CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207924Orig1s000

SUMMARY REVIEW

Executive Summary

To: Baricitinib, NDA 207924

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Subject: Summary of Resubmission and DPARP/OND Recommendations

Date: May 31, 2018

The following is a summary of the division considerations and recommendations following the April 23, 2018, FDA Arthritis Advisory Committee (AAC) meeting to discuss the new drug application (NDA) 207924 submitted by Eli Lilly and Company (Lilly) for baricitinib an oral Janus associated kinase (JAK) inhibitor proposed for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or are intolerant to methotrexate (MTX).

The original NDA for baricitinib was submitted on January 14, 2016. Safety concerns were identified, including the risk of venous thrombosis, and the application received a Complete Response (CR) action on April 12, 2017 because the overall benefit-risk assessment of baricitinib 2 mg and 4 mg once daily was not favorable. Specific deficiencies included the potential thrombotic risk, inadequate safety exposure for baricitinib 2 mg, inability to demonstrate consistent efficacy advantage of baricitinib 4 mg over 2 mg dose, and questions regarding dose-selection, given identified dose-related toxicities. To address the CR letter deficiencies, the Applicant re-submitted the application on December 4, 2017.

Resubmission Summary

Lilly submitted a response to the CR action on December 4, 2017. The re-submission included data from a completed study in RA patients (JAGS), but this study did not include the baricitinib 2 mg dose group. The re-submission included an update of the accumulated safety information

for baricitinib 2 mg and 4 mg doses in RA, including events of deep vein thrombosis (DVT) and pulmonary embolism (PE). These analyses were consistent with the findings from the first review cycle. Lilly also provided epidemiological data on the incidence of venous thrombosis in the RA population and historical data on venous thrombosis for other RA therapies with comparisons to the data from the baricitinib program; however, our DEPI colleagues noted limitations of these data sources.

In the re-submission, Lilly proposed a different indication and dosing strategy for baricitinib shown in the table below. While Lilly submitted a rationale for the dosing recommendations, it is based on post-hoc analyses which are exploratory, at best, and not sufficient to provide substantial evidence to inform the benefit-risk analysis in the proposed subpopulation of patients who have failed two or more DMARDs. The FDA post-hoc statistical analyses do not support this new proposed dosing regimen.

Lilly's Proposed Indication and Dosage and Administration for Baricitinib		
	Baricitinib 2 mg	**Baricitinib 4 mg**
Indication		
Original Submission	adult patients with moderately to severely active rheumatoid arthritis	
Resubmission	adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate	
Dosage and Administration		
Original Submission	For some patients, a dose of 2 mg once daily may be acceptable	Recommended dose
Resubmission	Recommended dose 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.	For patients with an inadequate response or intolerance to more than one disease modifying antirheumatic drug (DMARD), a dose of 4 mg once daily is recommended.

Arthritis Advisory Committee

An Arthritis Advisory Committee (AAC) was convened on April 23, 2018 to discuss this NDA.[1] The following is a brief summary of the voting and discussion from the AAC meeting.

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.
   - *There may be some differences between the doses with respect to speed of response (faster with 4 mg dose), radiographic progression, and some*

[1] https://www fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm601797.htm

additional benefit in sicker patients. The tapering study also suggested greater efficacy with the 4 mg dose. Patients need more options.

2. **VOTE (Efficacy 2 mg):** Do the data provide substantial evidence of the efficacy of baricitinib 2 mg 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?
   - *14 Yes, 1 No, 0 Abstain*
   - *The single no vote was because of the lack of robust radiographic progression data with the 2 mg dose.*

3. **VOTE (Efficacy 4 mg):** Do the data provide substantial evidence of the efficacy of baricitinib 4 mg 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?
   - *15 Yes, 0 No, 0 Abstain*

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:
   -Adequacy of safety database for the 2 mg dose of baricitinib
   -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
   - 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.
   - *Rheumatologists do not typically monitor for VTE events. We do not fully understand the VTE risk with the 4 mg dose and there is even less data with the 2 mg dose. It is not clear what to do with the change in platelets; it is not predictive of VTE. The risk of VTE appears to be less than with oral contraceptives.*

5. **VOTE (Safety 2 mg):** Are the safety data adequate to support approval of baricitinib 2 mg 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?
   - *9 Yes, 6 No, 0 Abstain*
   - *Panelists noted there was not enough safety data with the 2 mg dose and no new data since the CR action. Some data suggest the 2 mg is safer than the 4*

mg dose, which may be considered an upper bounds for the safety issues. Additional data are needed with the 2 mg dose.

6. **VOTE (Safety 4 mg):** Are the safety data adequate to support approval of baricitinib 4 mg 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?
    - *5 Yes, 10 No, 0 Abstain*
    - *One panelist wanted to switch his vote from yes to no. There is a clear signal with VTE in the 4 mg dose that needs further evaluation. At least 2 of the panelists that voted "yes noted this was in the context for refractory patients and another who voted yes, referenced the efficacy of the higher dose.*

7. **VOTE (Benefit/Risk 2 mg):** Is the benefit-risk profile adequate to support approval of baricitinib 2 mg 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?
    - *10 Yes, 5 No, 0 Abstain*
    - *At least 2 of the panelists noted that they would like baricitinib available for patients who failed biologics. Postmarketing studies would be necessary.*

8. **VOTE (Benefit/Risk 4 mg):** Is the benefit-risk profile adequate to support approval of baricitinib 4 mg 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?
    - *5 Yes, 10 No, 0 Abstain*
    - *There is a need for more data. Several panelists did note that benefit/risk could be acceptable for a refractory population.*

Benefit Risk Assessment

In considering a recommendation regarding approval of baricitinib, it is helpful to consider elements of the benefit/risk framework.

Analysis of Condition

Rheumatoid arthritis is a serious disease associated with significant morbidity and increased mortality.

Current Treatment Options

While there are many treatment options available, the AC panel and patient testimony at the AC meeting clearly noted that more treatment options are needed, particularly for those patients with

refractory disease who have failed other therapies. Another JAK inhibitor, tofacitinib, is available. While it is not known if patients would respond differently to tofacitinib and baricitinib, there are differences between the JAK inhibition between products - baricitinib preferentially inhibits JAK1 and JAK2, while tofacitinib preferentially inhibits JAK1 and JAK3. These differences may translate into differences in clinical efficacy and safety profiles and individual responses to treatment. Availability of baricitinib would provide another oral treatment option for RA patients.

Benefit

The efficacy of both the 2 mg and 4 mg dose of baricitinib for signs and symptoms of RA, as well as for physical function assessed by HAQ-DI response have been established by the baricitinib clinical development program. Data do not consistently show a benefit of 4 mg over the 2 mg dose. Both the 2 and 4 mg doses of baricitinib demonstrated efficacy in more refractory patients that had an inadequate response to TNF inhibitors (JADW). The data on structural progression assessed by radiographic response showed consistent efficacy for baricitinib 4 mg dose, while the data for 2 mg was not as robust. The AC panel was nearly unanimous that available data support the efficacy of both doses of baricitinib.

Risk and Risk Management

The safety profile of baricitinib is consistent with that of a potent immunosuppressant with major safety risks of serious and some fatal infections, including opportunistic infections and tuberculosis, malignancy, laboratory abnormalities of increase in platelet counts, decrease in neutrophil counts, and increases in lipid parameters, and serum creatine phosphokinase (CPK). While the laboratory abnormalities appeared to be dose-dependent, other AE of special interest, such as serious infections and malignancies did not clearly show a dose response - although the limited data in the 2 mg group prevents adequate dose response assessment. Additionally, arterial and venous thromboses were observed in association with baricitinib treatment. While many of the adverse reactions listed are typical for immunosuppressive therapy used for RA patients, the dose dependent platelet elevations and reports of thrombotic events are noteworthy and were not identified in the tofacitinib development program.

For the baricitinib 4 mg dose, a signal for thromboembolic (TE) adverse reactions was noted in the baricitinib development program. There is uncertainty about the TE risk with the 2 mg dose due to the limited safety database, but other data (laboratory parameters) suggest a dose response in safety profile, which may translate into a lower risk of serious adverse events of interest, such as serious infection.

Labeling will be the primary method to communicate the risks of baricitinib. Given the seriousness of TE events, a Boxed Warning would be appropriate. Additional information will be necessary to further quantify the TE signal for both baricitinib doses.

Recommendations for Regulatory Action

Based upon the available data and the feedback from the Advisory Committee meeting, we recommend the following for the baricitinib NDA:

- 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 to one or more TNF antagonist therapies.

Approval of baricitinib 2 mg would provide an additional oral treatment option for patients who are refractory to other therapy. While the limited safety database with 2 mg does introduce uncertainty, the dose related pharmacodynamic changes, including laboratory abnormalities and experience with tofacitinib, as another JAK inhibitor, would suggest that the risk of serious adverse events of interest are also dose-related. Thus, the baricitinib 2 mg dose would be expected to have a better safety profile than the 4 mg dose. Given that the efficacy data do not show a significant difference between the 2 mg and 4 mg dose, the benefit/risk assessment is more favorable for baricitinib 2 mg, based on the data submitted to the NDA.

The AC panel recommended approval of baricitinib 2 mg in patients who are MTX-IR; however, some members voiced preference to reserve baricitinib for patients with an incomplete response to biologic therapy. There is precedent for limiting an RA product to a TNF-IR patient population, based upon benefit/risk assessment. When Actemra was approved in January 2010, it was limited to patients with an incomplete response to TNF inhibitors because of concerns with the safety profile. Approval of the 2 mg dose of baricitinib balances the uncertainty of the limited 2 mg safety database with the availability of another treatment option for more refractory RA patients and makes the benefit/risk assessment more favorable.

(b) (4)

Postmarketing Recommendations

- Postmarketing Requirements (PMRs)

A PMR is recommended for an active controlled clinical trial to further define the long term safety of baricitinib, particularly the risk of VTE events. The proposed PMR language is shown below.

> *Controlled clinical trial to evaluate the long term safety of baricitinib in patients with rheumatoid arthritis. The trial should include* (b) (4) *two doses of baricitinib and an active comparator. The trial should be of sufficient size and duration to evaluate safety events of interest, including venous thromboembolic events, cardiovascular adverse events, opportunistic infections, and malignancy.*[2]

Results of the PMR would be utilized to update the product label for baricitinib and provide data about the serious risks of baricitinib with the 2 mg dose. The data may also be useful to inform the benefit/risk assessment for the broader indication of MTX-IR RA patients. (b) (4)

- Postmarketing Commitments (PMCs)

The clinical pharmacology team has determined that, based on the data submitted, baricitinib exposure is increased approximately two-fold in subjects with moderate renal impairment compared to subjects with normal renal function or when co-administered with strong OAT3 (organic anion transporter 3) inhibitors. To address the need for dose adjustment in these settings, the following PMC is listed below:

> *Develop baricitinib tablet with 1 mg dosing strength for dose adjustment in patients with moderate renal impairment or patients taking strong OAT3 inhibitors*

2 (b) (4)
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- Risk Evaluation and Management Strategies (REMS)

A REMS is not recommended based on the submitted data. Review by the Division of Risk Management (DRISK) has also concluded that a REMS is not necessary for this application.

Pediatrics

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Thus, baricitinib approval for RA triggers PREA. With this NDA, the Applicant submitted a pediatric assessment, consistent with the agreed iPSP (initial Pediatric Study Plan). The pediatric assessment included a request for partial waiver of studies for children 0 to <2 years of age, because studies in this age group are highly impractical to complete due to the rarity of PJIA in children under 2 years of age and a deferral of studies in children ages 2 to <18 years of age because the risk/benefit of baricitinib has been characterized in adults and studies can commence in children. The proposed pediatric assessment includes the following studies: 1) Bioequivalence study of baricitinib suspension compared to commercial tablet formulation in healthy adults and 2) A randomized, withdrawal, double-blind, placebo-controlled, safety and efficacy study of oral baricitinib in children from 2 to less than 18 years old with polyarticular juvenile idiopathic arthritis (pJIA).

The baricitinib pediatric program was discussed at the Pediatric Review Committee (PeRC) meeting on May 2, 2018. The PeRC agreed with the requested waiver and deferral. At the meeting, an additional consideration was discussed. Specifically, if the adult RA population is to be restricted to patients with moderately to severely active rheumatoid arthritis who have intolerance or inadequate response to TNF inhibitors (TNF-IR), then the Applicant may provide a justification for requesting a waiver of the requirement for pediatric studies in patients 2 to <18 years of patients with PJIA who are TNF-IR because this subpopulation is too small to perform feasible studies. The Applicant amended the application with such justification. The Division and PeRC are in agreement with this request and justification for granting a full waiver of pediatric studies in this narrow subpopulation.

If in the future, the RA indication is broadened, then the pediatric program can be re-evaluated.

Labeling

- Proprietary name

The proposed proprietary name for baricitinib 2 mg is Olumiant. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and by the Office of Prescription Drug Promotion (OPDP) and was found to be acceptable.

