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Testimony Before the FDA's Arthritis Advisory Committee
Regarding New Drug Application 207924 for Baricitinib for Rheumatoid Arthritis:
No Unique Benefits, But Unique Serious Safety Concerns

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I am Dr. Michael Carome, Director of Public Citizen's Health Research Group. Public Citizen and I have no financial conflicts of interest.

We strongly oppose Food and Drug Administration (FDA) approval of baricitinib for treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or are intolerant to methotrexate, because the FDA correctly concluded — prior to issuing its April 12, 2017, Complete Response letter to the sponsor — that "the overall benefit-risk assessment of baricitinib 2 mg and 4 mg once daily was not favorable,"[1] and the sponsor, Eli Lilly, has not provided any data that substantially alters the agency's conclusion.

We therefore urge the committee to recommend that the FDA not approve baricitinib.

Efficacy assessment

Data submitted from four pivotal randomized controlled trials testing baricitinib at doses of 2 or 4 milligrams (mg) once daily in comparison with a placebo or active comparator (methotrexate or adalimumab) did demonstrate efficacy in improving the signs and symptoms of RA as assessed by the American College of Rheumatology 20 response and on other measures.[2]

Of note, the two trials that compared baricitinib at 2 mg and 4 mg once daily did not show consistent separation in efficacy outcomes between the two doses, with the dose response for the primary outcome measure being opposite in the two trials.[3]

Signal for major unique safety concern

Baricitinib causes numerous serious adverse reactions typical of many other potent immunosuppressive drugs, including the following: [4]

- Malignancies
- Sustained decreased neutrophil count

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[1] Food and Drug Administration. Briefing document for the April 23, 2018, meeting of the Arthritis Advisory Committee, NDA 207924 baricitinib, Janus kinase (JAK) inhibitor for RA. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM605061.pdf. Accessed April 19, 2018. PDF page 4.
[2] *Ibid.* PDF pages 84, 91
[3] *Ibid.* PDF page 86
[4] *Ibid.* PDF pages 96-104

- Opportunistic infections
- Tuberculosis
- Herpes zoster infection
- Gastrointestinal perforation

Risk of thrombotic events

However, as discussed in detail by FDA reviewers, baricitinib appears to have a unique risk of venous and arterial thrombotic events, a risk not seen with any small-molecule or biologic disease-modifying antirheumatic drugs (DMARDs).[5] Analyses of pooled data for baricitinib-group and placebo-group subjects in the phase 3 clinical trials demonstrated that events reported as deep venous thrombosis (DVT) and pulmonary embolus (PE) were seen only with baricitinib, but there was no clear difference between the 2-mg and 4-mg doses (see Table 3 below, excerpted from the FDA briefing document).[6] Review of the initial application revealed that there were 10 PEs reported with baricitinib; nine of those were serious, and one was fatal. There were 10 DVTs reported with the drug, and six were serious.[7]

Table 3. DVT and PE events analyses (pooled studies JADV, JADX, JADW, and JADZ, and their extension in JADY)

	Baricitinib 4 mg	Baricitinib 2 mg	Placebo**
0-16 weeks			
Total exposure, patient years	386.7	122.6	267.2
Patients with thrombotic events, n (rate)	4 (1.0)	0	0
0-52 weeks			
Total exposure, patient years	1694.9	304.8	365.0
Patients with thrombotic events, n (rate)	8 (0.5)	2 (0.7)	0
>52 weeks			
Total exposure, patient years	1300.6	210.2	-
Patients with thrombotic events, n (rate)	8 (0.6)	0	-
0-any duration *			
Total exposure, patient years	2995.6	515.0	365.0
Patients with thrombotic events, n (rate)	16 (0.5)	2 (0.4)	0

