FDA Arthritis Advisory Committee Meeting
FDA Opening Remarks

NDA 207924: Baricitinib for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have inadequate response to methotrexate

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Baricitinib

- Applicant: Eli Lilly & Co.
- New Molecular Entity (NME)
- Second in class for rheumatoid arthritis (RA)
- Small molecule, Janus Kinase (JAK) inhibitor for oral administration

Proposed Usage

- Indication and Usage
  - “Treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or are intolerant to methotrexate (MTX).”
- Dosage and Administration
  - “The recommended dose is 2 mg once daily. For patients with an inadequate response or intolerance to more than one disease modifying anti-rheumatic drug (DMARD), a dose of 4 mg once daily is recommended.
  - Dose tapering to 2 mg once daily may be considered for patients who have achieved sustained control of disease activity with 4 mg once daily.”

Clinical Program: Phase 2 Studies

Study	Patient population	Study design	Treatment arm	Patients per arm	Primary endpoint
JADC	cDMARD-IR	R, DB, PC	Baricitinib 4 mg Baricitinib 7 mg Baricitinib 10 mg PBO	32 32 32 31	ACR20 at Week 12
JADA	cDMARD-IR	R, DB, PC	Baricitinib 1 mg Baricitinib 2 mg Baricitinib 4 mg Baricitinib 8 mg PBO	49 52 52 50 98	ACR20 at Week 12
JADN	cDMARD-IR	R, DB, PC	Baricitinib 1 mg Baricitinib 2 mg Baricitinib 4 mg Baricitinib 8 mg PBO	24 24 24 24 49	ACR20 at Week 12

cDMARD=conventional DMARD; IR=inadequate response; R=randomized; DB=double-blind; PC=placebo controlled; ACR=American College of Rheumatology; PG=parallel group; PBO=placebo

Clinical Program: Phase 3 Studies

Study	Patient population	Study design	Treatment arms	Patients per arm	Major endpoints
JADV	MTX-IR	R, DB, PC and AC 52 weeks	Baricitinib 4 mg + MTX Adalimumab 40 mg QOW+ MTX PBO + MTX (→ Baricitinib 4 at Week 24) Rescue to Bari 4 mg, starting at Week 16	488 330 487	ACR20, HAQ-DI at Week 12 mTSS at Week 24
JADX	cDMARD-IR	R, DB, PC 24 weeks	Baricitinib 2 mg + cDMARD Baricitinib 4 mg + cDMARD PBO + cDMARD Rescue to Baricitinib 4 mg, starting at Week 16	229 227 228	ACR20, HAQ-DI at Week 12
JADW	TNF-IR	R, DB, PC 24 weeks	Baricitinib 2 mg + cDMARD Baricitinib 4 mg + cDMARD PBO + cDMARD Rescue to Baricitinib 4 mg, starting at Week 16	174 177 178	ACR20, HAQ-DI at Week 12
JADZ	Treatment naïve/early RA	R, DB, AC MTX titrated up to 20 mg weekly 52 weeks	MTX Baricitinib 4 mg Baricitinib 4 mg + MTX Rescue to Baricitinib 4 + MTX mg, starting at Week 24	213 160 215	ACR20, HAQ-DI at Week 24
JADY	Patients from P2 and P3 studies	LTE RW	Baricitinib 2 mg (patients from JADX and JADW) Baricitinib 4 mg	2539	Safety Efficacy

MTX=methotrexate; AC=active controlled; IR=inadequate response; TNF=tumor necrosis factor; QOW=every other week; P2=phase 2; P3=phase 3

Clinical Program: Phase 3 Studies

Study	Patient population	Study design	Treatment arms	Patients per arm	Major endpoints
JADV	MTX-IR	R, DB, PC and AC 52 weeks	Baricitinib 4 mg + MTX Adalimumab 40 mg QOW+ MTX PBO + MTX (→ Baricitinib 4 at Week 24) Rescue to Bari 4 mg, starting at Week 16	488 330 487	ACR20, HAQ-DI at Week 12 mTSS at Week 24
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JADY	Patients from P2 and P3 studies	LTE RW	Baricitinib 2 mg (patients from JADX and JADW) Baricitinib 4 mg	2539	Safety Efficacy

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Efficacy Considerations

- Both baricitinib doses, 2 mg and 4 mg once daily, are effective in reducing signs and symptoms and improving physical function in patients with RA versus placebo
  - Higher ACR20, 50, 70 response rates versus placebo
  - Improvement in Health Assessment Questionnaire-Disability Index (HAQ-DI) compared to placebo
  - Data not consistent in showing a meaningful benefit of 4 mg over the 2 mg dose
- Radiographic response
  - The data for 4 mg dose are robust
  - Some uncertainty about 2 mg dose, studied in only one study as an exploratory endpoint

Safety Considerations

- Serious infections, including H. zoster, opportunistic infections and tuberculosis
- Malignancy, including lymphoma and other malignancies
- Thrombosis, both venous and arterial
- Laboratory Abnormalities (often dose-dependent)
  - Decrease in neutrophils and hemoglobin
  - Platelet elevations
  - Lipid elevations
  - Liver test elevations

