# Food and Drug Administration
# Center for Drug Evaluation and Research

## Summary Minutes of the Arthritis Advisory Committee Meeting
## March 12, 2012

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

Issue: The committee discussed the anti-nerve growth factor (anti-NGF) drug class that is currently under development and the safety issues possibly related to these drugs. These drugs are being developed for the treatment of a variety of chronic painful conditions including osteoarthritis, chronic lower back pain, diabetic peripheral neuropathy, post-herpetic neuralgia, chronic pancreatitis, endometriosis, interstitial cystitis, vertebral fracture, thermal injury, and cancer pain. The committee was asked to determine whether reports of joint destruction represent a safety signal related to the anti-NGF class of drugs, and whether the risk benefit balance for these drugs favors continued development of the drugs as analgesics.

These summary minutes for the March 12, 2012 Arthritis Advisory Committee Meeting were approved on May 22, 2012.

I certify that I attended the March 12, 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.
Chair, AAC

**Summary Minutes of the Arthritis Advisory Committee Meeting**
**March 12, 2012**

The following is the final report of the Arthritis Advisory Committee meeting held on March 12, 2012. A verbatim transcript will be available in approximately six weeks, sent to the Division of Anesthetic, Analgesic and Addiction Products and posted on the FDA website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/ucm286552.htm

All external requests for the meeting transcript 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 March 12, 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, Pfizer Inc., Janssen Research and Development L.L.C., and Regeneron Pharmaceuticals, Inc. The meeting was called to order by Lenore Buckley, M.D., M.P.H. (Chair); the conflict of interest statement was read into the record by Philip Bautista, Pharm.D. (Designated Federal Officer). There were approximately 200 persons in attendance. There were three (3) Open Public Hearing speakers.

**Issue:** The committee discussed the anti-nerve growth factor (anti-NGF) drug class that is currently under development and the safety issues possibly related to these drugs. These drugs are being developed for the treatment of a variety of chronic painful conditions including osteoarthritis, chronic lower back pain, diabetic peripheral neuropathy, post-herpetic neuralgia, chronic pancreatitis, endometriosis, interstitial cystitis, vertebral fracture, thermal injury, and cancer pain. The committee was asked to determine whether reports of joint destruction represent a safety signal related to the anti-NGF class of drugs, and whether the risk benefit balance for these drugs favors continued development of the drugs as analgesics.

**Attendance:**
**AAC Members Present (Voting):** David Blumenthal, M.D.; Lenore Buckley, M.D., M.P.H. (Chair); Robert Lahita, M.D.; Ted Mikuls, M.D.; Tuhina Neogi, M.D., Ph.D.

**AAC Members Not Present (Voting):** Lisa Gualtieri, Ph.D. (Consumer Representative); Robert Kerns, Ph.D.; Peter Peduzzi, Ph.D.; Irwin J. Russell, M.D., Ph.D.; Carol Wallace, M.D.

**Temporary Members (Voting):** Warren Bilker, Ph.D.; John Block, M.D.; Mark Bothwell, Ph.D.; Brendan Boyce, M.B., Ch.B.; Susan Broyles, R.N. (Patient Representative); Thomas Clemens, Ph.D.; Penney Cowan (Acting Consumer Representative); Sherine Gabriel, M.D.; Louis Gerstenfeld, Ph.D.; Mustafa Haque, M.D.; John Kelly, M.D.; Jasvir.Khurana, M.D.; Elaine Morrato, Dr.P.H, M.P.H., C.P.H.; James Neaton, Ph.D.; Maria Suarez-Almazor, M.D..; Eric Walker, M.D.

**Acting Industry Representative to the Committee (Non-Voting):** Richard Leff, M.D. (Acting Industry Representative)

**Speaker (Non-Voting):** Joan Bathon, M.D.

**FDA Participants** (**Non-Voting):** Ellen Fields, M.D.; Sharon Hertz, M.D.; Bob Rappaport, M.D.; Curtis Rosebraugh, M.D.