- Physician labeling

Major issues with the originally-proposed labeling (version submitted December 04, 2017):

INDICATIONS AND USAGE section:

Proposed indication: "*TRADE is indicated 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).*"

- As discussed at the April 23, 2017 Arthritis Advisory Committee meeting (summarized above), members of the committee voted 10 to 5 not to approve the 4 mg once daily dose noting the clear signal with VTE with that dose and the need for further evaluation. While the committee voted 10 to 5 for approval of the 4 mg once daily dose, they also noted the limited safety database with that dose. Some of the panelists noted that baricitinib would be more appropriate for patients who failed biologics therapies.

- To address the committee benefit-risk considerations and the limitations of the small safety database with the 2 mg once daily dose, the indication was revised to: "*OLUMIANT is a Janus kinase (JAK) inhibitor indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.*"

- Further, due to potential risk of increase in serious infections with the co-administration of baricitinib with other potent immunosuppressants, the following limitation of use was included: "*Limitation of Use: Use of OLUMIANT in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.*"

DOSAGE AND ADMINISTRATION section:

Proposed dosage and administration: "*The recommended dose of OLUMIANT 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.*"

- (b) (4) the dosing recommendation was revised as follows: "*The recommended dose of OLUMIANT is 2 mg once daily. OLUMIANT may be used as monotherapy or in combination with methotrexate or other DMARDs.*"

BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections:

The originally submitted prescribing information included a Boxed Warning limited to the risk of serious infections including active tuberculosis, invasive fungal infections, tuberculosis, opportunistic infections, lymphoma and other malignancy.

- The Boxed Warning was revised to include the risk of venous and arterial thrombosis.

ADVERSE REACTIONS section:

The originally submitted prescribing information presented the safety data based on the integrated safety analyses from all four phase 3 studies, consistent with the labeling discussions during the first review cycle.

- However, this presentation has certain limitations, as discussed elsewhere in this document and in the original reviews. To address some of these limitations, and to more accurately represent the comparisons between baricitinib 2 mg, 4 mg, and placebo, the data presented in this section, were derived from the phase 2 and phase 3 placebo-controlled studies that studied placebo, baricitinib 2 mg, and/or 4 mg dose (JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY, and JADW/JADY). The same integrated data were used in the CDTL review and presented at the April 23, 2018 Arthritis Advisory Committee. Comparisons to placebo are presented for Week 0 to 16, and comparisons between baricitinib 2 mg and 4 mg once daily dose are presented also for Week 0 to 52. Data beyond these time periods were not presented due to limitations of the study design and the overall baricitinib program, as discussed elsewhere in the reviews.

USE IN SPECIFIC POPULATIONS section:

Renal impairment: Renal function was found to significantly affect baricitinib exposure. Thus baricitinib is not recommended for use in patients with moderate or severe renal impairment (estimated GFR of less than 60 mL/min/1.73 m^2).

CINICAL STUDIES section:

The data are presented for two dose-ranging placebo-controlled studies, JADA and JADN, which studied both baricitininb 2 and 4 mg once daily doses to provide information on the exposure-response of doses between 1 and 8 mg once daily.

(b) (4)

the labeling includes the following statement: "*The OLUMIANT clinical development program included two dose-ranging trials and four confirmatory phase 3 trials. Although other doses have been studied, the recommended dose of OLUMIANT is 2 mg once daily.* " Thus, data from only two of four confirmatory phase 3 studies are

presented in this section, JADX and JADW. Further, only placebo and baricitinib 2 mg data are presented for the confirmatory studies.

Additional considerations on specific claims:

- Removed information on SDAI (Simplified Disease Activity Index), because that instrument is redundant with the ACR response rates as it captures the same component as the ACR response rates which are reflected in the labeling.
- Information was added on the DAS28-hsCRP results to also indicate how many active joints patients have despite having DAS28-CRP<2.6, consistent with regulatory precedent.
- Revised data from figures and tables beyond the placebo controlled period.
- [redacted] (b) (4)
- Information related to severity of morning stiffness and worst tiredness are removed as they have been studied for the 2 mg once daily dose in only one of the two phase 3 studies.

- Patient labeling

Minor edits and formatting revisions were incorporated based on the patient labeling review team recommendations.

- Carton and container labeling

Acceptable from CMC and DMEPA perspective.

REVIEW OF NDA RE-SUBMISSION

Introduction

On January 15, 2016, the Applicant submitted new drug application (NDA) 207924 to support the use of baricitinib for the proposed indication for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate (MTX). Baricitinib is a small molecule inhibitor of Janus associated kinases (JAK). JAKs are intracellular enzymes that transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function.

On April 12, 2017, a complete response (CR) letter was issued concluding that the overall benefit/risk profile for baricitinib was not favorable given the association of baricitinib with venous thrombotic events (VTE) in the RA clinical program.

In the CR letter issued to the Applicant on April 12, 2017, the Applicant was notified of the following deficiencies to address:

- There was an imbalance in thrombotic events in the baricitinib RA program with potential thrombotic risk with use of baricitinib in RA
- There was inadequate safety exposure for 2 mg of baricitinib
- There were 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.

To address the FDA's concern, the Applicant conducted several post-hoc analyses in subgroups of patients from the studies previously reviewed in the original NDA submission. The analyses were used to support a proposed dosing regimen that was modified from the proposed dosing regimen in the original NDA submission in order to address benefit risk concerns. The Applicant proposed that the potential thromboembolic risk be managed through labeling, by adding a warning to the prescribing information about the potential risk of thrombosis, as well as through communications to health care professionals, postmarketing safety studies, and routine pharmacovigilance.

The Applicant's resubmission includes the following components intended to address the CR letter:

- Additional analyses for the dose ranging studies to justify the dosing strategy carried out in the phase 3 studies
- Additional post-hoc efficacy analyses in patients who had failed more than one disease modifying anti-rheumatic drug (DMARD) to support the new dosing recommendations in the Applicant's proposed prescribing information
- Safety analyses with an updated cut-off date, April 01, 2017 (the safety data lock for the original NDA was August 10, 2015)

- Comparative analyses of the retrospective cohort studies from the Sentinel and Truven Marketscan databases with the prospective baricitinib studies in RA to evaluate venous thromboembolic risk
- Updated prescribing information to change the indication, dosage, and administration to address the 2 mg and 4 mg doses
- Updated prescribing information to change the warnings and precautions to include a warning about the potential risk of thrombosis.

Safety Update

In the original NDA submission, the major toxicities of concern identified with baricitinib are related to immunosuppression. Baricitinib use was associated with infections, including opportunistic infections and tuberculosis. Additional potential risks included malignancy, gastrointestinal perforations, and thrombosis. Many of the identified safety signals, such as laboratory abnormalities, opportunistic infections, tuberculosis, and venous thrombosis, had a numerically higher incidence rate with the 4 mg than 2 mg dose. For many adverse events of special interest, such as cardiovascular events, there were few events observed overall limiting the ability to rule out increases in risk based on the available data. Baricitinib treatment was also associated with dose-dependent laboratory abnormalities, including neutropenia, lymphopenia, platelet elevations, and increases in liver enzymes and lipids.

One potential risk which appeared unique to baricitinib was the increased incidence of thrombosis which was considered important in the benefit-risk assessment during the original NDA review and was considered one of the deficiencies of the application, as detailed in the Complete Response letter.

To address the deficiencies in the CR letter, in this re-submission, the Applicant provided a safety update to include:

- Accumulated safety from previously reviewed clinical studies with a cut-off date of April 1, 2017
- Limited additional safety from one more completed study in RA using the 4 mg baricitinib dose versus placebo, JAGS, and two completed studies in non-RA indications.
- Epidemiological data on venous thrombosis from patients on DMARD with diagnosis of RA in the IMEDS (Innovation in Medical Evidence Development and Surveillance) Distributed Database and the Truven Health Marketscan Commercial Claims and Encounters Databases (Truven Marketscan Database)

This information will be summarized in the following sections.

Accumulated Safety (as of April 1, 2017 cut-off date)

In this re-submission, the Applicant provided an updated safety database that comprises the accumulated safety from all previously reviewed clinical studies with a cut-off date of April 1, 2017, and additional safety from one more completed study in RA, JAGS, and two completed studies in non-RA indications, JAHH in systemic lupus erythematosus (SLE), and JAHG in atopic dermatitis. A summary of the safety database sources is presented in Table 1.

Table 1. Summary of Safety Database Sources

	Applicant submissions						FDA requested datasets (0-52 weeks)	
	Initial submission		Resubmission safety update				Division director review	CDTL memo
Database	All BARI RA:	All BARI:	All BARI RA	Phase 3 RA study	Non-RA indications:	Total	Information request from 1/6/2017	Ext BARI 2 mg/4 mg PC
Studies included	JADA/Y, JADB, JADC, JADN, JADV/Y, JADW/Y, JADX/Y, JADZ/Y	JADA/Y, JADB, JADC, JADN, JADP, JAGQ, JADV/Y, JADW/Y, JADX/Y, JADZ/Y	JADA/Y, JADB, JADC, JADN, JADV/Y, JADW/Y, JADX/Y, JADZ/Y	JAGS	JAHH in SLE and JAHG in atopic dermatitis		JADV/Y, JADW/Y, JADX/Y, JADZ/Y	JADC, JADN, JADA/Y, JADV/Y, JADW/Y, JADX/Y
Patients. n	3464	3822	3492	278	433	4203	1668	1476
Total patient years	4214	4452	7860	212	259	8332	2000	1318

Source: FDA reviewer
Abbreviations: CDTL=cross disciplinary team leader, BARI=baricitinib, RA=rheumatoid arthritis, Ext=extended, SLE=systemic lupus erythematosus

The re-analysis includes 3492 patients and 7860 patient-year exposure in the ALL BARI RA analysis set which includes all patients who participated in a phase 2 or phase 3 baricitinib RA study and received at least one dose of baricitinib. The Applicant includes another 278 patients from the phase 3 RA study JAGS which was conducted predominantly in China and 75 patients from an atopic dermatitis study (JAHG). The patients from study JAGS are not integrated into the resubmission safety update.

In addition to the ALL BARI RA analysis and other analyses conducted by the Applicant, the Applicant provided additional analyses requested by the FDA. The Division Director memo and the cross disciplinary team leader (CDTL) memo report results from two different approaches to analyze integrated safety data provided by the Applicant.

The CDTL memo focused primarily on an integrated safety database that consisted of six placebo-controlled phase 2 and phase 3 studies of baricitinib in RA (and the extension study JADY). Because study JADZ had an active comparator arm of optimized MTX and did not include a placebo arm, study JADZ was not included. The CDTL memo presented results from analyses that included all time on the initially randomized treatment arm and did not include events that occurred after patients escaped to other arms of the study.

The approach included six studies to increase the baricitinib exposure for the 2 mg and 4 mg doses and to gain as much precision as possible in the evaluation of rare adverse events of special interest. However, there were some limitations to this approach. Studies JADV and JADC did not include a 2 mg of baricitinib study arm but had a 4 mg of baricitinib study arm and a placebo arm. Furthermore, analyses that include data after the first time point of escape (16 weeks) could lead to biased results against the 4 mg dose, as the placebo and 2 mg study arms were censored at rescue and the 4 mg dose arm was not.

The Division Director review used a different FDA requested analysis with results pooled from the four phase 3 RA studies, including Study JADZ, and patients who continued in the extension study, JADY (see Table 1). The safety database was locked on August 10, 2015 during the original review cycle for this FDA requested analysis.

The analysis incorporated the pooled events that occurred in all the phase 3 studies that had either a placebo or a baricitinib arm. No active comparator arms were used in this analysis. This analysis included data collected after patients escaped from placebo or 2 mg to 4 mg or were tapered down to 2 mg from 4 mg dose in the extension study JADY. Events reported in this analysis were attributed to the study drug the patient was taking at the time of the adverse event. Therefore, the baricitinib 4-mg group includes data from patients receiving baricitinib 4 mg via randomization as well as those receiving baricitinib 4 mg after rescue or switch from treatment with placebo, baricitinib 2 mg, adalimumab, or MTX. The baricitinib 2 mg group includes data from patients receiving baricitinib 2 mg via randomization as well as those receiving baricitinib 2 mg after step-down from baricitinib 4 mg during the long-term extension. This analysis is used to present the safety update from the resubmission as of the updated database lock of April 1, 2017.

An advantage of this analysis is that it uses all the exposure time in the phase 3 studies and extensions for the placebo and baricitinib arms. This allowed for increased precision in the evaluation of rare events and events with long latency periods to be observed.

However, there are limitations using this approach. The integrated analysis includes a study without a placebo arm, which could induce confounding by study in placebo comparisons. Furthermore, the inclusion of data after escape could induce further biases against the 4 mg dose arm. Events were censored in the placebo arm at time of escape so comparisons of the placebo and baricitinib arms were quite limited beyond 16 weeks of study duration. In patients who were randomized to the 2 mg baricitinib arm, events were also censored at the time of escape. Events that occurred in patients who were randomized to either placebo or 2 mg of baricitinib and escaped to 4 mg of baricitinib were attributed to the 4 mg dose of baricitinib. Also, patients who were stable on 4 mg of baricitinib at entry to JADY and were randomized to 2 mg of baricitinib had adverse events attributed to 2 mg of baricitinib. Thus, in general, patients who were having increased activity of their RA (and may have had a higher underlying risk of certain AEs) were being placed on the 4 mg dose of baricitinib and patients who were doing well on 4 mg baricitinib could be placed on the lower dose of 2 mg. Only two of three study arms in JADZ were included in the analysis. The two arms included were baricitinib 4 mg monotherapy and combination baricitinib 4 mg and optimized MTX. The comparator arm, optimized MTX, was not a placebo-control and thus was not included. All events that occurred in study JADZ for this analysis were attributed to the 4 mg baricitinib dose arm.