Safety Data Limitations

- Limited placebo-controlled data
  - Duration of baricitinib versus placebo controlled data pre-escape was limited to 16 weeks
- Overall safety exposure data limited for baricitinib 2 mg vs 4 mg
  - Four of the seven phase 2 and 3 clinical studies included 2 mg and 4 mg baricitinib dose arms
  - Patient escape/cross-overs
    - Patients on placebo were switched or escaped to 4 mg of baricitinib
    - Patients who escaped from 2 mg baricitinib were placed on 4 mg of baricitinib
    - Patients who were eligible for escape from 4 mg of baricitinib remained on 4 mg of baricitinib
  - Patients in study JADY who had a pre-defined response* to 4 mg of baricitinib were eligible to be randomized to 2 mg vs 4 mg of baricitinib

*CDAI≤10 for 3 months in study JADY or CDAI≤2.8 from study JADZ; patients originating from study JADA were not eligible

Benefit-Risk Considerations

Benefits

- Superior efficacy of both baricitinib doses compared to placebo:
  - Signs and symptoms
  - Physical function
  - No consistent meaningful benefit of 4 mg over 2 mg
- Radiographic response:
  - Data for 4 mg dose are robust
  - Some uncertainty about 2 mg dose, studied in only one study as an exploratory endpoint

Risks

- Serious infections
- Herpes zoster, opportunistic infections and TB
- Malignancies
- Thrombosis
  - Both arterial and venous
- Laboratory abnormalities
  - Many dose-dependent, including platelet elevations

Regulatory History: Original Submission

- Original NDA was submitted on January 14, 2016
  - Indication: “Moderately to severely active rheumatoid arthritis (RA).”
  - Dosage and Administration: Proposed dose was 4 mg once daily, with an added notation that “for some patients a dose of 2 mg once daily may be acceptable.”
- Review clock was extended by three months for review of new safety analyses
- Complete Response action on April 12, 2017
  - An imbalance in thrombotic events in the baricitinib RA program with potential thrombotic risk with use of baricitinib in RA
  - Inadequate safety exposure for 2 mg of baricitinib
  - Not consistent findings to conclude greater efficacy with 4 mg over 2 mg
  - Lower doses of baricitinib should be considered for use in RA as there was evidence that lower doses may be effective for treatment of RA
  - Cases consistent with drug-induced liver injury were observed with baricitinib use and need to be described

Regulatory History: Re-submission

- Re-submission on December 04, 2017
- A revised proposal
  - Indication and Usage: “Moderately to severely active RA who have had an inadequate response or are intolerant to methotrexate (MTX).”
  - Warnings and Precautions: Warning about the potential risk of thrombosis
  - Dosage and Administration: “Proposed dose is 2 mg once daily. For patients with an inadequate response or intolerance to more than one DMARD, a dose of 4 mg once daily is recommended. Dose tapering to 2 mg once daily may be considered for patients who have achieved sustained control of disease activity with 4 mg once daily.”
- Information provided in the re-submission
  - Updated analyses of accumulated safety (cut-off date, April 01, 2017 vs. August 01, 2015)
  - Epidemiological data comparing rates of VTE/PE from retrospective cohorts to those from the prospective baricitinib studies in RA
  - Post-hoc efficacy analyses in patients who had failed more than one DMARD to support the new dosing recommendations

Discussion Points and Voting Questions

1. **DISCUSSION:** Discuss the efficacy data for baricitinib for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate (MTX). Include a discussion of the 2 mg and 4 mg doses of baricitinib and whether available data support a benefit of one dose over the other.

Discussion Points and Voting Questions

2. **VOTE:** Do the data provide substantial evidence of the efficacy of baricitinib 2 mg once daily for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate (MTX)?
   - If no, what data are needed?

3. **VOTE:** Do the data provide substantial evidence of the efficacy of baricitinib 4 mg once daily for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate (MTX)?
   - If no, what data are needed?

Discussion Points and Voting Questions

4. **DISCUSSION:** Discuss the safety data for baricitinib for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate (MTX) Include a discussion of the following issues:

   a) Adequacy of safety database for the 2 mg dose of baricitinib

   b) Safety issues of interest and whether data suggest a dose response

   - Thromboembolic events
   - Malignancy
   - Serious infections, opportunistic infections, herpes zoster, tuberculosis
   - Abnormal laboratory parameters, specifically platelet count elevations

   c) Overall safety profile of the 2 mg dose and the 4 mg dose, and whether the data are more favorable for one dose versus the other.

Discussion Points and Voting Questions

5. **VOTE:** Are the safety data adequate to support approval of baricitinib 2 mg once daily for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate (MTX)?
   - If no, what data are needed?

6. **VOTE:** Are the safety data adequate to support approval of baricitinib 4 mg once daily for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate (MTX)?
   - If no, what data are needed?

Discussion Points and Voting Questions

7. **VOTE:** Is the benefit-risk profile adequate to support approval of baricitinib 2 mg once daily for the proposed indication of the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate (MTX)?
   - If no, what data are needed?

8. **VOTE:** Is the benefit-risk profile adequate to support approval of baricitinib 4 mg once daily for the proposed indication of the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate (MTX)?
   - If no, what data are needed?


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