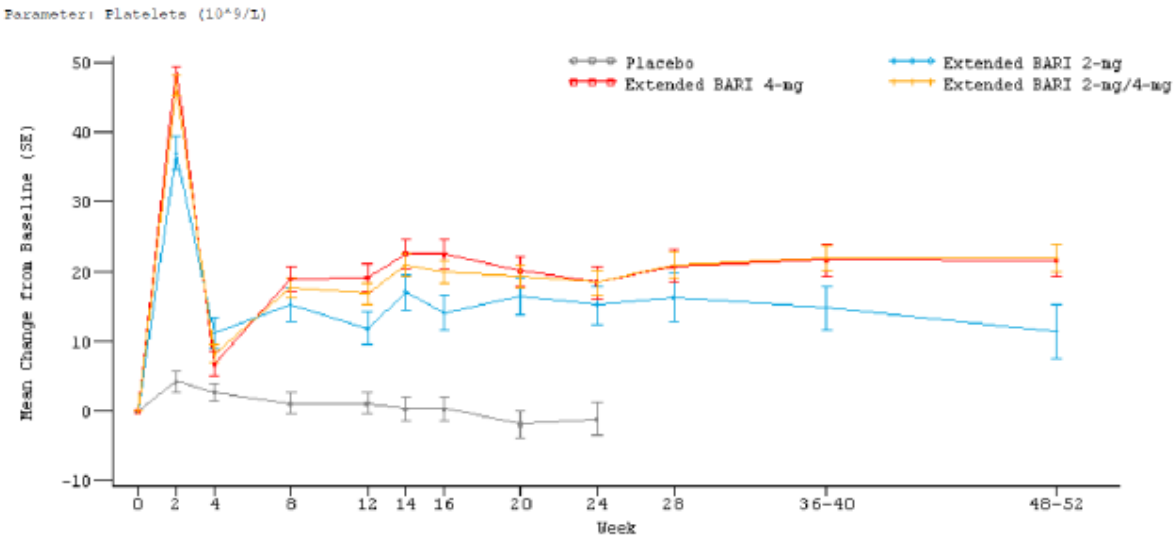
* Events occurring before the safety data lock of August 10, 2015; **JADZ had MTX active control. One case discussed below.

The initial application also revealed that in the phase 3 trials, there were three cases of arterial thrombosis in subjects who received baricitinib, two involving the leg and one involving the brachial artery.

Baricitinib also clearly causes an increase in platelet count, an effect that, according FDA reviewers, has not been seen with other Janus kinase (JAK) inhibitors (such as tofacitinib for RA) or other DMARDs (see Figure 1 below, excerpted from the FDA briefing document).[8] Of note, there was not a clear relationship between the occurrence of thrombotic events and platelet count elevations.[9]

[5] *Ibid.* PDF page 73
[6] *Ibid.* PDF page 140
[7] *Ibid.* PDF page 140
[8] *Ibid.* PDF pages 96, 137-139
[9] *Ibid.* PDF page 105

Figure 1. Mean Change in Platelets in Pooled Datasets for Placebo-controlled studies



Liver toxicity

In addition, more subjects receiving baricitinib 4 mg were discontinued from drug due to liver enzyme elevations than those in comparator groups.

FDA's original benefit-risk assessment

Dr. Badrul Chowdhury, Director of the Center for Drug Evaluation and Research's (CDER's) Division of Pulmonary, Allergy, and Rheumatology Products, prior to the issuance of the FDA's Complete Response letter, noted the following in his benefit-risk assessment of baricitinib:[10]

> The thrombosis findings are of particular concern because these events are not predictable, and some were associated with death. As for laboratory parameters, it is worth noting that 2 patients were withdrawn from the studies for meeting platelet threshold criteria for withdrawal, both were from baricitinib 4 mg dose. Lilly argues against the thrombosis risk by comparing to population data. Comparison to population data is not relevant because the risk with baricitinib was seen in controlled clinical studies. …
>
> On further review and consideration, I now question if the baricitinib 4 mg dose is not safe, why the lack of safety of the 4 mg dose would not be applicable to the 2 mg dose. The safety database of the 2 mg dose is not large enough to independently assess safety of the 2 mg dose and compare that to the 4 mg dose. Furthermore … the safety finding that is of particular concern is the thrombosis event. The [biologic DMARDs] and tofacitinib do not have this safety risk. **There will need to be further safety data generated to understand**