The overall safety profile of baricitinib was similar, regardless of the safety database integration strategy used. These strategies, however, cannot overcome the limited placebo control data and limited safety database with the baricitinib 2 mg dose.

Deaths and Serious Adverse Events (SAEs)

Table 2 shows the deaths and serious adverse events (SAE) that occurred in the baricitinib phase 3 program. Only 3 deaths occurred by week 16. By week 52, numerically more deaths were seen in the 4 mg baricitinib group (n=6) as compared to the placebo group (n=3), but given the

difference in exposure, the incidence rate of deaths was numerically higher in the placebo group (0.8 per 100 patient years) compared to the 4 mg baricitinib group (0.4 per 100 patient years). Comparison of the 4 mg and 2 mg dose using any duration of study showed a small increase in deaths (0.4 per 100 patient years for the 4 mg baricitinib dose and 0.2 per 100 patient years for the 2 mg baricitinib dose). Overall, given the limited number of deaths in the program, it is difficult to make conclusions about death related to use of baricitinib.

The rate of SAEs did not suggest an increase for baricitinib compared to placebo during the 16 week period and the 52 week period. After 52 weeks, the incidence rate of SAEs was slightly higher for the 4 mg dose versus the 2 mg dose as shown in the "any duration" period from the original submission (10.3 SAEs per 100 patient years for 4 mg of baricitinib and 9.1 SAEs per 100 patient years for the 2 mg dose). The resubmission had similar numbers for "any duration" (9.5 for 4 mg and 8.2 for 2 mg). Overall, there was not a large, consistent difference in rate of SAEs between the two doses of baricitinib.

Table 2. Updated Overview of Deaths and SAEs 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
All cause death, n (EAIR)	1 (0.3)	0	2 (0.7)
SAE, n (rate)	49 (12.7)	11 (9)	37 (13.8)
0-52 weeks			
Total exposure in patient years	1695	305	365
All cause death, n (EAIR)	6 (0.4)	0	3 (0.8)
SAE, n (rate)	193 (11.4)	34 (11.2)	50 (13.7)
> 52 weeks			
Total exposure in patient years	1300	210	NA
All cause death, n (rate)	5 (0.4)	1 (0.5)	
SAE, n (rate)	146 (11)	15 (7)	
0-any duration			NA
Total exposure in patient years	2996	515	
All cause death, n (rate)	11 (0.4)	1 (0.2)	
SAE, n (rate)	310 (10.3)	47 (9.1)	
Resubmission Update, April 1, 2017 Data Lock			
>52 weeks			
Number of patients	2441	703	NA
Total exposure in patient years	4125	957	
All cause death, n (rate)	18 (0.4)	2 (0.2)	
SAE, n (rate)	412 (10)	73 (7.6)	
0-any duration			
Number of patients	2717	929	
Total exposure in patient years	5820	1261	NA
All cause death, n (rate)	24 (0.4)	2 (0.2)	
SAE, n (rate)	552 (9.5)	104 (8.2)	

Source: Information request response dated March 20, 2018 p. 8, Division Director review, p. 25
Abbreviations: BARI=baricitinib, SAE=serious adverse event, EAIR= exposure adjusted incidence rate, n=number of events

Infections, Including Serious and Opportunistic Infections

Table 3 summarizes serious infections, opportunistic infections, tuberculosis, and herpes zoster (HZ) that occurred in the baricitinib phase 3 RA program. Data from the baricitinib program showed a numerically higher rate of HZ with baricitinib compared to placebo, but the rate of HZ infections was similar between the 2 and 4 mg dose groups. In terms of serious infections and

opportunistic infections, there was not a large consistent trend among the treatment groups during the 16 and 52 week period.

In the resubmission, there was a numerically higher incidence rate per 100 patient years of serious infections (3.1 versus 2), opportunistic infections (0.6 versus 0.3), tuberculosis (0.2 versus 0.1), HZ (3.3 versus 2.6) and multi-dermatomal HZ (0.3 versus 0.2) in the 4 mg dose group versus the 2 mg group when viewing the any duration time period.

Table 3. Updated Summary on Serious Infections, Opportunistic Infections, Tuberculosis, and H. Zoster 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 serious infection, n (rate)	13 (3.4)	4 (3.3)	13 (4.9)
Patients with opportunistic infections, n (rate)	4 (1)	0	2 (0.7)
Patients with tuberculosis, n (rate)	0	0	0
Patients with herpes zoster, n (rate)	15 (3.9)	5 (4.1)	4 (1.5)
0-52 weeks			
Total exposure in patient years	1695	305	365
Patients with serious infection, n (rate)	57 (3.4)	12 (3.9)	17 (4.7)
Patients with opportunistic infections, n (rate)	7 (0.4)	1 (0.3)	2 (0.5)
Patients with tuberculosis, n (rate)	2 (0.1)	0	0
Patients with herpes zoster, n (rate)	57 (3.4)	11 (3.6)	4 (1.1)
> 52 weeks			
Total exposure in patient years	1301	210	NA
Patients with serious infection, n (rate)	44 (3.4)	6 (2.9)	
Patients with opportunistic infections, n (rate)	7 (0.5)	1 (0.5)	
Patients with tuberculosis, n (rate)	5 (0.4)	0	
Patients with herpes zoster, n (rate)	38 (2.9)	6 (2.9)	
0-any duration			
Total exposure in patient	2996	515	NA

years			
Patients with serious infection, n (rate)	97 (3.2)	17 (3.3)	
Patients with opportunistic infections, n (rate)	14 (0.5)	2 (0.4)	
Patients with tuberculosis, n (rate)	7 (0.2)	0	
Patients with herpes zoster, n (rate)	94 (3.1)	17 (3.3)	
Resubmission Update, April 1, 2017 Data Lock			
>52 weeks			
Number of patients	2441	703	NA
Total exposure in patient years	4125	957	
Patients with serious infection, n (rate)	132 (3.2)	14 (1.5)	
Patients with opportunistic infections, n (rate)	24 (0.6)	3 (0.3)	
Patients with tuberculosis, n (rate)	9 (0.2)	1 (0.1)	
Patients with herpes zoster, n (rate)	136 (3.3)	22 (2.3)	
0-any duration			
Number of patients	2717	929	NA
Total exposure in patient years	5820	1261	
Patients with serious infection, n (rate)	182 (3.1)	25 (2)	
Patients with opportunistic infections, n (rate)	34 (0.6)	4 (0.3)	
Patients with tuberculosis, n (rate)	11 (0.2)	1 (0.1)	
Patients with herpes zoster, n (rate)	190 (3.3)	33 (2.6)	
Source: Information request response dated March 22, 2018 p. 6, Division Director review, p. 32-33 Abbreviations: BARI=baricitinib			

Malignancy, Excluding Non-Melanoma Skin Cancer (NMSC)

Table 4 shows the malignancies excluding non-melanoma skin cancer (NMSC) that occurred in the baricitinib RA program. The incidence rate of malignancies was fairly similar between treatment arms up to Week 52. In the original review, numerically higher cumulative incidence rates of malignancy were observed in the "0 to any duration" period for the 4 mg dose group compared with 2 mg group (0.8 vs. 0.4, respectively). However, in the resubmission, such differences were not seen (0.9 malignancies per 100 patient years for the 4 mg dose and 0.8 per 100 patient years for the 2 mg dose).

Table 4. Update of Malignancy excluding NMSC 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
Any malignancy excluding NMSC, n (rate)	2 (0.5)	1 (0.8)	0
0-52 weeks			
Total exposure in patient years	1695	305	365
Any malignancy excluding NMSC, n (rate)	10 (0.6)	2 (0.7)	2 (0.5)
> 52 weeks			
Total exposure in patient years	1301	210	NA
Any malignancy excluding NMSC, n (rate)	15 (1.2)	0	
0-any duration			
Total exposure in patient years	2996	210	NA
Any malignancy excluding NMSC, n (rate)	25 (0.8)	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	
Any malignancy excluding NMSC, n (rate)	45 (1.1)	8 (0.8)	
0-any duration			
Number of patients	2717	929	NA
Total exposure in patient years	5820	1261	
Any malignancy excluding NMSC, n (rate)	55 (0.9)	10 (0.8)	

Source: Information request response dated March 20, 2018, p. 8, Division Director review, p. 30
Abbreviations: BARI=baricitinib; NMSC=non-melanoma skin cancer

Major Adverse Cardiovascular Events (MACE)

Table 5 shows the major adverse cardiovascular events (MACE) that occurred in the baricitinib RA program. Through Week 16, MACE rates were balanced between the placebo and 4 mg groups. In the original submission through "any duration" the incidence rate was higher in the 4 mg baricitinib group when compared to the 2 mg group. This trend continued with the

resubmission. For the resubmission, the incidence rate of MACE was 0.6 per 100 patient years for 4 mg and 0.2 per 100 patient years for 2 mg.

Table 5. Update of Major Adverse Cardiovascular Events in Baricitinib RA program

	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
MACE, n (rate)	2 (0.5)	0	2 (0.7)
0-52 weeks			
Total exposure in patient years	1695	305	365
MACE, n (rate)	7 (0.4)	1 (0.3)	2 (0.5)
> 52 weeks			
Total exposure in patient years	1300	210	NA
MACE, n (rate)	8 (0.6)	0	
0-any duration			NA
Total exposure in patient years	2996	515	
MACE, n (rate)	15 (0.5)	1 (0.2)	
Resubmission Update, April 1, 2017 Data Lock			
>52 weeks			
Number of patients	2441	703	NA
Total exposure in patient years	4125	957	
MACE, n (rate)	29 (0.7)	1 (0.1)	
0-any duration			
Number of patients	2717	929	
Total exposure in patient years	5820	1261	NA
MACE, n (rate)	36 (0.6)	2 (0.2)	

Source: Information request response dated March 20, 2018, p. 8, Division Director review, p. 34-35
Abbreviations: BARI=baricitinib; MACE=major adverse cardiovascular event

Discussion on Thrombosis

Both venous and arterial thromboses occurred in patients treated with baricitinib in the RA clinical program as summarized in Table 6 and Table 7, which appeared to distinguish baricitinib from previously approved RA therapies.

Venous Thrombosis

In the first 16 weeks of study duration in the original submission there were 4 events in the baricitinib 4 mg group (corrected by the Applicant to 5 events in the re-submission) and no

events in the 2 mg or placebo groups. Additional events accumulated in the 2 mg and 4 mg groups through Week 52.

In the resubmission, the incidence rate of 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.

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

Arterial Thrombosis

Table 7 shows the arterial thrombosis events that occurred during the baricitinib clinical RA program. At 16 weeks, there were 5 arterial thrombosis events across the 3 treatment groups. baricitinib. Arterial thrombosis continued to accumulate in the baricitinib arms during the any duration period with 16 total events in the baricitinib 4 mg group (0.5 events per 100 patient years) and 2 total events in the 2 mg group (0.4 events per 100 patient years).

Table 7. Arterial Thrombosis in Baricitinib Clinical Program in RA

	BARI 4	BARI 2	Placebo
0-16 weeks			
Number of patients	1265	403	892
Total exposure in patient years	387	123	267
Patients with thromboses, n (rate)	2 (0.5)	2 (1.6)	1 (0.4)
0-52 weeks			
Number of patients	2457	403	
Total exposure in patient years	1695	305	365
Patients with thromboses, n (rate)	8 (0.5)	3 (1)	1 (0.3)
> 52 weeks			
Number of patients	2441	703	NA
Total exposure in patient years	4125	957	
Patients with thromboses, n (rate)	21 (0.5)	1 (0.1)	
0-any duration			
Number of patients	2717	929	NA
Total exposure in patient years	5820	1261	
Patients with thromboses, n (rate)	28 (0.5)	4 (0.3)	
Source: Information request response dated March 20, 2018, p. 8 Abbreviations:BARI=baricitinib			

Epidemiological Data on Venous Thromboembolism in RA

To further address the imbalance in thrombotic events seen in the baricitinib RA program, the Applicant provided comparisons of the rates of VTE with baricitinib use within the international clinical studies to the population-based rates of VTE observed in patients using other approved RA therapies, including DMARDs.

