Testimony before the FDA's Arthritis Advisory Committee Regarding Baricitinib for Rheumatoid Arthritis: No Unique Benefits, But Unique Risks

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(I have no financial conflicts of interest)

Major Comment

Public Citizen strongly opposes 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," and the sponsor, Eli Lilly, has not provided any data that substantially alters the agency's conclusion.

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 ACR 20 response and on other measures.

Non-Unique Safety Issues

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

- Malignancies
- Sustained decreased neutrophil count
- Opportunistic infections
- Tuberculosis
- Herpes zoster infection
- Gastrointestinal perforation

Unique Risk: Thrombotic Events and Thrombocytosis

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 bDMARDs. 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.

Unique Risk: Thrombotic Events and Thrombocytosis (2)

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

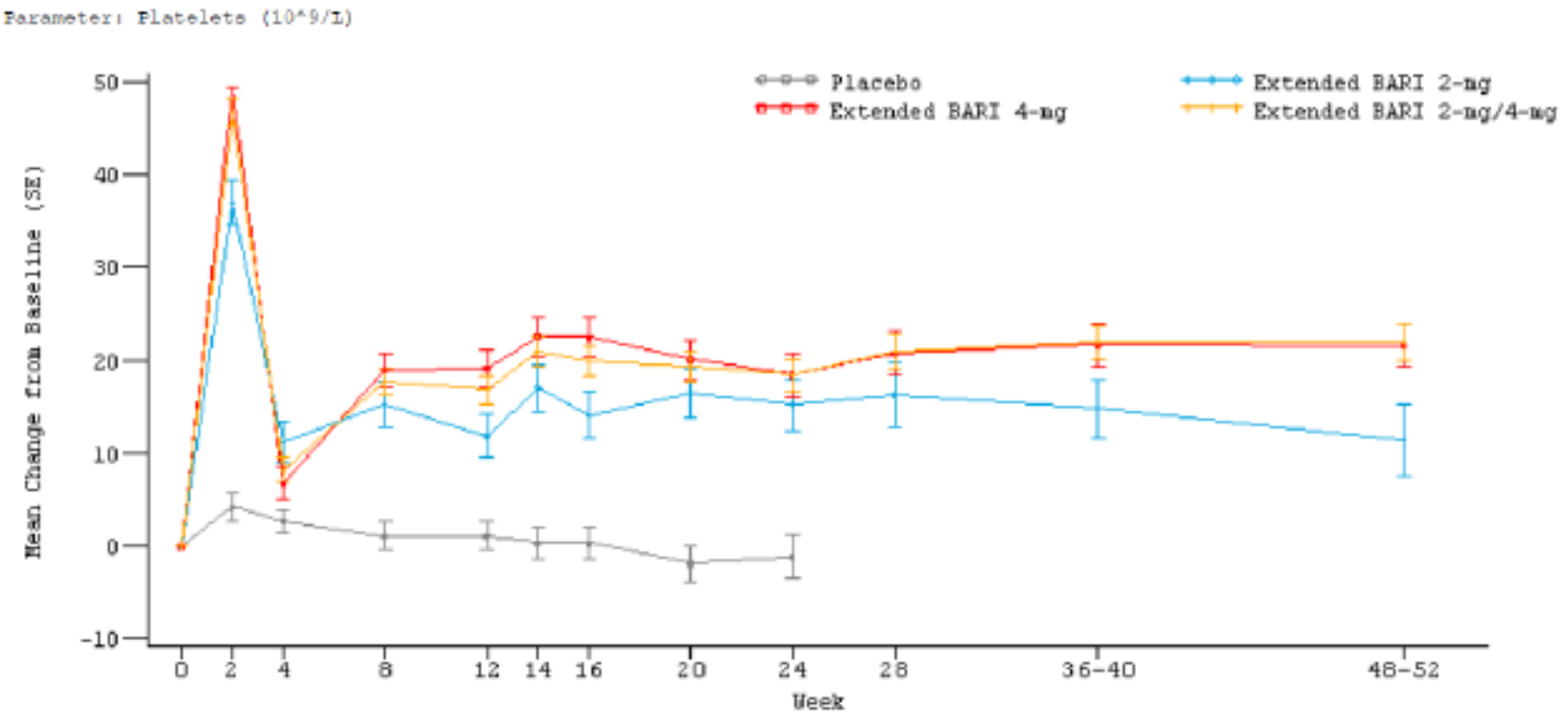
* Events occurring before the safety data lock of August 10, 2015; **JADZ had MTX active control. One case discussed below.

Unique Risk: Thrombotic Events and Thrombocytosis (3)

Baricitinib also clearly causes an increase in platelet count, an effect that, according FDA reviewers, has not been seen with other JAK inhibitors (such as tofacitinib for RA) or other DMARDs

Unique Risk: Thrombotic Events and Thrombocytosis (4)

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



FDA's Original Risk-Benefit Assessment

Dr. Badrul Chowdhury, Director of CDER's Division of Pulmonary, Allergy, and Rheumatology Products:

"There will need to be further safety data generated to understand the thrombosis risk for baricitinib, and it would be reasonable to obtain the data and address this safety risk pre-approval."

"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 bDMARDs 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."

FDA's Original Risk-Benefit Assessment (2)

Dr. Mary Tran Thanh Hai, Deputy Director of CDER's Office of Drug Evaluation II:

"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… ."

"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. …"

FDA's Original Risk-Benefit Assessment (3)

Dr. Mary Tran Thanh Hai, Deputy Director of CDER's Office of Drug Evaluation II:

"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."

Sponsors' Resubmitted Application

To address the FDA's concerns, the sponsor submitted the following, among other things:

- **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

FDA's Review of Resubmitted Application

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."

FDA's Review of Resubmitted Application (2)

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, which was very similar to the rates reported with the sponsor's initial submission.

FDA's Review of Resubmitted Application (3)

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

FDA's Review of Resubmitted Application (4)

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:

> "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 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…"

FDA's Review of Resubmitted Application (5)

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."

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.

Conclusions (2)

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