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Testimony to the FDA's Arthritis Advisory Committee
on Safety Issues Related to Anti-Nerve Growth Factor Agents
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My name is Dr. Michael Carome, Deputy Director of Public Citizen's Health Research Group. I am testifying on behalf of myself and Dr. Sidney Wolfe, Director of Public Citizen's Health Research Group. We have no financial conflicts of interest.

We strongly urge the Food and Drug Administration (FDA) to permanently suspend the clinical development of these anti-nerve growth factor (anti-NGF) agents for the treatment of pain because of the dramatic safety signal seen in clinical studies of these agents demonstrating an unusually high incidence of rapid joint destruction.

In particular, we note the following:

(1) The occurrence of rapid joint damage with all three anti-NGF agents likely represents a class effect of these drugs.
(2) Data for tanezumab shows the risk of rapidly progressive osteoarthritis (OA) rises as the dose and duration of exposure increases.[1] While use of nonsteroidal anti-inflammatory drugs (NSAIDs) further increases the risk, the same trends in risk are apparent in subjects receiving tanezumab alone.
(3) Data for fulranumab also suggests a possible dose-response trend with respect to the incidence of joint replacement surgery in OA patients.[2]
(4) No adequately tested dose of any anti-NGF agent has failed to cause such adverse events.
(5) The FDA in its review of the available data note the following:[3]

> There appears to be a safety signal of rapid joint destruction … associated with both Anti-NGF agent monotherapy and Anti-NGF agent plus NSAID therapy. The incidence of this event is more pronounced in patients receiving both the Anti-NGF agent and NSAID concurrently, but is clearly present in both treatment groups. The occurrence of these events was markedly disproportional, favoring drug treatment over placebo treatment, which supports that these events of joint destruction are related to drug treatment, and are not occurring as part of the natural history of [OA]. In fact, some cases occurred in patients without a history of OA, which further supports this conclusion.

(6) The sponsors of the three anti-NGF agents seek to market them for treating chronic pain due to numerous common conditions. Widespread use of these drugs in the expected target populations will result in an epidemic of anti-NGF induced arthropathy.

In conclusion:

(1) Data for the anti-NGF agents confirm the appropriateness of the FDA's decision to place studies of these agents on clinical hold. There is no role for the further development of these drugs for anyone with OA. There are FDA-approved agents with demonstrated efficacy and acceptable risk-benefit profiles for treating OA. In contrast, anti-NGF agents have been shown to have an unacceptable risk-benefit profile. These agents, intended to treat a symptom of a non-life-threatening disorder, can actually accelerate the underlying disease process. Avoidance of co-treatment with NSAIDs and use of lower doses will not sufficiently limit this risk.
(2) There is also no role of ongoing development of anti-NGF agents for chronic pain from other conditions. Many patients with other disorders causing chronic pain have OA, a common disorder, and thus would be at risk for developing anti-NGF induced joint destruction. Furthermore, the adverse effects on joints can occur in the absence of OA.
(3) Given the existing data showing a serious and unusual safety signal with anti-NGF agents, it is inconceivable that the FDA would approve these drugs for long-term treatment of chronic pain.
(4) Therefore, further human studies of these agents would be unethical and not approvable under FDA regulations for the protection of human subjects because the risks outweigh the potential benefits to subjects and the importance of the knowledge (or lack thereof) that is expected to result.

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[1] Pfizer. Tanezumab Arthritis Advisory Committee briefing document. February 2, 2012. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM295205.pdf. Accessed March 8, 2012.

[2] Janssen Research & Development, L.L.C. Advisory committee briefing document: Briefing book for 12 March 2012 Arthritis Advisory Committee meeting: JNJ-42160443 (fulranumab). January 31, 2012. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM295204.pdf. Accessed March 8, 2012.

[3] Food and Drug Administration. Addendum to the background package for the March 12, 2012, AAC Meeting, regarding the agency adjudication of cases of joint replacements occurring in clinical trials of anti-NGF agents. March 2, 2012. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM295203.pdf. March 8, 2012.