The VTE incidence rate for all patients exposed to baricitinib in the phase 2/3 clinical trial (referred to as the ALL BARI RA cohort) was compared to population-based VTE rates. The Applicant conducted a descriptive, population-based study using the FDA Sentinel System (Innovation in Medical Evidence Development and Surveillance [IMEDS] Program) and Truven Marketscan Commercial Claims and Encounters Database (Truven, including Medicare). Briefly,

patients with a diagnosis of RA (defined as at least 2 RA diagnosis codes [ICD-9-CM: 714.0, 714.1, 714.2] within 7-365 days of each other plus the use of any DMARDs by the index date ± 1 month) and age 18 years or older at index date were included. Patients were required to be continuously enrolled for medical and pharmacy coverage from 12 months prior to the index date through follow-up. Patients were excluded from the cohort if they had a diagnosis for a VTE in any care setting within the 365 days prior to or on their index date. Incidence rates were calculated as the number of events per 100 patient years (PY) and were stratified by age, gender and calendar year. However, the Applicant only provided the age-stratified rates in their report.

VTE incidence rate for all baricitinib-exposed patients in the ALL BARI RA cohort was 0.53 per 100 person years (PY) (95% confidence interval [CI] = 0.38 - 0.71), 0.38 per 100 PY (95% CI = 0.25 - 0.54) for deep vein thrombosis (DVT) and 0.24 per 100 PY (95% CI=0.14-0.37) for pulmonary embolism (PE; Table 8). The incidence of VTE per 100 PY was 1.34 (95% CI = 1.24 – 1.44) in IMEDS and 1.05 (95% CI = 1.01 – 1.09) in Truven. The Applicant concluded that the rates of VTE, DVT and PE among baricitinib patients were lower than or within the lower range of the VTE rates observed within the RA population treated with DMARDs.

Table 8. Outcome Incidence Rates Per 100 Patient Years by Study Groups

Study Groups (Data Source)	VTE IR (95% CI)	DVT IR (95% CI)	PE IR (95% CI)
Baricitinib (ALL BARI RA)	0.53 (0.38, 0.71)	0.38 (0.25, 0.54)	0.24 (0.14, 0.37)
DMARDs (IMEDS)	1.34 (1.24, 1.44)	1.97 (1.85, 2.09)[‡]	0.77 (0.70, 0.84)[‡]
DMARDs (Truven – Def. 1*)	0.68 (0.65, 0.71)	0.55 (0.52, 0.58)	0.26 (0.24, 0.28)
DMARDs (Truven – Def. 2*)	1.05 (1.01, 1.09)	0.84 (0.80, 0.87)	0.38 (0.36, 0.41)
DMARDs (Truven – Def. 3*)	1.63 (1.58, 1.69)	1.36 (1.31, 1.40)	0.46 (0.43, 0.49)

Abbreviations: CI= confidence interval, def= definition, DMARDs= disease modifying antirheumatic drugs, IR= incidence rates VTE=venous thromboembolism, DVT=deep vein thrombosis, PE=pulmonary embolism

* DEFINITION 1: diagnostic code + anticoagulant w/in 31 days of VTE, DVT, PE

DEFINITION 2: inpatient diagnostic code for venous or PE or phlebitis and thrombophlebitis or DVT or outpatient diagnostic code + anticoagulant within 31 days of VTE

DEFINITION 3: Diagnostic code for venous embolism or phlebitis and thrombophlebitis or DVT in an inpatient, outpatient or emergency department care setting

‡ The mid-P exact test 95% confidence intervals have been calculated by the DEPI-II reviewer using Open Epi Software.

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:

1. *The data collection methods for medical history, rheumatoid arthritis information, and baseline drug exposure differed between the clinical trials and observational studies.* For example, the IMEDS/Truven captures drug exposure 3 months before baseline while ALL BARI RA dataset captures drug use at baseline. Also, the IMEDS/Truven patients appear to be the least healthy compared to both US and non-US ALL BARI RA populations.

2. *The inclusion and exclusion criteria differed between the clinical trials and the observational studies.* For example, the sponsor compared baricitinib users from ALL BARI RA who survived DMARD use to incident DMARD users in the IMEDS/Truven data.

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).* Due to differing VTE rates between Western and Eastern countries, we asked the sponsor to stratify the data by US and non-US sites.[3,4] However, the differences in study methods and patient populations previously mentioned prevent an appropriate comparison of the data.

4. *Data from ALL BARI RA, IMEDS and Truven included patients with current anticoagulant use, potentially for the treatment of a prior VTE.* The VTE rates were stratified by anticoagulant use at baseline. Due to differences in ascertainment of the drug exposure variable (i.e. anticoagulants) between the trials and observational study, the stratified VTE rates cannot be compared.

   In conclusion, the VTE rates from the baricitinib clinical trials should not be compared to the VTE rates among DMARD users assessed in the observational data.

Proposed Safety Labeling Statements to Address the Potential Risk of Thrombosis

Recognizing the potential thrombotic risk with use of baricitinib in RA, the Applicant proposes to add the following language to the US prescribing information Warnings and Precautions section:

> *"Venous thromboembolic events, including deep venous thrombosis (DVT) and pulmonary embolus (PE), have been reported in clinical studies with OLUMIANT. There was no clear relationship between platelet count elevations and thrombotic events. The role of JAK inhibition in these events is not known. OLUMIANT should be used with caution in patients who may be at increased risk of venous thrombosis. If clinical features of DVT/PE occur, OLUMIANT treatment should be temporarily interrupted and patients should be evaluated promptly and treated appropriately."*

Laboratory Evaluations

Baricitinib treatment is associated with dose-dependent laboratory abnormalities, including neutropenia, lymphopenia, decreases in hemoglobin, platelet elevations, and increases in liver enzymes and lipids. These were previously reviewed in the original NDA submission. Thus, only pertinent safety updates will be discussed in this subsection of the summary of the re-submission.

[3] Wang K-L, Yap ES, Goto S, Zhang S, Siu C-W, Chiang C-E. The diagnosis and treatment of venous thromboembolism in Asian patients. Thrombosis Journal. 2018;16(1):4.
[4] Wendelboe AM, Raskob GE. Global Burden of Thrombosis: Epidemiologic Aspects. Circ Res. 2016;118(9):1340-1347.

Hepatic Enzyme Abnormalities

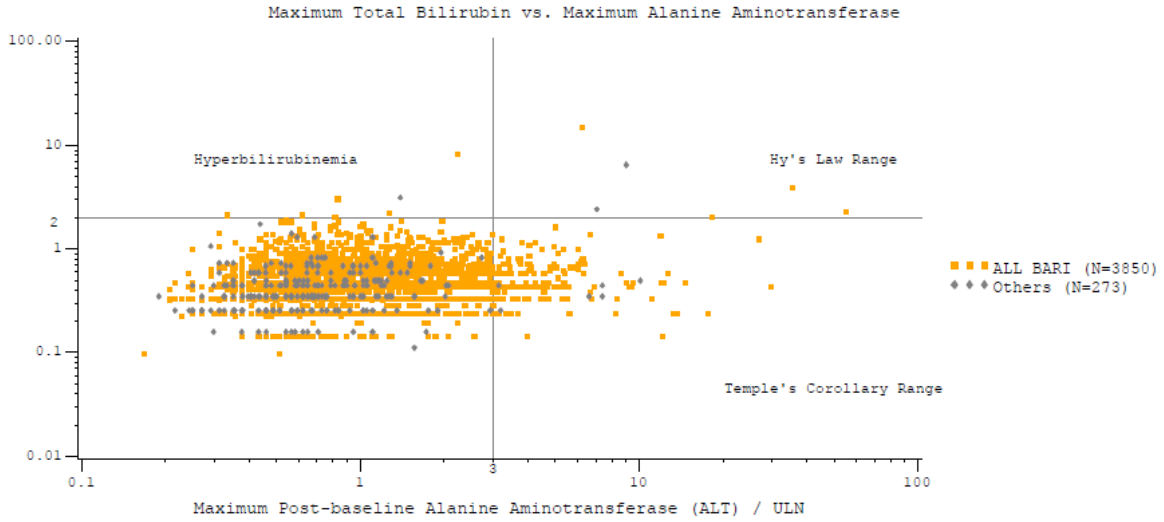
As noted in the reviews from the first review cycle, the use of baricitinib was associated with liver function test elevations and withdrawal of patients meeting the pre-specified criteria for permanent discontinuation due to such abnormalities (ten on baricitinib 4 mg dose, two on baricitinib 2 mg dose, two on adalimumab, and one on placebo). In a collaborative consult performed by FDA liver experts in Division of Gastroenterology and Inborn Errors Products (DGIEP) and Office of Surveillance and Epidemiology (OSE), it was observed that while there were no cases meeting Hy's law criteria,[5] there were patients who had symptoms and laboratory findings suggestive of drug-induced liver injury (DILI) but definitive association with baricitinib treatment could not be established given data presentation. Thus, the Complete Response letter requested additional data from phase 2 and 3 studies to be submitted in Evaluation of Drug-Induced Serious Hepatotoxicity (e-DISH) format along with patient narratives for subjects with laboratory criteria of Hy's law.

In response, the Applicant provided eDISH plots of ALT vs total bilirubin (Figure 1) and of AST vs total bilirubin (Figure 2) for patients in the 'All Bari' analysis set. Importantly, all acute liver injury cases of interest in the Hy's law range, the right upper quadrant (RUQ) of the graphic displays, were individually analyzed by the Applicant's internal hepatologist and a hepatic and gastrointestinal safety committee. Of 8 cases in the RUQ, six were associated with baricitinib treatment. From the individual narratives provided in the Appendix of the Safety Update Report, plausible alternative diagnostic etiologies have been found and described for each of the cases. The led to a conclusion by the Applicant's analysts that in this dataset there are no cases with biochemical criteria consistent with Hy's law that are causally linked to baricitinib exposure. Based on the available new clinical and diagnostic data, the FDA hepatology consultants have concluded that there were no cases with biochemical criteria consistent with Hy's law that are causally linked to baricitinib exposure, since in each of these cases, a more likely alternative explanation of liver injury has been demonstrated.

[5] Hy's law is used during clinical development to assess a drug's potential of inducing fulminant hepatic failure with larger/longer exposure, which is a rare and usually fatal event. Approximately 10% of Hy's law cases develop acute liver failure. The components of Hy's law are:

- Evidence of hepatocellular injury by any elevated aminotransferase of >3xULN,
- Evidence of liver dysfunction by increase in bilirubin ≥2xULN and without evidence of cholestasis by ALP <2xULN
- No other cause such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

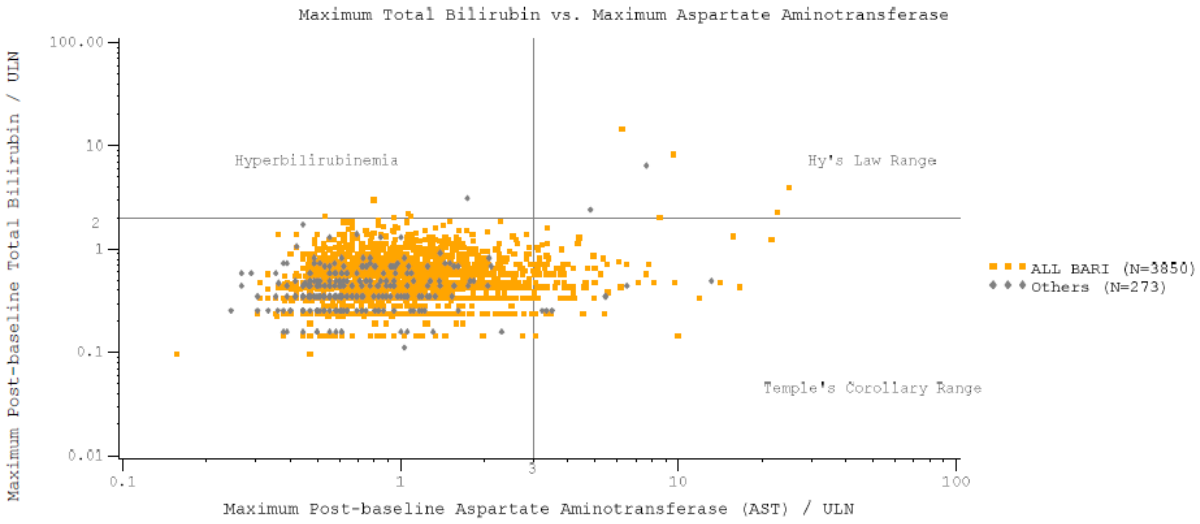
Figure 1. eDISH plots of ALT vs total bilirubin



Abbreviation: ULN = upper limit of normal.

Source: Applicant's resubmission safety update, p. 151

Figure 2. eDISH plots of AST vs Total Bilirubin



Abbreviation: ULN = upper limit of normal.

Source: Applicant's resubmission safety update, p. 153

In the original hepatology consult (April 10, 2017), the consult team had additional recommendations pertaining to (1) the potential for drug/drug interaction that could increase baricitinib's risk of DILI, especially with concurrent exposure to methotrexate, (2) risks of long-term exposure in RA patients and the potential for adaptation to occur vs. the risk for baricitinib to cause chronic liver injury (e.g., chronic hepatitis, fibrosis etc.), (3) monitoring to detect cases of liver injury, and an algorithm for response to occurrences of liver enzyme elevations with use of baricitinib, and (4) a consideration for a consult from the Divisions of Pharmacovigilance in OPE to interrogate the FAERS database for serious post-marketing adverse events marked by either acute or chronic hepatotoxicity, associated with the currently marketed JAK inhibitors, tofacitinib or ruxolitinib. Given the determination that no cases with biochemical criteria consistent with Hy's law are causally linked to baricitinib exposure and that the product will be approved at the low dose, 2 mg once daily, in a more refractory patient population (i.e. patients who have had an inadequate response to one or more TNF antagonist therapies) with a requirement for a controlled post-marketing safety study, it is reasonable to address these recommendations in the post-marketing safety study, rather than pre-marketing.

