I am Dr. Michael Carome, Deputy Director of Public Citizen’s Health Research Group (HRG), testifying on behalf of myself and Dr. Sidney Wolfe, the HRG Director. We have no financial conflicts of interest.

We strongly oppose the Food and Drug Administration’s (FDA’s) approval of rilonacept, a potent immunosuppressant that blocks interleukin-1 (IL-1), for the prevention of gout flares during initiation of uric-acid lowering therapy (ULT) in adult patients with gout because:

(1) With respect to benefits, the drug is not a major breakthrough treatment, has no unique advantages over current treatment options for prophylaxis against acute gout flares during initiation of ULT, and offers only marginal — in fact, trivial — clinical benefits in preventing gout flares, which are not life-threatening and, in most patients, are of short duration; and

(2) With respect to risks, IL-1 blockers, like rilonacept, have the known risks of serious infections, and the FDA’s review of safety data from the clinical trials of rilonacept in gout patients revealed important worrisome safety signals, including signals related to malignancies and adverse cardiovascular events.

Benefit Assessment

Regeneron Pharmaceutical, Inc., the sponsor of the BLA for rilonacept, is seeking approval to market the drug at a dose of 80 milligrams (mg) subcutaneously once weekly for 16 weeks for the prevention of gout flares during initiation of ULT in adult gout patients.

Although there were highly statistically significant differences between subjects receiving rilonacept and those receiving placebo for all pre-specified primary and secondary efficacy endpoints in the two phase 3 pivotal efficacy trials (studies 810 and 816; see Table 1), these differences were very small and represented marginal, if not trivial, clinical benefit. For example, for the primary efficacy endpoint, the number of flares per subject during the 16-week intervention phase, the placebo groups experienced a mean of approximately 1.1 to 1.2 flares per subject, whereas the rilonacept groups experienced a mean of approximately 0.3 flares per subject, yielding a reduction versus placebo of only 0.8 to 0.9 flares per subject over the 16-week intervention period.¹
Table 1: Summary of Efficacy Data from the Phase 3 Pivotal Trials of Rilonacept in Gout Patients

<table>
<thead>
<tr>
<th>Endpoints from Day 1 to Week 16</th>
<th>Study 810</th>
<th>Study 816</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rilonacept 80 mg N=80</td>
<td>Rilonacept 160 mg N=81</td>
</tr>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number of flares per subject, (SD)</td>
<td>0.3 (0.8)</td>
<td>0.2 (0.54)</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of subjects with ≥ 1 flare</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>% of subjects with ≥ 2 flares</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Mean # of flares days/subject (SD)</td>
<td>2.4 (11.4)</td>
<td>1.0 (3.0)</td>
</tr>
<tr>
<td>Mean # of days with pain score ≥ 5/subject (SD)</td>
<td>0.8 (3.9)</td>
<td>0.3 (1.3)</td>
</tr>
</tbody>
</table>

Likewise, for the secondary endpoints, the mean number of flare days per subject during the 16-week intervention phase was reduced by only 3-9 days, and the mean number of days with moderate to severe pain scores (≥ 5 on a ten-point scale) was reduced by only 1-3 days.

Further, in a post-hoc analysis by the FDA that excluded gout flares lasting more than 30 days — which were apparently due to a few subjects not providing end dates for their flares — the mean number of flare days per subject during the 16-week intervention phase was reduced by only 3-4 days, and the mean number of days with moderate to severe pain scores (≥ 5 on a ten-point scale) was reduced by only 1-2 days.3

Underscoring how clinically insignificant prophylactic treatment with rilonacept appears to be in preventing gout flares in adult patients undergoing initiation of ULT are the following points:

1. Many patients with gout do not develop gout flares during the initiation of ULT. Indeed, in the two pivotal trials for rilonacept, approximately 50 percent of subjects on placebo, who were not permitted to take any other standard prophylactic therapy for prevention of gout flares, had no gout flares during the 16-week intervention phase of the study.4 Thus, half of patients treated with rilonacept under the proposed indication would have no benefit and would only be exposed to the risks of the drug.

