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July 19, 2011

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
WO51/Room 6133
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Woodcock:

These comments from the Public Citizen Health Research Group (HRG) are being submitted to follow up on our testimony presented at the June 21, 2011 meeting of the Food and Drug Administration's (FDA) Arthritis Advisory Committee (AAC) regarding the supplemental Biologics License Application (sBLA) #125319 for the drug canakinumab (ILARIS).

Additional reasons for not approving canakinumab for acute gout attacks

(1) We urge the FDA to accept the June 21 AAC recommendations against approval of canakinumab at a dose of 150 milligrams (mg) for treatment of gouty arthritis attacks in patients who cannot obtain adequate response with nonsteroidal anti-inflammatory drugs (NSAIDs) or colchicine. Like the AAC, we oppose the approval of canakinumab, a potent immunosuppressant agent, for the treatment of gouty arthritis attacks because the drug has serious, life-threatening risks that far outweigh the drug's clinical benefits, which are limited primarily to relief of pain from acute gout flares in this patient population. A copy of our complete testimony before the AAC is enclosed.

(2) During the AAC meeting, FDA staff asked committee members whether any data from the already conducted clinical trials of canakinumab in gouty arthritis patients provide sufficient evidence of the safety and efficacy of canakinumab if the proposed indications for use were constructed for a more narrowly defined group of gouty arthritis patients (e.g., for treatment of gouty arthritis attacks in patients who failed or cannot tolerate treatment with NSAIDs, colchicine, and glucocorticosteroids). We think the existing data clearly are insufficient for approving canakinumab for treating any patients with gouty arthritis for the following reasons:

(a) Given the inclusion and exclusion criteria for enrollment of subjects in the already conducted studies, there are no efficacy data for canakinumab use in

treating acute gout attacks in an even more narrowly defined group of gouty arthritis patients. New clinical trials would need to be conducted in such a population.

(b) As we noted in our testimony, there are insufficient long-term safety data regarding "on-demand," repeat dosing of canakinumab, in *any* group of gouty arthritis patients. In the already conducted canakinumab trials, only 118 subjects with gout were treated with more than one injection of the proposed dose, and only 43 subjects were treated with more than two doses. Clinical trials involving multiple repeat doses of canakinumab, with collection of long-term safety data, would need to be conducted in gouty arthritis patients.

Concerns about ongoing clinical trials with canakinumab

A search on the ClinicalTrials.gov website reveals that Novartis, in what can only be described as a "shotgun" approach to research with this drug, is conducting numerous clinical trials of canakinumab in subjects with type 1 diabetes mellitus, type 2 diabetes mellitus, cardiovascular disease, osteoarthritis, and polymyalgia rheumatica, among others. Several studies involve repeated dosing over a prolonged time period. Presumably, these studies are being conducted with the knowledge, and possibly endorsement, of the FDA.

Given the toxicity seen with a single dose of canakinumab in gouty arthritis, the FDA should promptly assess all ongoing clinical trials involving this drug and determine whether they need to be suspended or terminated, since the predictable risks to subjects may outweigh the potential benefits of the research. Furthermore, for any trial allowed to continue, the FDA should assess whether the informed-consent process has an appropriate and complete disclosure of the known risks of canakinumab, including those safety concerns identified in other trials.

We are particularly concerned that the following two studies are unethical and fail to satisfy the requirements of the FDA human subjects protection regulations. We therefore urge the FDA to immediately place these studies on clinical hold until the agency fully investigates our concerns:

(1) *A Randomized, Double-Blind, Placebo-Controlled, Event Driven Trial of Quarterly Subcutaneous Canakinumab in the Prevention of Recurrent Cardiovascular Events Among Stable Post-Myocardial Infarction Patients With Elevated hsCRP.*[1]

This multicenter study is evaluating the effects of treatment with canakinumab in patients who were diagnosed with myocardial infarction (MI) at least one month prior to study entry and who have an elevated high-sensitivity C-reactive protein ($\geq$2 mg/liter [L]), a systemic marker of inflammation. Approximately 7,200 subjects older than 18 years are to be randomly assigned to either canakinumab or placebo injections quarterly. The primary outcome measure is the time to first occurrence of a major adverse cardiovascular event, which is a composite of cardiovascular death, nonfatal MI, and stroke.

Given the serious risks of even a single dose of canakinumab, including the documented risk of life-threatening infections and the possible risk of malignancies because of the marked immunosuppression (particularly for a subject population that is likely to already have many comorbid conditions), and given the apparent lack of any preliminary data regarding potential benefits of this drug in preventing cardiovascular events, there appears to be no reasonable justification for initiating such a large phase 3 clinical trial at this time. Furthermore, there appears to be no reasonable basis on which to make the following determinations required by the institutional review board (IRB) under the FDA regulations at 21 CFR 56.111(a)(1) and (2):

- Risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.

- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result.

We therefore call upon the FDA to promptly investigate the adequacy of the IRB review for all sites participating in this study and to provide a timely response to the following questions:

- Did each IRB make the required determinations under 21 CFR 56.111(a) and provide a reasonable justification for its determinations?

- Were there any IRBs that refused to approve the study? If so, why?