Thrombocytosis

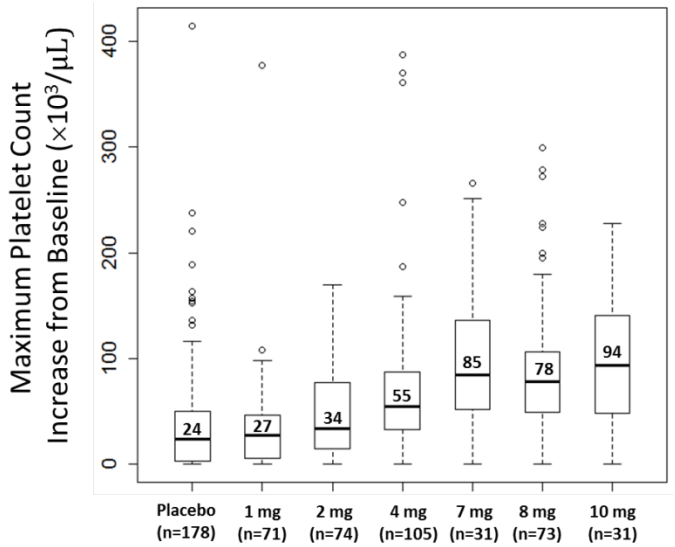
As noted in the original reviews, baricitinib use was also associated with dose-dependent platelet elevations, which appear unique to this product and deserves further consideration. To further explore these observations, the FDA review team considered potential underlying pathogenic mechanisms based on the purported mechanism of action of baricitinib as discussed in this subsection.

The mean platelet counts were higher in baricitinib treatment groups versus placebo with peak elevations occurring at approximately 2 weeks post treatment initiation and the mean levels remained higher than placebo during the controlled period.

Platelet counts were pooled from three phase 2 dose ranging studies (Studies JADC, JADA and JADN). In general, there is a trend of elevation of mean platelet count from baseline following baricitinib $\geq$ 2 mg treatment compared to placebo treatment. In addition, there is a dose-dependent increase of maximal platelet count elevation from baseline within Week 13, from 1 mg QD to $\geq$ 7 mg.

Figure 3 shows maximal platelet count increase from baseline by different doses of baricitinib within Week 13. Platelet counts are pooled from dose ranging Studies JADC, JADA and JADN.

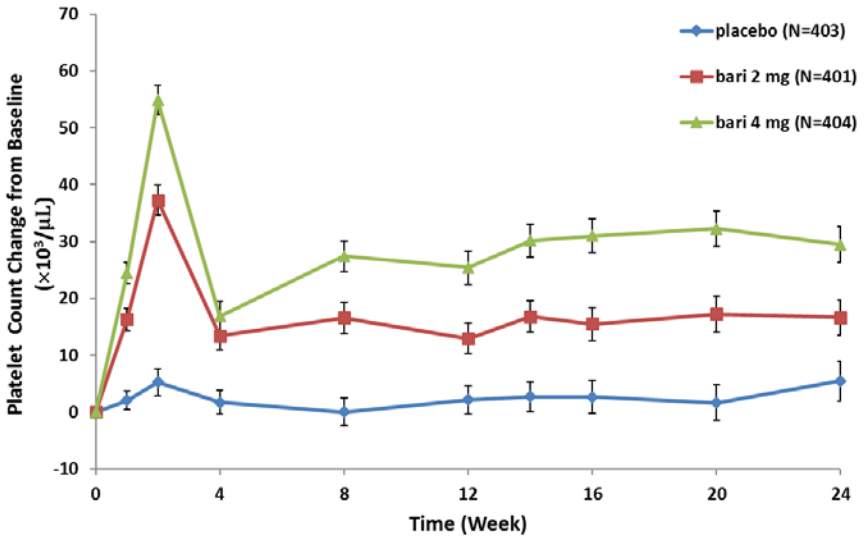
Figure 3. Maximal Platelet Count Increase from Baseline by Baricitinib Dose.



Source: platelet.xpt dated on 2/15/2018

The same dose-dependent trend was observed in two phase 3 studies (JADX and JADW) which investigated both 2 mg and 4 mg doses of baricitinib (Figure 4). The elevation of mean platelet count peaked around Week 2 following baricitinib once daily treatment and was $37\times10^3/\mu L$ and $55\times10^3/\mu L$ higher than the baseline in the 2 mg group and 4 mg group, respectively. After Week 8, the mean platelet count remained stable in the baricitinib groups with an approximately $15\times10^3/\mu L$ and $30\times10^3/\mu L$ increase from baseline in the 2 mg group and 4 mg group, respectively. Figure 4 shows mean platelet count change from baseline over time by placebo (blue), baricitinib 2 mg (red) and baricitinib 4 mg (green) groups from pooled results from Studies JADX and JADW.

Figure 4. Pooled JADX and JADW: Mean Platelet Count, Change from Baseline to Week 24



Source: Study JADW and Study JADX

Potential Biological Mechanisms Underlying Baricitinib-induced Platelet Elevations

The following section is adapted from the Pharmacology Toxicology Team Review Memo, March 01, 2017 and the April 23, 2018 Arthritis Advisory Committee meeting background.

Baricitinib Pharmacology

Cytokine receptors lack intrinsic enzymatic activity. The intracellular portion of Class I and Class II cytokine receptors are constitutively associated with Janus kinase (JAK) enzymes, which transduce the biologic effects of cytokine binding. The JAK family of tyrosine kinases is comprised of 4 enzymes: JAK1, JAK2, JAK3, and TYK2. Inhibition of cytokine signaling by disrupting the JAK-STAT pathway can target multiple processes involved in inflammation, cellular activation, and proliferation of immune cells associated with RA. Eli Lilly designed baricitinib with the intention to be selective for JAK1, JAK2 and TYK2 relative to JAK3. The rationale for sparing JAK3 inhibition was to limit the immune suppressive effects associated with pan-JAK inhibition. Clark et al.[6] explored the specificity of 5 separate JAK inhibitors (including baricitinib) in cell-free and cell-based (human whole blood) assays in a 2014 publication. This paper showed that baricitinib preferentially inhibited JAK1 and JAK2

[6] Clark, J. et al. (2014) Discovery and development of Janus Kinase inhibitors for inflammatory diseases. *Journal of Medicinal Chemistry*. 57, 5023 – 5038.

followed by TYK2. In contrast, baricitinib spared JAK3 inhibition in both cell-free and cell-based assays (Table 9).

Table 9. Summary of Inhibitory Potency of Selected JAK Enzymes in Cell-free and Whole Blood Assays

			Cell-free assay IC_{50} (nM)					Cell-based assay (whole blood) IC_{50} (nM)					
Compound	Sponsor	Intended target	JAK1	JAK2	JAK3	TYK2		JAK1/2 or JAK1/TYK2[a]	JAK1/3[b]	JAK1/TYK2[c]	JAK2/JAK2[d]	JAK2/TYK2[e]	JAK2/TYK2[f]
Baricitinib	Lilly	JAK3 – sparing	4 0	6 6	787 0	61 0		21 1	259	28 7	87 8	149	81 9
Tofacitinib	Pfizer	Pan-JAK inhibitor	15 1	77 4	55 0	489		75 4	55 8	35 0	302	409	229
Ruxolitinib	Incyte	JAK3-sparing	6 4	8 8	487 0	30 1		298	1,850	194	677	1,090	818
Decernotinib	Pfizer	JAK3-specific	112	619	74 4	>10,000		1,870	932	1,290	>20,000	16,400	11,200
Filgotinib	Galapagos	JAK-1 specific	363	2,400	>10,000	2,600		918	2,140	1,500	13,200	13,362	10,123

Source: Adapted from Clark et al (2014) J Med Chem 57, 5023-5038
[a] IL-6 induced pSTAT1; [b] IL-15 induced pSTAT 5; [c] IFNα induced pSTAT3; [d] EPO induced pSTAT5; [e] IL-12 induced pSTAT4; [f] IL-23 induced pSTAT3
Abbreviations: JAK=Janus kinase, TYK=tyrosine kinase; pSTAT=phosphorylated STAT

Platelet production mechanisms

Normal human platelet levels are reported to be 150,000 – 400,000 per µl of blood. The steady state platelet count is maintained by production and removal of 10^{11} platelets per day[7]. Platelets circulate with a lifespan of approximately 7 - 10 days in humans[8].

Platelets are anucleated cells that are released into the blood from megakaryocytes present in the bone marrow. Megakaryocytes are formed through the process of megakaryopoiesis. Megakaryopoiesis involves the differentiation and maturation of hematopoietic stem cells (HSCs) residing in the bone marrow into megakaryocyte progenitors and ultimately into mature megakaryocytes (MKs)[9]. Megakaryopoiesis is primarily mediated by thrombopoietin (TPO), a glycoprotein hormone produced mainly in the liver. Additional factors that contribute to megakaryopoiesis include Stem cell factor (SCF), IL-3, IL-6, and IL-11[10].

TPO binds to TPO receptors (known as myeloproliferative leukemia protein, Mpl) expressed on HSCs and megakaryocyte progenitors and stimulates the differentiation of HSCs to megakaryocytes. Mpl is a homodimeric receptor that associates with JAK2. The effects of TPO binding to Mpl are transduced by JAK2 activity.

[7] Grozovsky et al. (2015) Regulating billions of blood platelets: glycans and beyond. *Blood*. 126: 1877-1884.
[8] Li, R. et al (2016) Glycans and the Platelet Life Cycle. *Platelets*. 27, 505 – 511.
[9] Geddis A. (2010) Megakaryopoiesis. *Seminars in Hematology*. 47: 212-219.
[10] Nurden, A. (2018) The biology of the platelet with special reference to inflammation, wound healing and immunity. *Frontiers in Bioscience (Landmark Edition)*. 23, 726-751.

Platelet clearance

Platelets are cleared from the circulation by multiple mechanisms including antibody mediated clearance (by spleen macrophages), apoptotic mechanisms, and via ingestion and degradation by hepatocytes. Young platelets express sialic acid on their surface. Sialic acid is removed from circulating platelets as they age by sialidases in the blood. Removal of sialic acid exposes galactose oligosaccharide chains which are recognized by the Ashwell-Morrell receptor (AMR) expressed on the surface of hepatocytes. Platelets are subsequently ingested. This process stimulates hepatic TPO mRNA expression via a JAK2-STAT3 mediated mechanism, and subsequent TPO release into the plasma[11]. This provides for evidence of a feedback mechanism whereby removal of platelets by hepatocytes stimulates production and release of TPO in the liver, which can subsequently act to stimulate megakaryocyte differentiation in the bone marrow.

Role of JAK2 function in platelet production

Conditional knockout of the *Jak2* gene in HSCs/progenitor cells induced anemia and thrombocytopenia in mice[12]. In contrast, thrombocytosis was observed in mice in which *Jak2* was selectively deleted in megakaryocytes and mature platelets[13]. Ng et al. showed that selective deletion of *Mpl* in megakaryocytes and mature platelets in mice also led to thrombocytosis[14].

The explanation for the observed thrombocytosis in both the *Mpl* and *Jak2* conditional knockout mice is based on dysregulated TPO turnover. Under normal conditions, Mpl expressed on circulating platelets bind to and internalize circulating TPO for subsequent degradation via a JAK2 dependent mechanism. In this way, circulating TPO levels are maintained at an appropriate level. With the loss of Mpl or JAK2 function in mature platelets, TPO is not effectively removed from the blood, resulting in elevated circulating TPO levels. Mpl and JAK2 function are maintained in HSCs and MK progenitors in both animal models. Elevated TPO levels activate Mpl in HSCs and MK progenitors and stimulate expansion of these cells resulting in the observed thrombocytosis.

The results of the Meyer et al.[13] and Ng et al.[14] studies provide a potential framework to explain the biologic mechanisms behind the observed increased platelet counts in patients treated with baricitinib. The underlying hypothesis is that, at clinical doses, baricitinib may have a more profound inhibitory effect on JAK2-mediated removal of TPO by platelets than it does on JAK2-mediated signaling in stem/progenitor cell populations. Under these conditions, increased circulating TPO could stimulate the expansion of stem/progenitor cells that retain Mpl function, resulting in an increased platelet population. Platelet counts reached a maximum at approximately 2-weeks post-initiation of dosing, followed by a sharp decrease. The increased platelet population could be expected to reduce circulating TPO via Mpl-mediated removal to

[11] Kile, B. (2015) Aging platelets stimulate TPO production. *Nature Medicine*. 21: 11 – 12.
[12] Grisouard et al. (2014). Selective deletion of Jak2 in adult mouse hematopoietic cells leads to lethal anemia and thrombocytopenia. *Haematologica*. 99: e52 – e54.
[13] Meyer S. et al. (2014) Genetic studies reveal an unexpected negative regulatory role for Jak2 in thrombopoiesis. *Blood*. 124: 2280 – 2284.
[14] Ng A. et al. (2014) Mpl expression on megakaryocytes and platelets is dispensable for thrombopoiesis but essential to prevent myeloproliferation. *PNAS*. 111, 5884-5889.

levels below those observed during the initial phase of treatment, thus attenuating the stimulus for platelet production in bone marrow. Total platelets would subsequently decline. Platelet counts were elevated chronically in baricitinib-treated patients ($15 – 20 \times 10^3/\mu L$ over baseline at week 24). TPO levels are expected to be chronically elevated via baricitinib-mediated inhibition of JAK2 in platelets. The bone marrow baricitinib concentration at the doses tested clinically may not be sufficient to completely mitigate the effects of elevated TPO on stem/progenitor cell populations.