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

**Open Public Hearing Speakers:** Michael A. Carome, M.D. (Public Citizen); Julian Phillips; Seth D. Ginsberg (Global Healthy Living Foundation)

***The agenda proceeded as follows:***

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| Call to Order and Introduction of Committee | **Lenore Buckley, M.D.**<br>Chair, AAC |
| Conflict of Interest Statement | **Philip Bautista, Pharm.D.**<br>Designated Federal Officer, AAC |
| FDA Introductory Remarks | **Bob Rappaport, M.D.**<br>Director<br>Division of Anesthesia, Analgesia and Addiction Products (DAAAP)<br>Office of Drug Evaluation II (ODE II)<br>Office of New Drugs (OND), CDER, FDA |
| **INDUSTRY PRESENTATIONS** | |
| Introduction | **Ken Verburg, Ph.D.**<br>Senior Vice President<br>Medicines Development Group<br>Pfizer, Inc. |
| Perspectives on Chronic Pain | **Tom Schnitzer, M.D., Ph.D.**<br>Professor of Medicine<br>Northwestern University, Feinberg School of Medicine |
| Tanezumab | **Ken Verburg, Ph.D.** |
| Fulranumab | **David Upmalis, M.D.**<br>Senior Director, Neuroscience<br>Janssen Research and Development, L.L.C. |
| REGN475 | **Ned Braunstein, M.D.**<br>Executive Director, Regulatory<br>Regeneron Pharmaceuticals, Inc. |

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| Concluding Remarks | **Nathaniel Katz, M.D.**<br>President, Analgesic Solutions |

Clarifying Questions to Industry

**BREAK**

**FDA PRESENTATION**

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| The Natural History of Osteoarthritis and Potential Causes of Joint Destruction | **Janet W. Maynard, M.D., M.H.S.**<br>Clinical Reviewer<br>Division of Pulmonary, Allergy, and Rheumatology Products<br>ODE II, OND, CDER, FDA |
| Anti-NGF Drug Class Efficacy and Safety | **Anjelina Pokrovnichka, M.D.**<br>Medical Officer, DAAAP<br>ODE II, OND, CDER, FDA |
| CDRH Adjudication Review | **Nona T. Colburn, M.D.**<br>Medical Officer<br>Restorative Devices Branch<br>Division of Surgical, Orthopedic, and Restorative Devices<br>Office of Drug Evaluation<br>Center for Devices and Radiological Health (CDRH), FDA |

**LUNCH**

**SPEAKER PRESENTATION**

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|---|---|
| Adverse Articular Events in Studies of Anti-NGF Agents | **Joan M. Bathon, M.D.**<br>Professor of Medicine<br>Director, Division of Rheumatology<br>Columbia University College of Physicians and Surgeons |

Clarifying Questions to the FDA and Speaker

Open Public Hearing Session

**BREAK**

Charge to the Committee

Questions to the Committee/Committee Discussion

**ADJOURNMENT**

***Questions to the Committee:***

1) **DISCUSSION:** The data presented today describe a safety signal seen in clinical studies of anti-nerve growth factor (anti-NGF) agents that are under development for the treatment of pain due to a variety of disorders. Please discuss whether these adverse events of painful, rapid joint destruction are occurring with an unusually high incidence in the populations studied and/or are unusually severe compared to joint-related events that occur in this population.

   ***Committee Discussion:*** *The committee agreed that the adverse events of painful, rapid joint destruction occurred with an unusually high incidence in the populations studied and are unusually severe compared to joint-related events that occur in this population. The committee also agreed that the pathology of these events is not yet clear and noted that these events occurred in patients without a previous history of osteoarthritis. Please see the transcript for details of the committee discussion.*

2) **DISCUSSION:** Do you agree with the sponsors' interpretation of the data which states that:

   a) Rapidly Progressing Osteoarthritis (OA) has been identified as a safety signal in the tanezumab and fulranumab clinical programs.

      ***Committee Discussion:*** *The committee agreed that destructive joint events have been identified as a safety signal in the tanezumab and fulranumab clinical programs.*

   b) Osteonecrosis does not represent a safety signal.

      ***Committee Discussion:*** *The committee could not agree with the statement that osteonecrosis does not represent a safety signal as there is not enough data to suggest this.*

   c) Rapidly progressive osteoarthritis type 2 (Pfizer) is a relatively distinct finding in the tanezumab studies.