[10] *Ibid*. PDF pages 115-117

> **the thrombosis risk for baricitinib, and it would be reasonable to obtain the data and address this safety risk pre-approval**. …
>
> It is possible that in real life post-approval use by a wide range of patients with rheumatoid arthritis, the 2 mg dose may turn out to carry the same safety risk that is worrisome for the 4 mg dose. Also, as discussed above, it is possible that a dose lower than the 2 mg dose may be effective as well and have a better safety profile. **Given that baricitinib is another member of the DMARD class that has many choices, and baricitinib is not serving an unmet medical need that is above and beyond [biologic DMARDs] and tofacitinib**, it would be reasonable to not approve any of the doses of baricitinib at this time and have Lilly assess efficacy of a dose or doses lower than 2 mg and assess safety of these doses with a larger exposure database. It is possible that the 2 mg dose may ultimately be the appropriate dose, but that needs to be supported by a dose-ranging study exploring doses lower than 1 mg.
>
> [Emphasis added]

Likewise, Dr. Mary Tran Thanh Hai, Deputy Director of CDER's Office of Drug Evaluation II stated the following in her benefit-risk assessment:[11]

> Although the number of thrombotic events was low…, the absolute number and imbalance to controls during the first 16 weeks of pivotal studies distinguishes baricitinib from other approved RA therapies, particularly tofacitinib…
>
> Given the infrequency of the thrombotic events in this program, the serious safety concerns associated with other approved RA therapies (some overlapping with baricitinib), and the efficacy demonstrated with baricitinib 2 and 4 mg in several Phase 3 trials, I considered whether a subgroup of patients could be identified where the benefit-risk calculus of baricitinib 4 or 2 mg could be favorable and also provided an advantage over other available therapies. Identification of such a population might at least allow for an approval limited to a select group of patients. There were two studies in which baricitinib 4 mg demonstrated superiority over an active comparator. In JADV, baricitinib 4 mg was superior to adalimumab in RA patients who had inadequate response to MTX. In JADZ, baricitinib 4 mg was superior to MTX in RA patients naïve to drug treatment. Despite these findings, **I could not justify the risks associated with baricitinib 4 mg over the active comparator because the currently marketed JAK-inhibitor, tofacitinib, had also been shown effective in these two populations but without the risk of thrombosis**. …
>
> If it were the first-in-class oral JAK-inhibitor, there may be a justifiable basis for carving out a niche population for baricitinib 2 and 4 mg. However, the evidence with tofacitinib in its premarketing application and subsequent Phase 4 trials since its approval in 2012 has established its efficacy in RA patients across a spectrum of disease severity, its efficacy relative to adalimumab and MTX, and its ability to reduce radiographic progression. **These**

[11] *Ibid*. PDF pages 125-126

> **are the same populations and endpoints for which baricitinib is seeking approval; however, without the concerning thrombotic risk that appears unique to baricitinib**.
>
> **In conclusion, review of this NDA has identified a serious safety risk of thrombosis not observed in other marketing applications for available RA therapies, especially tofacitinib. Absent an advantage of baricitinib over available therapies, the applicant will need to explore whether a lower dose can provide efficacy without this safety concern**.
>
> [Emphasis added]

The sponsor's resubmitted application

In response to the FDA's April 2017 Complete Response letter, the sponsor resubmitted its NDA on December 4, 2017.[12] To address the FDA's concerns, the sponsor submitted the following, among other things:[13]

- Several post-hoc analyses in subject subgroups from trials previously reviewed by the FDA
- Safety analyses with an updated cut-off date
- Comparative analyses of retrospective cohort studies from the Sentinel and Truven MarketScan databases with the prospective baricitinib studies in RA to evaluate venous thromboembolic risk

The sponsor also proposed a modified dosing regimen and that the thromboembolic risk be managed through warnings in the label, communications with health professionals, and routine pharmacovigilance.[14]

Regarding the post-hoc analyses that purport to demonstrate superior efficacy of the baricitinib 4-mg dose over the 2-mg dose in patients with inadequate response or intolerance to at least two DMARDs, the FDA concluded that these analyses should be "considered exploratory and hypothesis-generating rather than confirmatory." [15]

