FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

Background Materials

Meeting of the
Arthritis Advisory Committee (AAC)

FDA White Oak Campus-Building 31 Great Room
Silver Spring, MD

March 12, 2012

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. The committee will be asked to discuss safety findings associated with the Anti-Nerve Growth Factor products under development for the treatment of chronic pain, and to weigh the risk versus benefit of continuing to develop these products for this indication. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Division Director Memo

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

M E M O R A N D U M

DATE: February 13, 2012

FROM: Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Arthritis Advisory Committee (AAC)

RE: Overview of the March 12, 2012, AAC Meeting to Discuss Safety Issues Related to the Anti-Nerve Growth Factor Agents

At this meeting of the AAC, we will be discussing a safety signal identified during the clinical development of anti-nerve growth factor (anti-NGF) agents being studied primarily for the treatment of chronic pain associated with osteoarthritis (OA), and the impact of this signal on the overall risk-benefit assessment of these agents. Having a public discussion of this topic at an advisory committee meeting is unusual in that these products are still in the Investigational New Drug (IND) phase of development and are not already approved or under review as New Drug Applications (NDAs).

NGF has an established role in promoting the survival and development of sensory and sympathetic neurons. More recently, NGF has been proposed to play an important role in various pain states based on evidence from in vitro and in vivo models as well as knowledge of rare genetic mutations in humans in which disruptions in NGF signaling confer insensitivity to pain. NGF may induce hyperalgesia in various disease states through multiple molecular mechanisms which ultimately result in sensitization of peripheral nociceptors, axonal sprouting and sensory and sympathetic fiber innervation into damaged tissues. Therefore, anti-NGF agents are designed to attenuate this

process and represent a potentially significant and novel strategy for the treatment of pain. NGF has also been proposed to play additional physiological roles, including the promotion of wound repair, tissue remodeling, and angiogenesis. It is uncertain if the safety signal under consideration today may be a result of interfering with these proposed beneficial activities.

There are three Sponsors that have conducted clinical trials with anti-NGF agents, Pfizer (tanezumab), Janssen (fulranumab), and Regeneron (REGN475). These drugs are all monoclonal antibodies directed against nerve growth factor, and are being developed for the treatment of a variety of chronic painful conditions including osteoarthritis, chronic low back pain, diabetic peripheral neuropathy, post-herpetic neuralgia, chronic pancreatitis, chronic prostatitis, endometriosis, interstitial cystitis, vertebral fracture, thermal injury, and cancer pain. Pfizer has the largest subject exposure to date having conducted a number of Phase 3 studies, while Janssen and Regeneron are in Phase 2 of clinical development.

In April, 2010, the Division became aware of a potential safety signal based on reports of unusual and unexpected joint-related adverse events in tanezumab-treated patients with osteoarthritis in ongoing and completed Phase 2 and 3 trials being conducted in support of the OA indication. These events were reported as osteonecrosis and avascular necrosis (AVN), all leading to joint replacement. There were no cases reported for patients who received placebo or active comparator. In addition, for several cases, the affected joint was not the index joint identified in the trial. (Also, reports of non index joint AVN of the shoulder were received between April, 2010 and July, 2011) In addition to the AVN reports, several cases of atraumatic (pathological) bone fracture were reported, all in subjects exposed to tanezumab. In June 2010, the tanezumab OA and chronic low back pain development programs were placed on clinical hold.

In December, 2010, a pathologically verified case of AVN of the hip was reported by Janssen in a patient with no known history of OA exposed to fulranumab in a study of chronic low back pain. Between December, 2010 and January, 2011, the Agency placed the three active INDs for the anti-NGF agents on clinical hold. The concern was that these serious, irreversible events of joint destruction appeared to be due to an anti-NGF antibody drug class effect. However, studies were allowed to proceed in terminal cancer patients with intractable severe pain due to bone metastases, where the benefit of the treatment might outweigh the risks.

Janssen and Pfizer submitted complete responses to the clinical holds, in June and July of 2011, respectively. These submissions included adjudication of all reports of joint replacements, in order to determine the nature of the events leading to joint replacement, and whether there is an actual safety signal related to treatment with these agents. Both Sponsors assembled independent expert committees to conduct the adjudications according to prespecified protocols. You will be hearing the results of these adjudications during this meeting. Regeneron also submitted additional information regarding reports of joint replacements during their trials. The Sponsors agree that there is a signal. However, based on the adjudication and evaluation of the

Pfizer data, they believe the events are correlated with concomitant NSAID use, and that the risk can, therefore, be mitigated.

In order to determine whether we are in agreement with the adjudication conducted by the Sponsors, the Agency also conducted two separate adjudications of the joint replacement cases using the data provided by the Sponsors, one internal to the Agency, and one by an external academic expert. The approach taken by the Agency adjudicators was similar, but not identical to that taken by the Sponsors. The methods and results of the Agency adjudications will be presented during the meeting.