      ***Committee Discussion:*** *The committee agreed that rapidly progressive osteoarthritis 2 is a relatively distinct finding in the tanezumab studies.*

   d) Anti-NGF agents may represent an advantage in terms of efficacy over other analgesics for the treatment of OA and other painful conditions.

      ***Committee Discussion:*** *The committee agreed that that there is a need for newer classes of analgesics, and they agreed that this anti-NGF drug class has the potential to meet this need. However, some members of the committee commented that the anti-NGF drug products have demonstrated only a modest advantage in terms of efficacy over other analgesics for the treatment of OA. Additionally, it was*

*noted that efficacy of the anti-NGF products was not well evaluated in other painful conditions thus there is not enough data to suggest this in other painful conditions.*

e) The risk-benefit profile of tanezumab monotherapy in the treatment of OA is favorable compared to treatment with placebo, non-steroidal anti-inflammatory drugs (NSAIDS), or extended-release oxycodone.

***Committee Discussion:*** *The committee could not agree with the statement that the risk-benefit profile of tanezumab monotherapy in the treatment of OA is favorable compared to treatment with placebo, non-steroidal anti-inflammatory drugs (NSAIDS), or extended-release oxycodone as there is not enough data to support this claim. The committee stated that more studies are required to make a final determination.*

f) The risk-benefit profile of tanezumab/NSAID combination therapy is unfavorable compared to NSAID treatment alone and to tanezumab monotherapy.

***Committee Discussion:*** *The committee agreed that the risk-benefit profile of tanezumab/NSAID combination therapy is unfavorable compared to NSAID treatment alone and to tanezumab monotherapy.*

g) The data suggest that many events were pre-existing or associated with a subchondral insufficiency fracture of the knee or atrophic OA of the hip.

***Committee Discussion:*** *The committee agreed that the data suggest that many events were pre-existing or associated with a subchondral insufficiency fracture of the knee or atrophic OA of the hip. However, the committee also noted that these events also occurred in joints not affected by OA. One panel member commented that not all joints were systematically evaluated at baseline.*

h) NSAID use up to 90 days did not elevate risk.

***Committee Discussion:*** *The committee could not agree with the statement that NSAID use up to 90 days did not elevate risk as there was not enough data since NSAID use was not well captured in the studies.*

i) The data suggest that a possible mechanism for this safety signal is an increased load on a susceptible joint in the presence of pain relief.

***Committee Discussion:*** *The committee could not agree with the statement that the data suggest that a possible mechanism for this safety signal is an increased load on a susceptible joint in the presence of pain relief.*

*Please see the transcript for details of the committee discussion.*

3) **DISCUSSION:** Anti-NGF agents have been studied in a variety of conditions that represent very large populations, such as osteoarthritis and low back pain, with a number of approved therapies, and also in smaller populations that lack effective therapies, such as interstitial cystitis. Considering what is known thus far about the risks and benefit associated with this class of biologic agents, are there any populations for which further clinical development would be acceptable? If yes, discuss which specific patient populations/painful conditions may be appropriate for further study, as defined below.

***Committee Discussion:*** *The committee agreed that considering what is known thus far about the risks and benefit associated with this class of biologic agents, further clinical development of anti-NGF agents could be acceptable in patient populations with pain disorders in which currently available therapies are inadequate, unless a patient is at high risk for joint destruction. The committee stated that more information is needed concerning which patient populations are at the most risk for these adverse drug events. Please see the transcript for details of the committee discussion.*

a) **VOTE:** There are approved agents that have demonstrated efficacy in reducing pain intensity in conditions such as osteoarthritis. Based on the risks-benefit profile of these agents, is there a role for the ongoing development of the anti-NGF agents?

***Vote: Yes= 21 No = 0 Abstain = 0***

***Committee Discussion:*** *Based on the risks-benefit profile of these agents, the committee unanimously agreed that there is a role for the ongoing development of the anti-NGF agents. The committee agreed that further studies are needed to elucidate which patient populations would benefit from this drug as well as the pathology behind the adverse events. The committee stated that any further clinical studies would be contingent upon a risk minimization strategy that would exclude patients who are predisposed to osteonecrosis and include informed consent detailing the adverse events. Please see the transcript for details of the committee discussion.*

i) **DISCUSSION:** Please discuss whether the anti-NGF agents should be studied only in patients refractory to current standard of care.

