Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Arthritis Advisory Committee Meeting
May 8, 2012

Location: FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland

Issue: The committee discussed supplemental biologics license application 125249, ARCALYST (rilonacept) injection, Regeneron Pharmaceuticals, Inc., for the following proposed indication: "ARCALYST (rilonacept) is an interleukin-1 blocker indicated for the prevention of gout flares during initiation of uric-acid lowering therapy in adult patients with gout. ARCALYST has not been studied for longer than 16 weeks in this clinical setting."

These summary minutes for the May 8, 2012 Arthritis Advisory Committee meeting were approved on June 23, 2012.

I certify that I attended the May 8, 2012 Arthritis Advisory Committee meeting and that these minutes accurately reflect what transpired.

_____/s/_____
Philip Bautista, Pharm.D.
Designated Federal Officer, AAC

_____/s/_____
Lenore Buckley, M.D., M.P.H.
Chairperson, AAC

Summary Minutes of the Arthritis Advisory Committee Meeting
May 8, 2012

The following is the final report of the Arthritis Advisory Committee (AAC) meeting held on May 8, 2012. 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/ArthritisAdvisoryCommittee/ucm286552.htm

All external requests for the meeting transcript 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 May 8, 2012 at the FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the background materials from the FDA and Regeneron Pharmaceuticals, Inc. The meeting was called to order by Lenore Buckley, M.D., M.P.H. (Chairperson); the conflict of interest statement was read into the record by Philip Bautista, Pharm.D. (Designated Federal Officer). There were approximately 100 persons in attendance. There were three Open Public Hearing speakers.

Issue: The committee discussed supplemental biologics license application 125249, ARCALYST (rilonacept) injection, Regeneron Pharmaceuticals, Inc., for the following proposed indication: "ARCALYST (rilonacept) is an interleukin-1 blocker indicated for the prevention of gout flares during initiation of uric-acid lowering therapy in adult patients with gout. ARCALYST has not been studied for longer than 16 weeks in this clinical setting."

Attendance:
AAC Members Present (Voting): David Blumenthal, M.D.; Lenore Buckley, M.D., M.P.H. (Chairperson); Lisa Gualtieri, Ph.D. (Consumer Representative); Tuhina Neogi, M.D., Ph.D.; Irwin J. Russell, M.D., Ph.D.

AAC Members Not Present (Voting): Robert Kerns, Ph.D.; Robert Lahita, M.D.; Ted Mikuls, M.D.; Peter Peduzzi, Ph.D.

AAC Member Present (Non-Voting): Brian Kotzin, M.D. (Industry Representative)

Temporary Members (Voting): Vernon M. Chinchilli, Ph.D.; John J. Cush, M.D.; Sherine Gabriel, M.D., M.Sc.; David A. Schoenfeld, Ph.D.; Richard Snarsky (Patient Representative); Maria E. Suarez-Almazor, M.D., Ph.D.;

FDA Participants (**Non-Voting):** Badrul Chowdhury, M.D.; Ruthanna Davi, Ph.D.; Banu Karimi-Shah, M.D.; Sarah Yim, M.D.

Designated Federal Officer (Non-Voting): Philip Bautista, Pharm.D.

Open Public Hearing Speakers: Michael A. Carome, M.D. (Public Citizen); Brandon Leonard (Men's Health Network); Alexey Salamakha (Global Healthy Living Foundation)

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Lenore Buckley, M.D.** Chairperson, AAC
Conflict of Interest Statement	**Philip Bautista, Pharm.D.** Designated Federal Officer, AAC
FDA Introductory Remarks	**Sarah Yim, M.D.** 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	**Regeneron Pharmaceuticals, Inc.**
Introduction	**George Yancopoulos, M.D., Ph.D.** Chief Scientific Officer Regeneron Pharmaceuticals, Inc.
Gout: Disease Awareness and Unmet Medical Need	**Michael A. Becker, M.D.** Professor Emeritus of Medicine University of Chicago Pritzker School of Medicine
Clinical Development and Efficacy	**Steven Weinstein, M.D., Ph.D.** Clinical Therapeutic Area Head Immunology and Inflammation Clinical Development and Regulatory Affairs Regeneron Pharmaceuticals, Inc.
Safety	**Ned Braunstein, M.D.** Head Regulatory Affairs Clinical Development and Regulatory Affairs Regeneron Pharmaceuticals, Inc.
Clinical Perspective	**N. Lawrence Edwards, M.D., FACP, FACR** Professor of Medicine Vice Chairman, Department of Medicine University of Florida, Gainesville
Clarifying Questions to Sponsor	
BREAK	

FDA PRESENTATIONS

Overview of the Clinical Program	**Deborah Seibel, M.D.** Clinical Reviewer, DPARP ODE- II, OND, CDER, FDA
Statistical Summary of Efficacy and Safety	**Ruthanna Davi, Ph.D.** Statistical Reviewer Division of Biometrics II (DB-II) Office of Biostatistics (OB) Office of Translational Sciences (OTS) CDER, FDA
Efficacy, Safety, and Risk-Benefit Considerations	**Banu Karimi-Shah, M.D.** Clinical Team Leader, DPARP ODE-II, OND, CDER, FDA
Clarifying Questions to the FDA	

LUNCH

Open Public Hearing

Charge to the Committee	**Sarah Yim, M.D.**
Questions to the Committee and Committee Discussion	

BREAK

Questions to the Committee and Committee Discussion

ADJOURNMENT

1) **DISCUSSION:** Discuss the efficacy data of rilonacept for the prevention of gout flares.
   a. Include a discussion of the effect of rilonacept on flare frequency and duration, and whether the observed treatment effect provides adequate justification for the use of rilonacept to prevent gout flares in a gout population that is not intolerant of or refractory to non-steroidal anti-inflammatory drugs (NSAIDs) and/or colchicine.