- Have the IRBs been provided with the safety data from all clinical trials involving canakinumab, including those trials involving gouty arthritis patients?

- Were subjects adequately informed about the nature of this research — particularly with respect to its serious risks and the lack of evidence regarding potential benefits — before informed consent was obtained?

(2) *Effects of Canakinumab on the Progression of Type 1 Diabetes in New Onset Subjects.*[2]

This study is a multicenter, randomized, double-blind, placebo-controlled trial. Approximately 66 subjects, age 6 to 45 years, with newly diagnosed type 1 diabetes mellitus, all of whom are receiving standard intensive diabetes treatment with insulin and dietary management, are to be randomly assigned to either canakinumab (2.0 mg/kilograms [kg]) or placebo subcutaneous injections monthly for 12 months (a total of 12 doses). The primary outcome measure is the C-peptide response to a mixed-meal tolerance test. C-peptide is a protein released into the bloodstream by the same cells in the pancreas that make insulin and is used as a marker of how

much insulin the pancreas is able to produce. After a meal, C-peptide levels increase in normal people but are low or undetectable in patients with type 1 diabetes mellitus

Again, given the known serious risks of even a single dose of canakinumab, and given the apparent absence of any preliminary data suggesting that canakinumab presents the prospect of direct benefits to adults or children with type 1 diabetes mellitus, it is unclear how any IRB could have approved this study for involvement of children under the FDA regulations at 21 CFR Part 50, Subpart D ("Additional Safeguards for Children in Clinical Investigations").

Since this study clearly involves much greater than minimal risk, it does not satisfy the requirements for approval under the FDA regulations at 21 CFR 50.51 ("Clinical investigations not involving greater than minimal risk") or at 21 CFR 50.53 ("Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition"). Therefore, the study may be conducted only if it satisfies the requirements under the FDA regulations at 21 CFR 50.52 ("Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects") or at 21 CFR 50.54 ("Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children").

With respect to the FDA regulations at 21 CFR 50.52, an IRB may approve the study only if the IRB makes and documents all of the following required findings:

- The risk is justified by the anticipated benefit to the subjects;
- The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
- Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 21 CFR 50.55.

Given the known serious risks of canakinumab and the absence of data in humans suggesting that canakinumab presents the prospect of any benefits to patients with type 1 diabetes mellitus, there is no reasonable basis on which to affirm the first two required findings cited above.

With respect to the FDA regulations at 21 CFR. 50.54, the research may be conducted only if the FDA Commissioner, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, and law) and following an opportunity for public review and comment, determines either of the following:

- That the clinical investigation in fact satisfies the conditions of 21 CFR 50.51, 50.52, or 50.53, as applicable; or

- That the following conditions are met:
    - The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
    - The clinical investigation will be conducted in accordance with sound ethical principles; and
    - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in 21 CFR 50.55.

To our knowledge, this study was not approved in accordance with the requirements of 21 CFR 50.54.

We therefore call upon the FDA to promptly investigate the adequacy of the IRB review for all sites participating in this study and to provide a timely response to the following questions:

- Under what category of research stipulated by 21 CFR Part 50, Subpart D did the IRBs approve the study?
- Did each IRB make the required determinations under Subpart D and provide a reasonable justification for its determinations?
- Were there any IRBs that refused to approve the study? If so, why?
- Have the IRBs been provided with the safety data from all clinical trials involving canakinumab, including those trials involving gouty arthritis patients?
- Were parents/subjects adequately informed about the nature of this research — particularly with respect to its serious risks and the lack of evidence regarding potential benefits — before parental permission/informed consent was obtained?

Since this study was funded by the National Institutes of Health, we are separately writing to the Office for Human Research Protections to ask for an independent investigation into this apparently unethical and illegal government-funded study.

We also request, pursuant to the Freedom of Information Act, 5 USC 552 as amended, copies of the sample informed-consent documents for all ongoing studies involving canakinumab. HRG requests a waiver of all fees associated with this request because it is a nonprofit, nonpartisan, tax-exempt public interest organization that educates the public about health and safety issues.

Thank you for taking our comments into account when considering action on the sBLA application #125319 for canakinumab.

Sincerely,

Michael A. Carome, M.D.
Deputy Director
Public Citizen Health Research Group

Sidney M. Wolfe, M.D.
Director
Public Citizen Health Research Group

Enclosure

cc: Dr. Margaret A. Hamburg, Commissioner, FDA
Dr. Badrul A. Chowdhury, Director, Division of Pulmonary, Allergy, and Rheumatology Products, Center for Drug Evaluation and Research, FDA
Division of Freedom of Information, Office of Shared Services, FDA

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[1] ClinicalTrials.gov. Cardiovascular risk reduction study (reduction in recurrent major CV disease events). (ClinicalTrials.gov identifier: NCT01327846). http://clinicaltrials.gov/ct2/show/NCT01327846. Accessed on June 29, 2011.
[2] ClinicalTrials.gov. Canakinumab study in individuals with newly diagnosed type 1 diabetes (anti IL-1). (ClinicalTrials.gov identifier: NCT00947427). http://clinicaltrials.gov/ct2/show/NCT00947427. Accessed on June 29, 2011.