2. The mean number of flares during the first 16 weeks of initiation of ULT in the average gout patient is very low without any prophylaxis.

3. Other safer, more extensively studied, and effective treatments for preventing gout flares are available, such as low-dose colchicine or nonsteroidal anti-inflammatory drugs (NSAIDs).5

4. When gout flares do occur, they generally are self-limited in most patients, and there are several short-term treatments that are very effective in abating the flares, including brief courses of
colchicine, NSAIDs, or corticosteroids. Also notable are the results of a study (study 814) showing that rilonacept is less effective than indomethacin for the treatment acute gout flares.

**Risk Assessment**

Given that rilonacept offers meager clinical benefits in preventing gout flares in the intended target population, approval of this drug would only be justified if (1) there was certainty that the drug was extremely safe, and (2) there was an absence of serious safety signals identified during the clinical development of the drug. However, this is not the case: IL-1 blockers, like rilonacept, have the known risks of serious infections, and the FDA’s review of safety data from the clinical trials of the drug in gout patients revealed important worrisome safety signals, including signals related to malignancies and adverse cardiovascular events.

**Infection risk**

Even though a significant imbalance in infections was not seen in the analysis of the pooled safety data for the gout trials of rilonacept, increased risk of infection has been seen with short-term use of other IL-1 blockers and is considered a risk of rilonacept. For this reason, the FDA-approved label for the drug — which previously was approved by the FDA in 2008 for the chronic treatment of the rare genetic disorders known as Cryopyrin-Associated Periodic Syndromes (CAPS) — includes the following warning:

> [IL-1] blockade may interfere with immune response to infections. Serious, life-threatening infections have been reported in patients taking ARCALYST. Discontinue treatment with ARCALYST if a patient develops a serious infection. Do not initiate treatment with ARCALYST in patients with active or chronic infections.

The clinical review of the original BLA for rilonacept for treatment of CAPS noted the following:

In the pivotal trial in Part A more infections were seen in the rilonacept treated patients compared to the placebo group. The difference appeared to be due to more upper respiratory infections … In the open-label trial there was one death from streptococcal meningitis. In another trial a patient with Adult Still’s developed an opportunistic infection, mycobacterium intracellulare bursitis.

Also, neutropenia (low white blood cell counts), which could contribute to the development of serious infections, occurred more frequently in subjects receiving rilonacept than placebo in the gout clinical trials.

**Malignancy safety signal**

The FDA’s review of the data from the safety population pooled from four clinical studies involving exposure of adult gout patients to rilonacept or placebo for 16 weeks (studies 810, 815, 816, and 819; 1,886 total subjects, with 162 exposed to rilonacept 80 mg weekly, 1,191 exposed to rilonacept 160 mg weekly, and 553 exposed to placebo) revealed the following:

There was an imbalance in malignant neoplasms in the pooled safety database, with 6 on-treatment malignancies reported on rilonacept therapy, and none in the placebo group. The types of malignancies varied, including 3 cases of prostate cancer, and one case each of gastric cancer, breast cancer, and oropharyngeal cancer. While these are the types of cancers that may be expected in the typical gout population, and the duration of exposure to drug was relatively short, it is notable that there were no malignancies reported in the placebo group. Statistical analysis … of the 4 cases of malignancy in study 815 alone, suggested a statistically significant risk.
Public Citizen                             May 8, 2012 Testimony Before FDA’s Arthritis Advisory Committee

... the apparent increase in the risk of malignancies with rilonacept may not be due simply to chance.\textsuperscript{11}

Given rilonacept’s potent immunosuppressive effects, it is biologically plausible that the drug could increase the risk of malignancies by blocking people’s natural tumor immunosurveillance. For this reason, the current FDA-approved label for rilonacept carries the following warning:

The impact of treatment with ARCALYST on … the development of malignancies is not known. However, treatment with immunosuppressants, including ARCALYST, may result in an increase in the risk of malignancies.\textsuperscript{12}

Regarding preclinical studies, the FDA noted that “[l]ong-term studies in animals have not been performed to evaluate the carcinogenic potential of rilonacept.”\textsuperscript{13}

Therefore, the imbalance in malignancies seen in the clinical development program for rilonacept in gout patients is very concerning and must be given significant weight when assessing the drug’s risks in comparison to its trivial clinical benefits.