      Committee Discussion: *The committee agreed that the observed treatment effect provides evidence of efficacy for the use of rilonacept to prevent gout flares. However, the committee stated that this effect is only modest. Additionally, the committee noted that the evidence was limited to the gout population that can tolerate and is not refractory to NSAIDs and/or colchicine and that this population is too broad. The committee stated that further studies are needed to determine the efficacy of rilonacept in refractory, difficult-to-treat, and intolerant patients, such as*

patients with tophaceous gout or patients with renal insufficiency. This would be the population that might benefit the most, and 16 weeks of treatment might not be an adequate duration for these patients.

b. Include a discussion of the clinical applicability of the proposed indication, addressing whether the efficacy data support treatment duration of 16 weeks.

Committee Discussion: *The committee agreed that the treatment duration of 16 weeks may not be adequate for many patients; particularly patients with difficult-to-treat disease, who would be most likely to benefit from this treatment, and that this drug product would likely be used for longer than 16 weeks in clinical practice.*

Please see the transcript for details of the committee discussion.

2) **DISCUSSION:** Discuss the safety profile of rilonacept for the prevention of gout flares.

a. Include a discussion of the malignancy imbalance.

Committee Discussion: *The committee agreed that it was difficult to draw conclusions from the numerical malignancy imbalance because the study may have been underpowered and of insufficient duration to evaluate malignancy. The committee further stated that the malignancy imbalance might have been due to chance and that some cases may have been pre-existing conditions. The committee added that infection was a concern with this agent, and the risk of infection in the setting of high-risk patients or patients receiving concomitant steroids with rilonacept was likely to be increased.*

b. Include a discussion of the adequacy of the currently available 16-week safety database to support the proposed use.

Committee Discussion: *The committee agreed that the currently available 16-week safety database is not adequate. The committee stated that this drug would likely be used beyond the 16 weeks in the proposed indication. The committee agreed that studies with durations longer than 16 weeks and studies that included more refractory and intolerant patients were necessary to further elucidate the safety of rilonacept.*

Please see the transcript for details of the committee discussion.

3) **VOTE:** Are the available efficacy data adequate and supportive of approval of rilonacept for the prevention of gout flares during the initiation of uric acid-lowering therapy in adult patients with gout?

Vote: ***Yes = 6*** ***No = 5*** ***Abstain = 0***

Committee Discussion: *The committee disagreed on whether the available efficacy data support approval of rilonacept for prevention of gout flares during the initiation of uric acid-*

lowering therapy in adult patients with gout. Those who voted "Yes" agreed that the efficacy data was supportive and statistically significant. Those who voted "No" expressed concern that the indicated population was not really representative of the population in which this product would be used and that efficacy data lacked context versus other available alternatives.

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

Committee Discussion: *The committee members who voted "No" stated that more efficacy data was needed in patients who are intolerant of or refractory to standard therapy, have more severe forms of gout (tophaceous), and low renal function. It was noted that equivalence trials would be helpful; however, it was acknowledged that these types of trials are not a regulatory requirement and are difficult to perform.*

Please see the transcript for details of the committee discussion.

4) **VOTE:** Are the available safety data adequate and supportive of approval of rilonacept for the prevention of gout flares during the initiation of uric acid-lowering therapy in adult patients with gout?

Vote: Yes = 3 No = 8 Abstain = 0

Committee Discussion: *Those who voted "Yes" did so because they felt the safety in the proposed population for the 16 week duration was adequate and supportive. However, the majority of the committee voted "No" out of concerns that rilonacept would be used in a population and for a duration which were not studied—namely in a higher risk, more severe population for longer periods of time. Even then, these committee members agreed that there was adequate and supportive safety data for the population and use studied and for the limited duration of 16 weeks.*

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

Committee Discussion: *The committee agreed that studies with durations longer than 16 weeks and studies that included more refractory and intolerant patients were warranted.*

Please see the transcript for details of the committee discussion.

5) **VOTE:** Do the efficacy and safety data support the approval of rilonacept 80 mg subcutaneously once weekly (following a 160 mg loading dose) for 16 weeks for the prevention of gout flares during the initiation of uric acid-lowering therapy in adult patients with gout?

Vote: Yes = 0 No = 11 Abstain = 0

Committee Discussion: *The committee unanimously agreed that the efficacy and safety data do not support the approval of rilonacept 80 mg subcutaneously once weekly (following a*

160 mg loading dose) for 16 weeks for the prevention of gout flares during the initiation of uric acid-lowering therapy in adult patients with gout.

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

Committee Discussion: *The committee agreed that there is a role for this type of agent in the treatment of gout. However, the committee stated that more efficacy data and long term safety data was needed in patients who are intolerant of or refractory to standard therapy, have more severe forms of gout (tophaceous), and low renal function. The committee also stated that these studies should have treatment durations and follow-ups longer than 16 weeks.*

Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 3:35 p.m.