** Diane Aronson (Acting Consumer Representative); David Felson, M.D., M.P.H.; Allan Gibofsky, M.D., J.D.; Gail Kerr, M.D.; Tuhina Neogi, M.D., Ph.D.; Peter Peduzzi, Ph.D.; Richard Snarsky (Patient Representative); Maria Suarez-Almazor, M.D., Ph.D.

**FDA Participants (Non-Voting):** Curtis Rosebraugh, M.D.; Badrul Chowdhury, M.D., Ph.D.; Sarah Okada-Yim, M.D.; Larissa Lapteva, M.D., M.H.S.; Ruthanna Davi, Ph.D.

**Designated Federal Officer:** Philip Bautista, Pharm.D.

**Open Public Hearing Speakers:** Michael Carome, M.D. (Public Citizen); Scott T. Williams (Men's Health Network); Burton Abrams; Seth D. Ginsberg (Global Healthy Living Foundation); Michael O'Grady

*The agenda proceeded as follows:*

Call to Order  
Introduction of Committee

**Kathleen O’Neil, M.D.**  
Chair, AAC

Conflict of Interest Statement

**Philip A. Bautista, Pharm.D.**  
Designated Federal Officer

Opening Remarks

**Sarah Yim, M.D.**  
Clinical Team Leader, Division of Pulmonary,  
Allergy & Rheumatology Products (DPARP)  
Office of Drug Evaluation II (ODE-II)  
Office of New Drugs (OND), CDER, FDA

**SPONSOR PRESENTATIONS**

**Novartis Pharmaceuticals Corporation**

Introduction

**Trevor Mundel, M.D., Ph.D.**  
Global Head of Development, Novartis Pharma AG

Gouty Arthritis: Unmet Medical Need

**N. Lawrence Edwards, M.D.**  
Professor and Program Director- Vice Chairman  
Department of Medicine University of Florida

Dose Selection and Efficacy

**Marjorie Gatlin, M.D.**  
VP, Head of Cardiovascular, Metabolism &  
Inflammatory Diseases Medical Unit  
Novartis Pharmaceuticals Corporation

Safety

**Michael Shetzline, M.D., Ph.D.**  
Global Program Head, Novartis Pharma AG

Benefit-Risk: Clinical Perspective

**Robert L. Wortmann, M.D.**  
Professor of Medicine, Rheumatology  
Dartmouth Medical School

Clarifying Questions for the Sponsor

**BREAK**

**FDA PRESENTATIONS**

Efficacy and Safety Considerations

**Larissa Lapteva, M.D., M.H.S.**  
Clinical Reviewer  
DPARP, ODE-II, OND, CDER, FDA

Statistical Considerations

**Ruthanna Davi, Ph.D.**  
Statistical Reviewer  
Division of Biometrics II (DB-II)  
Office of Biostatistics (OB)  
Office of Translational Sciences, CDER, FDA

Clarifying Questions for FDA

**LUNCH**

Open Public Hearing

Charge to the Committee

**Sarah Yim, M.D.**

Discussion/Questions to the Committee

**ADJOURNMENT**

***Questions to the Committee:***

- 1) Discuss the efficacy data of canakinumab for gout considering the following:
  - a. The dose ranging data and whether doses lower than 150 mg should be explored further.
  - b. Whether the proposed regimen (150 mg subcutaneous single-dose, with re-treatment on demand) represent acute treatment, or a more chronic treatment.
  - c. The limited information regarding repeat dosing and whether additional data on repeat dosing over time should be obtained, particularly in light of the intended population of patients, who may be at risk for more frequent flares (patients in the studies had an average of 6-7 acute flares in the previous year).

***Committee Discussion:*** *The committee concurred that the efficacy data for the 150 mg dose is robust, thus there is no need to explore lower doses for the acute treatment indication. It was noted that there was a significant difference in efficacy between the 90 mg dose and 150 mg dose, and that the 150mg dose was the most efficacious. Based on its pharmacokinetic profile, this drug appears to be more appropriate for patients who have recurrent gouty flares, and not for patients who do not need more chronic treatment. However, the committee agreed that there is limited data regarding repeat dosing. Some members felt that additional exploration of the lower dosing may be beneficial for the flare prophylaxis trial, where more chronic dosing will be employed. The committee recommended that if a patient registry were to be implemented as suggested by the Sponsor, then patients should be followed for the duration of at least 2-3 years. Please see the transcript for details of the Committee discussion.*

- 2) Discuss the overall safety profile of canakinumab for gout considering the following:
  - a. Safety signals of infections, increase in uric acid level, decline in renal function, and hypertriglyceridemia.
  - b. Potential risk of using canakinumab for gout on acute recurrent basis.

***Committee Discussion:*** *The committee concurred that the overall safety profile does not necessarily reflect the fact that canakinumab might be used repeatedly. Regarding the safety signals, the committee agreed that infection is the side effect of most concern and should be monitored, while the issue of hyperuricemia may not be a long term risk and may not be of much clinical significance. Additionally, the committee concurred that the decline in renal function has not been shown to be a clinical risk with the data provided. However, it was noted that patients who were older, at increased risk for infection, and have severe renal issues, were excluded from the trials. Per the committee, these types of patients represent the population that needs this drug. Therefore, more studies are warranted. Regarding the potential risk associated with acute recurrent use, the committee*

concluded that the use of this product might improve quality of life at the risk of life-threatening side effects. Please see the transcript for details of the Committee discussion.