A central question associated with the proposed mechanism is: why might baricitinib have a more pronounced inhibitory effect on JAK2-mediated TPO removal than it does on JAK2-mediated cell signaling in stem/progenitor cells? One potential explanation could include differential Mpl-expression between platelets and stem/progenitor cells. Lower relative Mpl-expression in platelets might allow for inhibition of Mpl-associated TPO removal at lower baricitinib concentrations than would be required for inhibition of Mpl-associated JAK2 function in stem/progenitor cells.

An additional potential explanation for the observed baricitinib-induced elevation in platelets is as follows: during the initiation of baricitinib treatment, JAK2 function is inhibited in circulating platelets (thus increasing TPO) but distribution of baricitinib to the bone marrow is incomplete, and insufficient to completely inhibit Mpl-associated JAK2 function and cell signaling in stem/progenitor cells. These conditions would allow for TPO-induced expansion of these cell types resulting in increased peripheral blood platelets. At later time points, bone marrow baricitinib concentrations are likely to be sufficient to inhibit JAK2 in HSCs and MK progenitors. A new steady-state would be reached whereby the potential stimulatory effects of elevated circulating TPO would be mitigated by the inhibitory effect of baricitinib on JAK2 function in HSCs and MK progenitors.

The selected dose of baricitinib and its pharmacokinetic properties may contribute to its observed effects on platelet counts prior to as well as after attainment of steady state drug concentrations. The mean plasma half-life for baricitinib is approximately 12 hours; the period of 2 half-lives between each daily dose might result in baricitinib concentrations that are insufficient to inhibit JAK2 function in stem/progenitor cells. Under these conditions, TPO could potentially continue to stimulate expansion of MK progenitors and increase platelet production explaining the chronic elevations observed following the initial peak at 2 weeks after the start of dosing.

Additional considerations

JAK2 is the enzyme that is most commonly associated with regulation of platelet homeostasis in the scientific literature. Baricitinib's inhibitory effects on JAK2 associated with Mpl in circulating platelets provides a potential mechanistic explanation for the clinical observations of increased platelet counts in RA patients treated with baricitinib. While baricitinib enhancement of platelet production currently appears to be the most plausible explanation for the observed increase in platelets, disruption of biologic processes associated with platelet removal cannot be ruled out.

Discussion on the Proposed Dosing Regimen

The following section is adapted from the Statistical Team Reviews and the April 23, 2018 Arthritis Advisory Committee meeting background.

Dosage and Administration

In the original NDA submission, the Applicant proposed the following dosage and administration:

> *The recommended dose of OLUMIANT is 4 mg once daily. A dose of 2 mg once daily may be considered for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering.*

In the NDA resubmission, the Applicant has modified from the proposed dosing regimen to address the benefit risk concerns as follows:

> *The recommended dose of OLUMIANT 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.*

Rationale for the Proposed Change in Dosage and Administration

The rationale for the recommended 2 mg dose is based on statistically significant improvement across several efficacy measures versus placebo with similar disease activity improvement relative to the 4 mg dose. These data are reviewed during the original submission and summarized in the CDTL, Division Director, and Office Director reviews, and will not be reviewed in this document.

In the resubmission, the Applicant proposed the 4 mg dose for the subpopulation of active RA patients who have failed 2 or more DMARDs.

To support this proposal, the Applicant provided a post-hoc analysis purported to support increased benefit for the 4 mg over the 2 mg dose for a particular subpopulation: patients failing to improve after treatment with at least two DMARDS.

The original submission provided results from four confirmatory studies. Two of the four studies (JADX and JADW) included baricitinib 4 mg, baricitinib 2 mg, and placebo study arms. Both studies demonstrated statistically significant effects of both baricitinib 4 mg and baricitinib 2 mg compared to placebo for the proportion of patients exhibiting a positive ACR20 response (Table 10 and Table 11), as well as for multiple secondary endpoints. Differences in ACR20 response at Week 12 between baricitinib 4 mg and baricitinib 2 mg were not statistically significant and did not trend in consistent directions across the two studies. Results at Week 24 were similar to those at Week 12.

Table 10. JADX: Proportion of ACR20 Responders

Week	% Responders (Responders/Total)			Odds Ratio (p-value) (95% CI)		
	BARI 4	BARI 2	Pbo	BARI 4:Pbo	BARI 2:Pbo	BARI4:BARI2
12	62 (140/227)	66 (151/229)	39 (90/228)	2.5 (<.001) (1.7, 3.7)	3.0 (<.001) (2.0, 4.4)	0.8 (.4) (0.6, 1.2)
24	65 (148/227)	61 (140/229)	42 (96/228)	2.6 (<.001) (1.8, 3.9)	2.2 (<.001) (1.5, 3.2)	1.2 (0.3) (0.8, 1.8)

Source: FDA statistical reviewer
Abbreviations: BARI=baricitinib; Pbo=placebo; CI=confidence interval

Table 11. JADW: Proportion of ACR20 Responders

Week	% Responders (Responders/Total)			Odds Ratio (p-value) (95% CI)		
	BARI 4	BARI 2	Pbo	BARI 4:Pbo	BARI 2:Pbo	BARI 4:BARI 2
12	55 (98/177)	49 (85/174)	27 (48/176)	3.4 (<.001) (2.2, 5.4)	2.7 (<.001) (1.7, 4.2)	1.3 (0.3) (0.8, 2)
24	46 (82/177)	45 (78/174)	27 (48/176)	2.4 (<.001) (1.5, 3.7)	2.3 (<.001) (1.5, 3.6)	1.0 (.9) (0.7, 1.6)

Source: FDA statistical reviewer
Abbreviations: BARI=baricitinib; Pbo=placebo; CI=confidence interval

For study JADX, ACR components at week 12 did not trend in favor of baricitinib 4 mg or baricitinib 2 mg as shown in Table 12. For study JADW, although none of the differences were statistically significant, there appeared to be an efficacy trend favoring baricitinib 4 mg over baricitinib 2 mg as shown in Table 13.

Table 12. JADX: ACR20 Response and Mean Change in ACR Components at Week 12

Endpoint	BARI 4	BARI 2	Pbo	BARI 4 vs BARI 2	(95% CI)
ACR20	62%	66%	39%	Odds Ratio 0.8	(0.6, 1.2)
ΔHAQ-DI	-0.56	-0.57	-0.36	Mean Difference 0.01	(-0.08, 0.11)
ΔTJC	-13	-13	-10	0	(-1, 1)
ΔSJC	-9	-9	-6	0	(-2, 2)
ΔPain	-23	-25	-16	2	(-2, 6)
ΔPaGA	-26	-25	-17	-1	(-5, 4)
ΔPhGA	-34	-32	-22	-3	(-6, 1)
ΔCRP	-9	-9	0	0	(-3, 2)

Source: FDA statistical reviewer
Abbreviations: BARI=baricitinib; Pbo=placebo; CI=confidence interval; Δ=mean change from baseline; HAQ-DI=Health Assessment Questionnaire-Disability Index; TJC=tender joint count; SJC=swollen joint count; Pain=patient pain score; PaGA=patient global assessment score; PhGA=physician global assessment score; CRP=C-reactive protein

Table 13. JADW: ACR20 Response and Mean Change in ACR Components at Week 12

Endpoint	BARI 4	BARI 2	Pbo	BARI 4 vs BARI 2	(95% CI)
ACR20	55%	49%	27%	Odds Ratio 1.3	(0.8, 2.0)
ΔHAQ-DI	-0.41	-0.37	-0.17	Mean Difference -0.03	(-0.14, 0.07)
ΔTJC	-14	-12	-9	-2	(-5.1, 0.4)
ΔSJC	-9	-7	-5	-2	(-3, 0.1)
ΔPain	-22	-17	-9	-5	(-10, -0.3)
ΔPaGA	-23	-20	-9	-3	(-7, 2.0)
ΔPhGA	-35	-31	-17	-5	(-9, 0.4)
ΔCRP	-9	-5	1	-4	(-8, 0.0)

Source: FDA statistical reviewer
Abbreviations: BARI=baricitinib; Pbo=placebo; CI=confidence interval; Δ=mean change from baseline; HAQ-DI=Health Assessment Questionnaire-Disability Index; TJC=tender joint count; SJC=swollen joint count; Pain=patient pain score; PaGA=patient global assessment score; PhGA=physician global assessment score; CRP=C-reactive protein

Noting the positive, albeit not statistically significant trend in study JADW, the Applicant conducted exploratory subgroup analyses of patients in study JADX who failed two or more DMARDS. All patients in study JADW had inadequate response to at least 2 DMARDs and 56% of patients in study JADX had inadequate response to at least 2 DMARDs.

Reported here are subgroup analyses in JADX of a broad sample of responder endpoints as well as the continuous endpoints HAQ-DI and DAS28-CRP. At Week 12, for the patient subpopulation who had prior inadequate response or intolerance to two or more DMARDs, the numerical trend favored baricitinib 4 mg over baricitinib 2 mg in 9 of 11 responder endpoints with none of the differences statistically significant as shown in Table 14. The responder

analyses were further explored by adding prior DMARD (<2, ≥2) and prior DMARD by treatment interaction to the statistical models. None of the interactions were significant (all p-values > 0.10), indicating that there was no evidence that number of prior DMARDS impacted the relative efficacy of the two doses.

In the analyses of continuous endpoints, there was a trend toward slightly greater efficacy for the baricitinib 4 mg dose with respect to DAS28 in the subgroup of patients with at least two prior DMARDs, but the mean difference (-0.27) was small and a similar trend was not observed for HAQ-DI (Table 15). Results (not shown) were generally similar at Week 24.

Table 14. JADX: Exploratory Subgroup Analysis of Responder Endpoints, Baricitinib 4 mg vs Baricitinib 2 mg, Week 12, ≥ Two Prior DMARDs

Endpoint	BARI 4 n=128	BARI 2 n=122	Pbo n=131	Odds Ratio BARI 4: BARI 2	95% CI
ACR20	64%	63%	44%	1.0	(0.6, 1.8)
ACR50	36%	30%	15%	1.4	(0.8, 2.4)
ACR70	17%	16%	5%	1.2	(0.6, 2.4)
DAS28CRP ≤ 2.6	26%	24%	9%	1.2	(0.6, 2.1)
DAS28CRP ≤ 3.2	43%	34%	18%	1.5	(0.9, 2.5)
DAS28ESR ≤ 2.6	8%	11%	2%	0.7	(0.3, 1.8)
DAS28ESR ≤ 3.2	21%	20%	7%	1.0	(0.6, 2.0)
EULAR Response	84%	76%	58%	1.7	(0.9, 3.2)
CDAI ≤ 2.8	9%	7%	2%	1.2	(0.4, 3.2)
SDAI ≤ 3.3	7%	7%	1%	1.1	(0.4, 3.0)
Δ HAQ-DI ≤ -0.3	55%	57%	48%	0.9	(0.6, 1.5)

Source: FDA statistical reviewer

Abbreviations: BARI=baricitinib; CI=confidence interval; Pbo=placebo; ACR=American College of Rheumatology response; DAS28=disease activity score based on 28 joints; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; CDAI=clinical disease activity index; SDAI=simplified disease activity index; HAQ-DI=Health Assessment Questionnaire-Disability Index

Table 15. JADX: Exploratory Subgroup Analysis of Mean Change from Baseline of Continuous Endpoints, Baricitinib 4 mg vs Baricitinib 2 mg, Week 12, ≥ Two Prior DMARDs

Endpoint	BARI 4 N=128	BARI 2 N=122	Pbo N=131	Difference BARI 4-BARI 2 (95% CI)
DAS28-CRP	-2.02	-1.76	-1.12	-0.27 (-0.56, 0.03)
HAQ-DI	-0.55	-0.55	-0.38	0 (-0.13, 0.13)

Source: FDA statistical reviewer
Abbreviations: BARI=baricitinib; Pbo=placebo; CI=confidence interval; DAS28=disease activity score based on 28 joints; CRP=C-reactive protein; HAQ-DI=Health Assessment Questionnaire-Disability Index

When the Applicant's exploratory methods were applied to evaluate the complementary subpopulation of JADX, patients who had prior inadequate response or intolerance to fewer than 2 DMARDs, trends in the opposite direction were seen. For example, at Week 12, in 10 of 11 responder endpoints examined, effectiveness was numerically greater in baricitinib 2 mg rather than in baricitinib 4 mg as shown in Table 16.