Cardiovascular safety signal

The FDA’s review of the data from the safety population for the clinical trials of rilonacept in adult gout patients revealed slightly greater frequency of cardiac adverse events in the rilonacept groups compared to placebo (see Table 2).\textsuperscript{14}

<table>
<thead>
<tr>
<th>System organ class MedDRA preferred term</th>
<th>Rilonacept 80 mg N=162</th>
<th>Rilonacept 160 mg N=1191</th>
<th>Placebo N=533</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥ 1 TEAE</td>
<td>105 (64.8)</td>
<td>786 (66.0)</td>
<td>318 (59.7)</td>
</tr>
<tr>
<td>All Cardiac Disorders</td>
<td>3 (1.9)</td>
<td>13 (1.1)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Serious Cardiac Disorders</td>
<td>0</td>
<td>8 (0.7)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0</td>
<td>2 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Cor pulmonale</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>2 (0.2)</td>
<td>0</td>
</tr>
</tbody>
</table>

In particular, cardiac serious adverse events occurred in 8 (0.7%) subjects in the rilonacept 160-mg group, 1 (0.2%) subject in the placebo group, and none in the rilonacept 80-mg group. In commenting on these events, the FDA noted the following:
The small numerical imbalance in cardiac SAEs and AEs in the 16-week gout safety database does not rise to the level of a clear safety signal, but does introduce some uncertainty as to the potential cardiac risk of rilonacept in the gout population [emphasis added].

Additional considerations regarding the risks of rilonacept

The concerns about the risks of rilonacept are magnified by the following factors:

1. If approved for the proposed indication, many gout patients likely would receive treatment courses of much longer than 16 weeks as well as multiple courses, increasing the risks for serious infections, malignancy, adverse cardiac events, and other adverse events. Indeed, the sponsor’s risk management plan acknowledges that some healthcare providers will treat gout patients with rilonacept for longer than 16 weeks.

2. The FDA recognized the need for more safety data in gout subjects exposed to rilonacept for much longer than 16 weeks. The agency on more than one occasion advised the sponsor of “the need for safety data from 1,000-1,500 gout patients treated for one year, and the importance of long-term safety data in a gout population not typically treated with immunosuppressive therapy.” Regeneron disregarded this advice.

Conclusions

In June 2011, the Arthritis Advisory Committee voted 11 to 1 against approval of another IL-1 blocker, canakinumab, for treatment of gouty arthritis attacks in patients who cannot obtain adequate response with NSAIDS or colchicine because of an unfavorable benefit-risk profile. In the case of rilonacept, the benefit-risk profile is even more unfavorable for the proposed indication.

The known risks and concerning safety signals related to rilonacept far outweigh the trivial clinical benefits seen in the pivotal trials of the drug for prevention of gout flares, which are not life-threatening, during initiation of ULT in adult gout patients. In fact, 50 percent of patients treated under the proposed indication would receive no benefit and only be exposed to serious risks.

In addition, other effective, safer, better studied — and likely significantly cheaper — treatments already are available for preventing and treating the acute flares of gout that occur during the initiation of ULT. Therefore, it would be irresponsible and reckless of the FDA to approve such a potent immunosuppressive drug for the proposed indication given its meager clinical benefit.

Furthermore, additional long-term clinical trials in adult gout patients undergoing ULT would be unnecessary and unethical. The drug’s known serious risks will never be outweighed by its trivial clinical benefits for the proposed target population and indication.

In closing, in the interests of protecting public health, we strongly urge the advisory committee to recommend that the FDA disapprove the supplemental BLA for rilonacept for the prevention of gout flares during initiation of ULT in adult gout patients.


16 Food and Drug Administration. Briefing materials for the May 8, 2012 Arthritis Advisory Committee meeting. Web page 35. Available at
