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Dear Dr. Woodcock and Dr. Rappaport:

These comments from Public Citizen's Health Research Group are being submitted in follow-up to our testimony before the Food and Drug Administration's (FDA's) Arthritis Advisory Committee (AAC) on March 12, 2012, regarding anti-nerve growth factor (anti-NGF) drugs.

As stated in our testimony (copy enclosed), we strongly urge the FDA to permanently suspend the clinical development of these 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.

The data presented during the AAC meeting clearly demonstrated that anti-NGF drugs cause severe rapidly progressive arthropathy. Data for the most studied anti-NGF agent, tanezumab, showed that the risk of rapidly progressive arthropathy rose as the dose and duration of exposure increased.[1] While use of nonsteroidal anti-inflammatory drugs (NSAIDs) further increased the risk, the same dose- and duration-dependent increases in risk were apparent in subjects receiving tanezumab alone.

A majority of the AAC members noted that the incidence and severity of rapidly progressive arthropathy seen in anti-NGF subjects were both unusually high and represented a unique and significant safety signal.

There are two basic hypothesized mechanisms for this drug-induced adverse event. The first is that decreased sensation leads to more activity and trauma to an osteoarthritic joint, ultimately resulting in neuropathic joint damage. The second hypothesized mechanism is that anti-NGF agents are directly toxic to bones and/or tendons and ligaments. Direct bone toxicity could cause increased bone fragility, leading to subchondral fractures and joint collapse. Tendon or ligament toxicity could lead to increased tendon or ligament fragility, rupture, and joint subluxation. While both hypothesized mechanisms may play a role, several observations noted during the AAC appear to favor the latter mechanism:

(1) There appeared to be no association between the incidence of rapid joint destruction and the effectiveness of pain control in subjects receiving anti-NGF agents.
(2) Rapid joint destruction occurred in subjects receiving anti-NGF agents across all grades of osteoarthritis seen in study subjects at baseline (grades 2, 3, and 4 on the Kellgren-Lawrence scale).
(3) Rapidly progressive joint destruction was seen in some joints without baseline osteoarthritis and in some joints in which the development of such arthropathy is considered unusual (e.g., shoulder and foot).
(4) There were a significant number of tendon ruptures seen in subjects receiving anti-NGF agents who developed rapidly progressive joint destruction.
(5) One AAC member noted evidence that anti-NGF may interfere with angiogenesis, which could lead to bone ischemia and subsequent damage.

Although not discussed during the AAC meeting, it is important to note that given that NGF receptor expression occurs in a wide range of normal and malignant human tissues — both within and outside the nervous system[2] — other risks of harm, in addition to rapid joint destruction, may result from long-term inhibition of NGF and would likely become apparent after long-term exposure of large numbers of patients to these agents. For example, there are studies in animals suggesting that blocking NGF activity may cause neurodegeneration,[3] herpes simplex virus reactivation,[4] and pathological changes similar to those seen in Alzheimer's disease.[5]

We acknowledge the need to develop more effective and safer analgesic drugs. However, 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. Widespread use of these drugs in the expected target populations almost certainly would result in an epidemic of anti-NGF–induced arthropathy. Avoidance of co-treatment with NSAIDs and use of lower doses of anti-NGF drugs will not sufficiently limit this risk.

Therefore, further human studies of anti-NGF drugs 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. The FDA should reject the recommendation of the AAC to resume clinical development of these drugs for management of chronic pain.

Thank you for taking our comments into account when considering action on the further clinical development of anti-NGF drugs.

Sincerely,

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Enclosure

[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] Chesa PG, Rettig WJ, Thomson TM, et al. Immunohistochemical analysis of nerve growth factor receptor expression in normal and malignant tissues. J Histochem Cytochem. 1988;36:383-389.
[3] Capsoni S, Tiveron C, Amato G, et al. Peripheral neutralization of nerve growth factor induces immunosympathectomy and neurodegeneration in transgenic mice. J Alzheimer's Dis. 2010;20:527-546.
[4] Hill JM, Garza HH, Helmy MF, et al. Nerve growth factor antibody stimulates reactivation of ocular herpes simplex virus type 1 in latently infected rabbits. J Neurovirol. 1997;3:206-211.
[5] Calissano P, Matrone C, Amadoro G. Nerve growth factor as a paradigm of neurotrophins related to Alzheimer's disease. Develop Neurobiol. 2010;70:372-383.