- 3) Considering the totality of data, has canakinumab at a dose of 150 mg subcutaneously demonstrated substantial evidence of efficacy for treatment of gouty arthritis attacks in patients who cannot obtain adequate response with non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine? (**Voting Question: YES/NO/ABSTAIN**)

YES: 11 NO: 1 ABSTAIN: 0

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

**Committee Discussion:** The majority of the committee agreed that canakinumab at a dose of 150 mg demonstrated substantial evidence of efficacy for treatment of gouty arthritis attacks in patients who cannot obtain adequate response with non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine. The committee member who voted “no” noted that there were substantial problems with the study exclusion criteria that did not lend to this. Please see the transcript for details of the Committee discussion.

- 4) Considering the totality of data, has canakinumab at a dose of 150 mg subcutaneously demonstrated substantial evidence of efficacy for the additional claim that canakinumab has shown to extend the time to next attack and reduce frequency of subsequent attacks? (**Voting Question: YES/NO/ABSTAIN**)

YES: 8 NO: 4 ABSTAIN: 0

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

**Committee Discussion:** The majority of the committee agreed that there was substantial evidence of efficacy for the additional claim that canakinumab at a dose of 150 mg has shown to extend the time to next attack and reduce frequency of subsequent attacks. Some of the members who voted “no” noted that the drug did extend the time to next attack, but the reduction of frequency of subsequent attacks was only a secondary endpoint in the study. Therefore, these members recommended that more trials be conducted with the reduction of frequency of subsequent attacks as the primary endpoint. Additional studies should also investigate if lower doses of canakinumab could also potentially reduce frequency of subsequent attacks. Please see the transcript for details of the Committee discussion.

- 5) Is the safety profile of canakinumab at a dose of 150 mg subcutaneously sufficient for approval for use as acute recurrent treatment of gout flares in the population who cannot obtain adequate response with NSAIDs or colchicine? (**Voting Question: YES/NO/ABSTAIN**)

YES: 0 NO: 12 ABSTAIN: 0

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

**Committee Discussion:** The committee unanimously agreed that the safety profile of canakinumab at a dose of 150 mg is not sufficient for approval for use as acute recurrent treatment of gout flares in the population who cannot obtain adequate response with NSAIDs or colchicine. The committee noted that there is a need for this type of drug; however, based on the data provided, canakinumab’s

risk-benefit would not be favorable in a broad patient population among patients who have other treatment options available to them, therefore, canakinumab should only be used in a very specific type of patient population, i.e. in those who can not tolerate NSAIDs and colchicine, and who are steroid-dependent with frequent recurrent flares. The indication, drafted by the Sponsor, is not restrictive enough to prevent improper use by practitioners. It was recommended that the labeling should state the product should be used in patients with 6-7 gouty flares per year. As discussed in question 2, more studies in a more complicated, refractory patient population are needed in order to further determine safety (i.e. patients with compromised renal function, elderly patients, steroid-dependent patients with tophaceous gout and frequent flares). In addition, it was noted that only 43 patients were observed for repeated dosing for only six months. Therefore, more studies are also needed to evaluate to evaluate the safety of this drug when used repeatedly in a larger group of patients and for a longer duration of time. Please see the transcript for details of the Committee discussion.

- 6) Do the efficacy and safety data provide substantial evidence to support approval of canakinumab at a dose of 150 mg subcutaneously for treatment of gouty arthritis attacks in patients who cannot obtain adequate response with NSAIDs or colchicine? (**Voting Question: YES/NO/ABSTAIN**)

YES: 1      NO: 11      ABSTAIN: 0

**Committee Discussion:** The majority of the committee agreed that the efficacy and safety data do not provide substantial evidence to support approval of canakinumab at a dose of 150 mg for treatment of gouty arthritis attacks in patients who cannot obtain adequate response with NSAIDs or colchicine. It was noted that although the drug has been shown to be efficacious, there is not enough long term safety data and data in high risk patients to support approval. The committee noted that further studies should evaluate patients who have cannot obtain adequate response with NSAIDs and colchicine and corticosteroids. The committee member who voted “yes” noted that this drug should be approved with a revised indication and a Risk Evaluation & Mitigation Strategy (REMS). Please see the transcript for details of the Committee discussion.

- 7) Do the efficacy and safety data provide substantial evidence to support approval of canakinumab at a dose of 150 mg subcutaneously for the additional claim that canakinumab has shown to extend the time to next attack and reduce frequency of subsequent attacks? (**Voting Question: YES/NO/ABSTAIN**)

YES: 0      NO: 12      ABSTAIN: 0

Please see the transcript for details of the Committee discussion.

**Committee Discussion:** The committee unanimously agreed the efficacy and safety data do not provide substantial evidence to support approval of canakinumab at a dose of 150 mg for the additional claim that canakinumab has shown to extend the time to next attack and reduce frequency of subsequent attacks. It was noted that there is not enough long term efficacy data and similar safety concerns as previously discussed. Please see the transcript for details of the Committee discussion.

The meeting was adjourned at approximately 3:45 p.m.