During this meeting, details regarding the overall safety profile of the anti-NGF agents, including an in depth description of the occurrence of serious joint-related events in the clinical studies, will be presented along with the results of the efficacy analyses from these studies. You will be asked to discuss the findings, and to weigh the risk versus benefit of continuing to develop the products for the treatment of chronic pain. If you determine that the risk-benefit profile favors continued clinical development, you will then be asked to address which specific patient populations may be appropriate for study, and what precautions should be included in clinical studies to ensure the safety of the subjects. Please keep in mind that the exact diagnoses, be they osteonecrosis, rapidly progressing arthritis, or another cause of joint destruction, for these unusual events, are not as important as the determination that there is an unusual, unexpected and serious adverse event occurring in the patients receiving anti-NGF agents that is resulting in joint destruction requiring replacement.

Although it would be ideal to be able to include the results and interpretation of the Agency's adjudications in this background package, due to restraints in time and resources, the processes that must be followed regarding disclosure of sponsor data, and the large amount of data to be reviewed by our adjudicators, this is not possible. Over the next few weeks we anticipate sending you background addenda that will include the results of the adjudications and our analyses of the findings.

I am grateful for your participation and thank you in advance for taking the time to provide your expertise and insights in order to assist us as we move forward with decisions regarding the continued development of the anti-NGF products as part of the analgesic armamentarium.

2 Draft Topics for Discussion

1. The data presented today describe a safety signal seen in clinical studies of 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.

2. Do you agree with the sponsors' interpretation of the data which states that:

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

    b. Osteonecrosis does not represent a safety signal.

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

    d. The benefit-risk profile of tanezumab monotherapy in the treatment of OA is favorable compared to treatment with placebo, NSAIDS, or extended-release oxycodone.

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

3. These 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, such as interstitial cystitis, that lack effective therapies. 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.

    a. There are approved agents that have demonstrated efficacy in reducing pain intensity in conditions such as osteoarthritis.

        i. Based on the risks-benefit profile of these agents, is there a role for the ongoing development of the anti-NGF agents?

ii. If so, should the osteoarthritis population studied be broad or should it be limited to patients unable to obtain relief or unable to tolerate NSAIDs, opioids or other available therapeutics?

b. Is there a role for the ongoing development of anti-NGF agents to manage the pain associated with conditions such as interstitial cystitis or chronic pancreatitis for which there are no agents with demonstrated analgesic efficacy. And, if so, should the anti NGF agents be studied only in patients refractory to other treatments?

4. If clinical trials are allowed to proceed, what screening procedures, safety monitoring and follow-up assessments should be included in the studies?

Pfizer has proposed the following:

a. Exclude chronic concomitant NSAID use with tanezumab

b. Exclude tanezumab 10 mg from further investigation in osteoarthritis and application of a more cautious approach to escalated doses in other non-osteoarthritic chronic pain conditions

c. Exclude patients with pre-existing rapidly progressive osteoarthritis from treatment with tanezumab

d. Discontinue patients who do not respond adequately to initial doses of tanezumab

e. Treat only those patients who have inadequate response or are intolerant to first-line therapy or patients who have contraindications for existing standard of care

f. Increased surveillance measures to be incorporated into all future studies of tanezumab:

i. Comprehensive evaluation of osteoarthritis medical history prior to study entry

(1) Pre-study assessment of joints with osteoarthritis (range of motion, pain in joints) to establish a baseline status

ii. Radiologic assessment of bilateral knee and hip for osteoarthritis structural disease

(1) All patients will undergo pre-study bilateral knee and hip x-rays

(2) All x-rays assessed by an expert Central Reader to determine patient eligibility for study participation

(3) Other joints may be included in pre-study assessments if signs or symptoms indicate presence of osteoarthritis

iii. Increased patient monitoring for severe persistent joint pain

(1) An interactive voice response system will be utilized to collect information from patients of severe persistent pain in non-index joints on a daily basis

(2) Patients with increased, severe, persistent joint pain during the study will undergo additional evaluation

iv. Pre-specified adjudication and protocol stopping rules for rapidly progressive osteoarthritis

(1) Events identified by Central Reader submitted for Adjudication Committee review

(2) A data safety monitoring board will conduct unblinded interim analyses according to pre-specified stopping rules

Janssen has proposed the following:

At baseline, the sponsor plans to collect the following information about potential risk factors:

a. Record use of NSAIDs prior to the study

b. X-rays of both joints for shoulders, hips and knees using standardized X-ray methods will be obtained and read centrally.

c. A comprehensive OA history, including signs and symptoms of OA and medical history will be obtained.

d. Serum and urine samples will be collected to study the potential association of biomarkers in the progression of OA (eg, those related to cartilage synthesis and degradation, bone synthesis and desorption, and markers of inflammation).

e. The presence of other possible risk factors for OA progression (e.g., congenital hip dysplasia, Legg-Calvé-Perthe's disease, gout, pseudo gout, various deformities, etc) will be documented.