Table 16. JADX: Exploratory Subgroup Analysis of Responder Endpoints, Baricitinib 4 mg vs Baricitinib 2 mg, Week 12, < Two Prior DMARDs

Endpoint	BARI 4 n=99	BARI 2 n=107	Pbo n=97	Odds Ratio BARI 4: BARI 2	95% CI
ACR20	59%	69%	34%	0.6	(0.4, 1.1)
ACR50	30%	38%	9%	0.6	(0.4, 1.2)
ACR70	19%	21%	1%	0.8	(0.4, 1.7)
DAS28CRP ≤ 2.6	25%	28%	8%	0.8	(0.4, 1.5)
DAS28CRP ≤ 3.2	34%	37%	16%	0.8	(0.5, 1.5)
DAS28ESR ≤ 2.6	11%	11%	2%	0.8	(0.3, 2)
DAS28ESR ≤ 3.2	22%	22%	8%	0.9	(0.5, 1.9)
EULAR Response	74%	82%	47%	0.6	(0.3, 1.3)
CDAI ≤ 2.8	10%	13%	1%	0.7	(0.3, 1.8)
SDAI ≤ 3.3	11%	11%	1%	1	(0.4, 2.4)
Δ HAQ-DI ≤ -0.3	58%	64%	38%	0.7	(0.4, 1.3)

Source: FDA statistical reviewer
Abbreviations: BARI=baricitinib; Pbo=placebo; CI=confidence interval; DAS28=disease activity score based on 28 joints; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; CDAI=clinical disease activity index; SDAI=simplified disease activity index; Δ=change from baseline; HAQ-DI=Health Assessment Questionnaire-Disability Index

In summary, the Applicant provided analyses which purport to demonstrate superior efficacy of baricitinib 4 mg over 2 mg in patients with prior inadequate response or intolerance to at least 2 DMARDs. However, the subgroup analyses were post-hoc, there was not evidence of an interaction between prior DMARD use and treatment effect, differences between doses within subgroups were not statistically significant, and magnitudes of estimated differences were generally small. Furthermore, similar analyses and interpretations in the complementary subgroup might lead to a likely implausible conclusion, i.e. that the lower 2 mg dose is superior to the higher 4 mg dose among patients with prior inadequate response or intolerance to fewer than 2 DMARDs. Therefore, the Applicant's subgroup analyses are considered exploratory and hypothesis-generating rather than confirmatory.

Perhaps the most reliable estimates comparing the efficacy of the two doses were provided by the Applicant in response to an information request by FDA for an integrated analysis of available placebo-controlled RA studies which randomized patients to both the baricitinib 2 mg and 4 mg doses (JADA, JADN, JADX, and JADW). We note that results of individual clinical trials are the focus of the evaluation of effectiveness, and that the placebo-controlled data from the individual phase 3 studies of baricitinib provided replicate, convincing evidence of efficacy for both the 2 mg and 4 mg baricitinib doses. That being said, when there are supportive questions such as the comparison between doses for which the individual studies may have limited statistical power, exploratory integrated efficacy analyses can be useful. These analyses were requested solely to increase the precision of estimated differences between doses. In addition to studies JADX and JADW, the integrated analysis included data from dose ranging studies JADA and JADN, which enrolled patients with active RA with inadequate response or intolerance to MTX and which provided randomized treatment as an add on to MTX.

Table 17 shows the results of the integrated analysis. The proportions of ACR20 responders for 4 mg of baricitinib, 2 mg of baricitinib, and placebo are shown at Weeks 2, 4, 8, and 12. The mean change in DAS28-CRP and HAQ-DI from baseline is also shown at Weeks 2, 4, 8, and 12.

For the proportion of ACR20 responders, the integrated analysis trends toward greater efficacy of baricitinib 4 mg over 2 mg at earlier timepoints. However, the advantage of baricitinib 4 mg in response rate appears to trend downward over time, from an absolute difference of 9% at Week 2 to 2% at Week 12. For mean changes from baseline in DAS28-CRP and HAQ-DI, the advantage of baricitinib 4 mg over baricitinib 2 mg was minimal considering commonly used estimates of minimally important clinical differences are approximately 0.6 and 0.22 for change from baseline DAS28(CRP) and HAQ-DI, respectively.

These analyses are generally consistent with the results of the individual trials, and with the results of the Applicant’s exploratory subgroup analyses, all of which suggest that there may be slightly greater efficacy with 4 mg than 2 mg, but that any true differences are likely small and should be interpreted in the context of the potential toxicity associated with baricitinib 4 mg vs baricitinib 2 mg.

Table 17. JADA, JADN, JADX, JADW: Integrated Efficacy Analyses of Baricitinib 4 mg vs Baricitinib 2 mg for ACR20, Mean Change in DAS28-CRP, and Mean Change in HAQ-DI

Endpoint	Week	BARI 4	BARI 2	Pbo	BARI 4-BARI 2 (95% CI)
ACR20 Response (%)	2	40%	31%	19%	9% (3%, 15%)
	4	54%	45%	28%	8% (2%, 15%)
	8	59%	53%	34%	7% (0%, 13%)
	12	61%	59%	35%	2% (-4%, 8%)
Mean Change DAS28-CRP	2	-1.26	-0.99	-0.60	-0.27 (-0.39, -0.15)
	4	-1.59	-1.33	-0.75	-0.27 (-0.40, -0.13)
	8	-1.86	-1.59	-0.95	-.0.26 (-0.41, -0.12)
	12	-1.97	-1.73	-1.02	-0.24 (-0.40, -0.09)
Mean Change HAQ-DI	2	-0.30	-0.23	-0.17	-0.06 (-0.11, -0.01)
	4	-0.37	-0.30	-0.20	-0.06 (-0.12, -0.01)
	8	-0.44	-0.39	-0.23	-0.05 (-0.11, -0.01)
	12	-0.47	-0.43	-0.24	-0.03 (-0.10, -0.03)

Source: Tables 4.5, 4.6, and 4.7 of applicant response, NDA 207924 Seq 0048
Abbreviations: BARI=baricitinib; Pbo=placebo; CI=confidence interval; DAS28=disease activity score based on 28 joints; CRP=C-reactive protein; HAQ-DI=Health Assessment Questionnaire-Disability Index

Additional considerations pertaining to the Applicant's proposed dosing regimen include the safety comparisons between patients with prior inadequate response or intolerance to one vs. two or more prior DMARDs, as summarized in Table 18. The table show adverse events that accrued during the first 16 weeks in the phase 2 and phase 3 RA studies that included both 2 mg and 4 mg baricitinib dose arms (JADA, JADN, JADX, and JADW). While the overall exposures in each of these subgroups was small, the incidence rates of SAEs, discontinuations due to adverse events, serious infections, and HZ were numerically higher in the 4 mg versus the 2 mg baricitinib arm which was more notable in the subgroup of patients with prior inadequate response or intolerance to two or more prior DMARDs. This could be a consideration in the overall benefit risk analysis for the Applicant's proposed dosing regimen of 4 mg daily for patients with inadequate response or intolerance to more than one DMARD.

Table 18. Comparison of Safety Between Patients with One vs. Two or More Prior DMARDs (Week 0-16)

	One prior DMARD			Two or more prior DMARDs		
n (IR)	Pbo N=172 PYE=45	BARI 2 N=141 PYE=40	BARI 4 N=143 PYE=39	Pbo N=378 PYE=51	BARI 2 N=335 PYE=46	BARI 4 N=335 PYE=46
Deaths	0	0	0	2 (2)	0	1 (1)
Patients with SAE	7 (15)	5 (12)	5 (13)	15 (14)	11 (11)	20 (20)
Permanent discontinuations due to AE	10 (21)	5 (12)	7 (17)	9 (8)	14 (14)	18 (18)
Serious infections	1 (2)	1 (2)	2 (5)	6 (6)	5 (5)	6 (6)
Herpes zoster	0	0	2 (5)	2 (2)	5 (5)	7 (7)
Opportunistic infections	0	0	0	0	0	0
Malignancies excluding NMSC	0	0	0	0	1 (1)	0
MACE	1 (3)	0	0	1 (1)	0	2 (2)
PE/DVT	0	0	2 (5)	0	0	0

Source: Applicant's resubmission safety update, p. 163
Abbreviations: DMARD=disease modifying anti-rheumatic drug, BARI=baricitinib, Pbo=placebo; IR=incidence rate, PYE=patient year exposure, SAE=serious adverse event, AE=adverse event, NMSC=non-melnoma skin cancer, MACE=major cardiovascular event, PE=pulmonary embolism, DVT-deep vein thrombosis

Additional Clinical Studies Included in the Re-submission

Study JAGS in RA

Study JAGS was a randomized, double-blind, placebo-controlled, phase 3 study evaluating the efficacy and safety of baricitinib 4 mg in patients with moderately to severely active RA who had inadequate response to MTX therapy. 145 patients were randomized to baricitinib and 145 were randomized to placebo. Patients were enrolled from 30 centers in 3 countries (China 231 patients, Argentina 43 patients, Brazil 16 patients). The study was conducted from November 2014 to May 2017. The primary objective was to determine whether baricitinib 4 mg was superior to placebo in the treatment of patients with RA who were MTX-IR as assessed by the proportion of patients achieving ACR20 at Week 12.

Overall, JAGS provided additional efficacy and safety information for baricitinib 4 mg. The results are generally consistent with the data submitted in the original application. No new safety signals were detected.

Efficacy, Clinical Response

Table 19 shows the results for the primary and secondary endpoints studied in JAGS. The comparison shown is between 4 mg of baricitinib daily and placebo. For the primary endpoint of ACR20 at Week 12, 59% of patients on baricitinib had a ACR20 response versus 28% in placebo. Similar trends were seen with the secondary endpoints favoring baricitinib treatment

over placebo. The exception was SDAI response rate where 4 mg of baricitinib did not show a statistically significant improvement over placebo.

Table 19. Summary of Clinical Response at Week 12, JAGS Study

	Placebo (N=145)	BARI 4 (N=145)	p-value
ACR20, week 12, n (%)	41 (28)	85 (59)	0.001
HAQ-DI change from baseline, LSM	-0.5	-0.7	0.001
DAS28-hsCRP change from baseline, LSM	-1.2	-2.2	0.001
SDAI≤3.3, n (%)	0	2 (1)	0.499
Duration of morning joint stiffness (diary), median	48	24	0.004
Severity of Morning Joint Stiffness NRS (Diary), LSM	4	3	0.002
Worst Tiredness NRS (Diary), LSM	4	3	0.001
Worst Joint Pain NRS (Diary), LSM	5	4	0.001

Source: JAGS-03-synopsis, p. 11
Abbreviations: BARI=baricitinib; ACR=American College of Rheumatology response; HAQ-DI=Health Assessment Questionnaire-Disability Index; DAS28=disease activity score based on 28 joints; hsCRP=high sensitivity C-reactive protein; SDAI= simplified disease activity index; NRS=numeric response scale; LSM=lest square mean

Efficacy, Radiographic Response

Table 20 shows the results for modified total Sharp score (mTSS) in the placebo and baricitinib groups in study JAGS. Mean change from baseline was significantly lower at Week 16 for baricitinib (0.2) versus placebo (0.7). There was a trend towards lower mTSS at Week 24. There was no significant difference in the percent of patients who had mTSS of zero or less at Week 16 (70% in placebo versus 77% in baricitinib) or Week 24 (70% in placebo versus 74% in baricitinib).

Table 20. Summary of Radiographic Response, by Modified Total Sharp Score, JAGS Study

mTSS	Week 16		Week 24		Week 52
	Pbo (N=145)	BARI 4 (N=145)	Pbo (N=145)	BARI 4 (N=145)	BARI 4 (N=145)
mTSS change from baseline LSM p-value	0.7	0.2 0.02	0.8	0.3 0.06	0.56
mTSS change≤0 from baseline n (%) p-value	92 (70)	106 (77) 0.23	94 (70)	104 (74) 0.45	95 (68)
Source: JAGS-03-synopsis, p. 14 Abbreviations: BARI=baricitinib; Pbo=placebo; mTSS=modified total Sharp score, BARI=baricitinib, LSM=least square mean					

Safety

Table 21 shows an overview of the adverse events that occurred in the first 24 weeks of study JAGS for the placebo and baricitinib groups. Overall more treatment emergent adverse events occurred in the baricitinib group (n=108, 75%) versus the placebo group (n=90, 62%). No deaths were observed in the first 24 weeks and serious adverse events were balanced (n=4, 3% in both the placebo and baricitinib groups).

There were more infections in the baricitinib group (n=61, 42%) versus the placebo group (n=41, 28%). There was one potential opportunistic infection that occurred in the baricitinib group. No malignancies or positively adjudicated MACE were noted in the first 24 weeks of study JAGS.