***Committee Discussion:*** *The committee did not agree that the anti-NGF agents should be studied only in patients refractory to current standard of care. Given its unique mechanism of action, the committee stated that this class of agents has the potential to be opioid-sparing and should not be limited to refractory cases. Please see the transcript for details of the committee discussion.*

b) **VOTE:** Is there a role for the ongoing development of anti-NGF agents to manage the pain associated with conditions for which there are no agents with demonstrated analgesic efficacy, such as interstitial cystitis or chronic pancreatitis?

***Vote: Yes= 20 No = 1 Abstain = 0***

***Committee Discussion:*** *The majority of the committee agreed that there is a role for the ongoing development of anti-NGF agents to manage pain associated with conditions for which there are no agents with demonstrated analgesic efficacy, such as interstitial cystitis and chronic pancreatitis. The committee agreed that more data is needed on the risk to bone and joints caused by this class of agents so that this risk can be mitigated by appropriate measures. Please see the transcript for details of the committee discussion.*

i) **DISCUSSION:** Please discuss whether the anti-NGF agents should be studied only in patients refractory to other treatments.

***Committee Discussion:*** *Considering question #3, the committee agreed that further discussion on this question was not warranted since it was redundant.*

4) If clinical trials are allowed to proceed:

a) **DISCUSSION:** What screening procedures, safety monitoring and follow-up assessments should be included in the studies?

***Committee Discussion:*** *In order to follow the progression of effects on joints, the committee agreed that extensive radiographs of target joints (hips, knees, shoulders) should be monitored at baseline, through the duration of the trials, and during at least 6 months of follow-up post-trials. The committee also agreed that Magnetic Resonance Imaging (MRI) should also be used during baseline and follow-up in order to collect data on bone, cartilage, and tendons (possible tendon rupture). It was commented that bone mineral density and biochemical bone markers should be measured in order to study the metabolic effects of the anti-NGF agents on bone. The committee agreed that long-term studies on propioceptive, kinesthetic, and neurological effects of these drugs should be performed especially after patients come off of these agents, and that number of falls should be collected during any trials. The committee also recommended that the sponsors should make use of a central lab to review histology, radiology, and pathology data so that there is consensus on the findings. The committee further agreed that certain patient populations, such as diabetics, should be excluded from these trials. Please see the transcript for details of the committee discussion.*

b) **DISCUSSION:** Do the data support allowing clinical trials to proceed with some amount of concurrent NSAID use?

***Committee Discussion:*** *The committee could not come to a consensus on whether the data supports allowing clinical trials on the anti-NGF agents to proceed with concurrent NSAID use, whether intermittent or chronic. Some members of the committee agreed that concurrent use with NSAIDS should be avoided, while others agreed that their concurrent use should be further studied, although cautiously, given that low doses of NSAIDS (e.g. aspirin) are used prevalently throughout the population. Please see the transcript for details of the committee discussion.*

i) **DISCUSSION:** If clinical trials study limited concurrent NSAID use, can NSAID use be limited post-approval?

***Committee Discussion:*** *The committee agreed that there would be difficulties in limiting concurrent NSAID use post-approval. However, the committee agreed that the use of Risk Evaluation and Mitigation Strategies (REMS) or other programs might be helpful in order to communicate and educate patients about these risks. Please see the transcript for details of the committee discussion.*

When answering the above questions, the committee referred to the sponsors' proposed safety measures outlined in the Regeneron Pharmaceuticals, Inc.'s slide presentation.

5) **DISCUSSION:** Are there additional nonclinical studies that can be conducted that may provide additional insight into the possible etiologies for the bone and joint adverse events noted during the clinical development of these anti-NGF agents?

***Committee Discussion:*** *The committee agreed that additional non-clinical studies should be conducted in order to provide additional insight into the possible etiologies for the bone and joint adverse events noted during the clinical development of these anti-NGF agents. The committee agreed that these additional non-clinical studies should look at the vascular effect, neurological and neurotoxic effects, effects on bone biomarkers, and histological effects from fractures. The committee also stated that these studies should also look at which receptors on other tissue may be responsive the anti-NGF agents or have toxic effects. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:35 p.m.