The following ongoing assessments of subjects will be performed to monitor the potential risk of RPOA:

a. Monitor joint signs and symptoms

b. Obtain radiographic studies of each knee, shoulder, and hip at pre-defined scheduled times (e.g., annually)

c. Obtain radiographic studies as part of the diagnostic work-up for subjects who develop a sustained unexplained increase in OA symptoms
d. Continue to monitor post-treatment safety for 6 months after the last dose of study drug

e. Monitor OMERACT-OARSI Responder Index

The sponsor plans to collect the following subject-specific safety data to characterize all joint replacements and joint-related adverse events:

a. Additional joint imaging may be requested by the sponsor as part of the diagnostic work-up for joint-related adverse events

b. External sources of information that inform the assessment of joint-related adverse events may be required. These external sources of information may include consultation reports; operative reports; imaging (X-rays, MRIs, ultrasounds etc); and histology and/or tissue specimens

c. Extended follow-up post-study to detect safety signals

d. Extended follow-up after joint replacement surgery to assess impact of study treatment

e. Explore subject activity levels

Risk Reduction for the Individual Subject

a. Dosing of individuals can be stopped at any time by the investigator based on clinical assessment of joint-related adverse events.

b. Dosing of any individual subject will be held if a persistent and unexplained clinically significant joint-related event occurs. The subject will be assessed, and findings will be submitted to the independent Adjudication Committee for case review and recommendation if dosing needs to be either stopped or resumed.

c. Radiologic changes consistent with RPOA may be identified early based on increased frequency of surveillance radiographs and focused monitoring of change in joint symptoms

Risk Reduction for the Study Population as a Whole:

a. Limit concomitant chronic NSAID use.

b. Joint replacements and other joint-related adverse events (JRAEs) will be considered as events of interest

c. All JRAEs to be prospectively assessed by an independent Adjudication Committee (with expertise in rheumatology, orthopedics & radiology) as to diagnosis and relationship to study drug

d. The Adjudication Committee will provide advice/consultation to the Independent DMC who will provide a recommendation to the sponsor

e. Possibly institute a central Adjudication Committee for all sponsors a sponsor/drug-specific Independent DMC

f. Based on the benefit/risk profile, the Independent DMC will determine whether an individual dosing group or the study needs to be changed or stopped

Regeneron has proposed the following:

a. Informed consent of patients and appropriate communication of the data and potential risks to investigators, institutional review boards (IRBs), and any national health authorities where study is being considered.

b. Risk minimization by excluding high risk patients such as those with a history of rapidly progressive osteoarthritis (RPOA), subchondral fractures, or joint dysplasia; minimizing the dose of anti-NGF treatment and excluding concomitant chronic NSAIDs. In non-OA indications, because of the apparent need for higher doses of anti-NGF, we would also exclude patients with evidence of mechanical/structural joint diseases.

c. Restricting use to high unmet need populations until such time that the data support the study of additional populations. These include OA and non-OA pain patients (e.g. with cancer, neuropathic, thermal injury, or visceral pain conditions) demonstrated to have an insufficient response to standard of care; patients intolerant to or with contraindications (absolute or relative) to standard of care; and patients awaiting total joint

replacement (TJR) surgery (for example, with an anticipated wait of 3 to 9 months).

d. Demonstrating efficacy in the selected populations that is superior to other options available (e.g., in patients with inadequate response to NSAIDs, demonstrating clinically meaningful superiority to NSAIDs).

e. Determining long-term general safety of the potential long-term consequences of chronic NGF blockade (e.g., on peripheral nerves, motor functioning, edema).

f. Defining joint safety risks that remain after instituting the risk minimization strategies above. This would include intention-to-treat (ITT) follow-up of all patients for the intended duration of the study to 6 months after the last planned dose and assessment of operative complications and outcomes in TJR cases.

g. Additional risk factor characterization by improving the baseline assessment of joint status and collecting data on potential prognostic indicators such as carboxy-terminal collagen crosslinks (CTX) biomarkers, imaging (e.g., ultrasound to determine joint space dimensions), and actimetry to identify factors that might contribute to any residual risks of therapy with REGN475.

h. Risk management by discontinuing patients who develop sentinel findings such as subchondral fracture or accelerated joint space narrowing, and having an independent data monitoring committee (IDMC) assess the emerging data to identify additional risk factors and recommend actions.

5. 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?

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