Regarding the safety analyses with an updated cut-off date, the updated incidence rate of venous thromboembolic events (VTE) was 0.6 per 100 patient years in the 4-mg baricitinib group and 0.4 per 100 patient years in the 2-mg dose group (see Table 6 below, excerpted from the FDA briefing document), which was very similar to the rates reported with the sponsor's initial submission.[16] The updated safety analysis also showed that additional arterial thrombosis events continued to accumulate with continued exposure to baricitinib.[17]

[12] *Ibid*. PDF page 4
[13] *Ibid*. PDF pages 149-150
[14] *Ibid*. PDF page 149
[15] *Ibid*. PDF page 178
[16] *Ibid*. PDF pages 160-161
[17] *Ibid*. PDF pages 161-162

Table 6. Update of VTE (DVT and PE) in Baricitinib Clinical Program in RA

	BARI 4	BARI 2	Placebo
Original Submission, August 10, 2015 Data Lock			
0-16 weeks			
Number of patients	1265	403	892
Total exposure in patient years	387	123	267
Patients with thromboses, n (rate)	5* (1)	0	0
0-52 weeks			
Total exposure in patient years	1695	305	365
Patients with thromboses, n (rate)	9* (0.5)	2 (0.7)	0
> 52 weeks			
Total exposure in patient years	1301	210	NA
Patients with thromboses, n (rate)	8 (0.6)	0	
0-any duration			
Total exposure in patient years	2996	515	NA
Patients with thromboses, n (rate)	17* (0.5)	2 (0.4)	
Resubmission Update, April 1, 2017 Data Lock			
> 52 weeks			
Number of patients	2441	703	NA
Total exposure in patient years	4125	957	
Patients with thromboses, n (rate)	25 (0.6)	3 (0.3)	
0-any duration			
Number of patients	2717	929	NA
Total exposure in patient years	5820	1261	
Patients with thromboses, n (rate)	34 (0.6)	5 (0.4)	

Source: Information request response dated March 20, 2018, p. 8, Division Director review, p. 35
*Corrected by the Applicant to 1additional event in the re-submission
Abbreviations: BARI=baricitinib

Regarding the comparative analyses of retrospective cohort studies from the Sentinel and Truven MarketScan databases with the prospective baricitinib studies in RA to evaluate venous thromboembolic risk, the FDA noted in its review that:[18]

> The VTE rates from the baricitinib clinical trials should not be compared to those of DMARD users in the IMEDS/Truven data to conclude that baricitinib is less safe, as safe as, or safer than DMARDs. The study designs and populations are fundamentally different

[18] *Ibid*. PDF pages 163-164

> and aim to address different objectives. The clinical trial incidence rates should not be compared to the observational study incidence rates to assess relative safety for four major reasons…
>
> 1. *The data collection methods for medical history, rheumatoid arthritis information, and baseline drug exposure differed between the clinical trials and observational studies. …*
>
> 2. *The inclusion and exclusion criteria differed between the clinical trials and the observational studies. …*
>
> 3. *The crude VTE rates from the US clinical trials cannot be compared to the rates from US observational data despite similar incidence rates (0.90 vs. 1.05, respectively). …*
>
> 4. *Data from ALL BARI RA, IMEDS and Truven included patients with current anticoagulant use, potentially for the treatment of a prior VTE.*
>
> [Emphasis in original]

In summary, the FDA's overall assessment of the additional data provided by the sponsor in the resubmitted application was that it "did not substantially alter the efficacy and safety data in the original submission."[19]

Conclusions

Given the available data, the only reasonable course of action for this committee and the FDA is to reject approval of the NDA for baricitinib. FDA approval, with reliance on warnings in the product labeling and postmarket pharmacovigilance, would be a reckless approach and would not be in the interests of public health. Approving another drug for treatment of RA that lacks any unique benefit over the very similar FDA-approved drug tofacitinib but causes unique life-threatening harms, such as venous and arterial thrombotic events, would show blatant disregard for the public health principles underlying the FDA's regulatory authority.

Therefore, we urge the committee to recommend that the FDA not approve baricitinib.

[19] *Ibid*. PDF page 186