Table 21. Overview of Safety, Weeks 0-24, JAGS Study

	Pbo (N=145) n (%)	**BARI 4 mg (N=145) n (%)**
Deaths	0	0
SAEs	4 (3)	4 (3)
Treatment emergent adverse events	90 (62)	108 (75)
Discontinuations from study due to AE or death	3 (2)	2 (1)
Infections	41 (28)	61 (42)
Serious infections	1 (1)	2 (1)
Herpes zoster	1 (1)	3 (2)
Tuberculosis	0	0
Potential opportunistic	0	1 (1)
Malignancies	0	0
MACE (positively adjudicated)	0	0

Source: JAGS-03-synopsis, p. 15
Abbreviations: BARI=baricitinib; Pbo=placebo; SAE=serious adverse event; AE=adverse event; MACE=major adverse cardiovascular event

There was one malignancy in a 31-year-old Asian male. The patient was randomized to the placebo group and switched to baricitinib on Day 168. 120 days after switching to baricitinib, the patient was reported to have lung adenocarcinoma. There were no gastrointestinal perforations in patients who were randomized to baricitinib or rescued to baricitinib. There were no events of deep vein thrombosis or pulmonary embolism observed. In study JAGS, a larger proportion of patients had a treatment-emergent abnormal high platelet count versus patients who received placebo. No SAEs or permanent discontinuations due to abnormal platelet count were reported in study JAGS.

Study JAHG in Atopic Dermatitis

Study JAHG was a 16-week, randomized, double-blind, placebo-controlled, phase 2 study to evaluate the safety and efficacy of baricitinib in patients with moderate-to-severe atopic dermatitis. Placebo, baricitinib 2 mg, and baricitinib 4 mg study treatment arms were included in the study. For the purposes of this summary, only safety was presented.

Table 22 shows the adverse events that occurred during the period of study in JAHG. No deaths occurred during the study. A higher incidence of SAEs, overall AEs, discontinuations, and adverse events of special interest were observed in the 4 mg baricitinib arm compared to 2 mg of baricitinib and placebo. Most of the adverse events of special interest were infections and a higher percent of patients on 4 mg of baricitinib had infections when compared to the 2 mg baricitinib and placebo study arms.

Table 22. Overview of Safety: Study JAHG

n, (%)	Pbo N=49	BARI 2 N=37	BARI 4 N=38
Treatment emergent AEs	25 (51)	19 (51)	28 (74)
SAEs	10 (20)	8 (22)	12 (32)
Discontinuations due to AEs	5 (10)	3 (8)	6 (16)
AEs of special interest	11 (22)	10 (27)	17 (45)
Infections	11 (22)	10 (27)	14 (37)

Source: Adapted from Applicant's JAHG synopsis p. 7 and clinical study report p. 220
Abbreviations: BARI=baricitinib; Pbo=placebo; AE=adverse event; SAE=serious adverse event

Study JAHH in SLE

JAHH was a 24-week phase 2 study in patients with active SLE. 314 patients were randomized. 105 received placebo, 105 received 2 mg of baricitinib daily, and 104 received 4 mg of baricitinib daily. For the purposes of this summary, only safety was presented.

The Applicant provided the 24-week safety for this study which is presented in Table 23. Adverse events were recorded over the 24 week treatment period and 30 days post-treatment.

Table 23. Overview of Safety Through Week 24: Study JAHH

n, (%)	Pbo N=105	BARI 2 N=105	BARI 4 N=104
Discontinuation due to AE	4 (4)	10 (10)	11 (11)
Serious adverse events	5 (5)	11 (11)	10 (10)
Serious infections	1 (1)	2 (2)	6 (6)
Herpes zoster	1 (1)	0	1 (1)
DVT	0	0	1 (1)
MACE	0	0	0
Malignancy	0	0	0
Death	0	0	0

Source: Adapted from Applicant's JAHH clinical study report synopsis, p. 6
Abbreviations: BARI=baricitinib; Pbo=placebo; AE=adverse event; DVT=deep vein thrombosis; MACE=major adverse cardiovascular event

There were numerically more serious adverse events, infections, and serious infections noted in the baricitinib groups when compared to placebo without a clear dose-dependence except for serious infections. There was one SAE of DVT which occurred in the 4 mg baricitinib group. The patient was reported as having preexisting antiphospholipid antibody syndrome and pain in the affected limb. Platelet count was not available in the synopsis.

Arthritis Advisory Committee Summary

An Arthritis Advisory Committee (AAC) was convened on April 23, 2018 to discuss this NDA. The discussion as summarized in the Executive Summary above.[15]

Resubmission Conclusions

Overall, the additional data provided in the resubmission did not substantially alter the efficacy and safety data in the original submission.

Both the 2 and 4 mg doses of baricitinib demonstrated efficacy compared to placebo in RA patients. However, the data do not consistently show a benefit of 4 mg over the 2 mg dose.

Baricitinib has the safety profile consistent with a potent immunosuppressive. However, thrombosis was also observed with the 4 mg once daily dose in the placebo-controlled periods of the clinical program which is a notable safety issue that impacts the benefit/risk profile of baricitinib. While thrombosis was also observed with the 2 mg dose group with longer exposures, there is uncertainty about the thromboembolic risk with the 2 mg dose due to the limited safety database. However, other data (laboratory parameters) suggest a dose response in safety profile, which may translate into a lower risk of serious adverse events of interest, such as serious infection. This uncertainty may be addressed by further limiting the patient population to that of refractory patients, such as patients who have had an incomplete response to TNF-inhibitors, consistent with the approach taken with the original approval of Actemra.

At this time, based on input from the Arthritis Advisory Committee, review of the additional data provided by the Applicant, and proposed changes to the labeling, the risk/benefit for the 2 mg dose may be reasonable for patients with RA who have had an incomplete response to TNF-inhibitors with appropriate labeling changes.

To further characterize the safety profile of baricitinib 2 mg once daily dose and the signal of thromboembolic risk in RA, a post-marketing study is recommended and generally agreed upon with the Applicant.

[15] https://www fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm601797.htm

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/s/

NIKOLAY P NIKOLOV
05/31/2018

RAJ NAIR
05/31/2018

SALLY M SEYMOUR
05/31/2018

MARY T THANH HAI
05/31/2018

Office Deputy Director Decisional Memo

Date	April 12, 2017
From	Mary Tran Thanh Hai, M.D.
Subject	Office Deputy Director Decisional Memo
NDA/BLA # **Supplement #**	207924
Applicant Name	Eli Lilly and Company
Date of Submission	January 15, 2016
PDUFA Goal Date	January 15, 2017; clock extended to April 15, 2017
Proprietary Name / **Established (USAN) Name**	Olumiant® (baricitinib)
Dosage Forms / Strength	2 and 4 mg once daily dosing proposed
Applicant Proposed **Indication(s)/Populations**	Adult patients with moderately to severely active rheumatoid arthritis
Action:	Complete Response

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Benefit-Risk Summary and Assessment

Baricitinib is a JAK-inhibitor proposed for the treatment of adult patients with moderate to severely active rheumatoid arthritis (RA). Tofacitinib is another JAK-inhibitor available in the U.S. for the treatment of RA. Two dosage strengths (2 and 4 mg) were evaluated for marketing but Eli Lilly is proposing that patients initiate with baricitinib 4 mg once daily whereas the 2 mg once daily dosing regimen could be considered "acceptable" in some patients, including patients with moderate renal impairment. Both doses were studied in two randomized, double-blind controlled trials. One trial was in patients who had an inadequate response to conventional DMARDs (JADX) and another was in patients who had an inadequate response to biologic DMARDs (JADW). Although treatment with both doses resulted in statistically significant improvements on the primary composite endpoint of ACR20 compared to placebo, there was not a consistent finding between these two studies to conclude greater efficacy with baricitinib 4 mg over 2 mg. In JADW, there was a numerically greater response with the 4 mg dose whereas in JADX, there was a numerically greater response with the 2 mg dose. Secondary efficacy measures tended to align with the primary efficacy results in each trial.

In vitro isolated enzyme assays showed selectivity of baricitinib for JAK1 and JAK2 over JAK3 and TYK2. JAK3 and TYK2 inhibition is thought to be associated with the immunosuppressive effects of tofacitinib and it was presumed that baricitinib would provide an advantage to this effect. However, cell-based assays conducted with human leukocyte preparations showed inhibition of all four intracellular kinases and laboratory and clinical findings of lymphopenia, neutropenia, opportunistic infections and cancer in Phase 2 and 3 trials at a higher rate with baricitinib than control contradicts the assertion that baricitinib is a selective JAK1/2 inhibitor and offers a safety advantage over tofacitinib. In contrast to tofacitinib, there was a consistent finding of thrombocytosis in both baricitinib 2 and 4 mg doses compared to controls and a numeric imbalance of thromboembolic events of baricitinib 4 mg during the controlled phase of the Phase 3 trials with continued accrual of such events in open-label extension trials. In addition, more patients on baricitinib 4 mg were discontinued from drug due to liver enzyme elevations than comparator groups.

Although the number of thrombotic events was low (16 VTE in Phase 3 trials, 2 VTEs in Phase 2 trials, 3 arterial thrombotic events in Phase 2/3 trials, and one pulmonary embolus in a non-RA trial), the absolute number and imbalance to controls during the first 16 weeks of pivotal studies distinguishes baricitinib from other approved RA therapies, particularly tofacitinib. Mean platelet counts were higher in baricitinib treatment groups versus placebo with peak elevations occurring at approximately 2 weeks post treatment initiation; however, mean levels remained higher than placebo during the controlled period. Thrombotic events occurred in patients without thrombocytosis and many patients with platelet elevations did not have a thrombotic event; hence, a clear association between thrombocytosis and thrombotic events was not identified. Although a mechanism for thrombotic risk associated with baricitinib could not be identified, mutations of the JAK2 gene in myeloproliferative disorders such as essential thrombocytosis have been identified[1] and patients with essential thrombocytosis are also at risk for thrombotic events. Consequently, drugs targeting JAK2 activity may have differential downstream effects or off-target effects specific for the moiety, including some that may induce thrombocytosis or potentially increase the risk for thrombosis. Regardless, the absence of a mechanism is not an acceptable argument for dismissing an imbalance in clinically serious thrombotic events with baricitinib.

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. Subgroup analyses performed by Eli Lilly also suggested comparable efficacy between baricitinib 2 and 4 mg in patients who had inadequate response to MTX thereby raising the possibility of limiting approval to baricitinib 2 mg. However, low and diminishing patient-exposure over time in the baricitinib 2 mg group precluded an adequate risk assessment of this dose. During the controlled periods of the Phase 3 trials, patient-yrs of exposure in the 2 mg group was one-third (122.6) that of the 4 mg group (386.7). By 52 weeks and beyond it was less than one-fifth: 304.8 vs 1694.9 at 0-52 weeks and 210.2 vs 1300.6 at > 52 weeks.

Consideration was also given to whether baricitinib could be limited to RA patients who have failed to respond to cDMARDs and biologics (JADW). Again, tofacitinib has also been shown to be effective in this patient population without the potential risk for thrombosis.

Given the current data from this NDA, I believe the relevant consideration is not whether FDA must identify a population for the safe and effective use of baricitinib 2 and 4 mg but whether the applicant must identify a safe and effective dose for baricitinib. 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 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic symmetric inflammation of joints and is the most common type of autoimmune inflammatory arthritis. RA significantly impacts the lives of patients due to pain, decreased physical function, and increased mortality. The goal of treatment is early and aggressive use of medications to try to prevent functional impairment and irreversible joint damage.	Rheumatoid arthritis is a serious condition and is the most common type of autoimmune inflammatory arthritis. Most patients have a chronic progressive disease that is associated with morbidity and increased mortality.
Current Treatment Options	All patients with RA are generally treated with disease modifying antirheumatic drugs (DMARDs). There are multiple drugs approved by the FDA for the treatment of RA. Generally, methotrexate (MTX) is the first line of therapy for RA. Treatment with a tumor necrosis factor-alpha (TNF-α) antagonist as add-on or as monotherapy is generally the recommended next line of treatment. However, approximately 30-40% of patients fail to respond or become intolerant to anti-TNF-α therapy. For these patients, additional anti-TNF-α therapies or therapies that target different pathwayscan be used. Tofacitinib is approved for the treatment of RA and is a Janus kinase inhibitor, similar to baricitinib.	Given the progressive nature of the disease and varying individual responses, multiple treatment options are important.
Benefit	The primary endpoint for evaluation of efficacy was ACR 20, a composite measure that considers signs and symptoms and objective measures of inflammation. Four randomized, double-blind, controlled trials were conducted to support efficacy for baricitinib 2 and 4 mg once daily dosing. Other endpoints included assessments of physical function and radiographic progression.	The trials were adequate and well-controlled and established efficacy of both doses on the primary endpoint. Differences in efficacy between the two doses were not established.
Risk	A total of 3,464 patients with RA were exposed to baricitinib in the RA studies. Long-term controlled data were limited beyond 24 weeks and exposure was predominantly at the highest proposed dose, 4 mg, which challenged the overall safety assessment for rare, unexpected adverse events. This was particularly the case for thrombosis where there were numeric imbalances (18 on baricitinib, 0 on placebo, 1 on MTX). Unlike other approved JAK-inhibitors, thrombocytosis was observed with baricitinib.	Certain class effects were observed including immunosuppression, anemia, neutropenia, lymphopenia, and lipid abnormalities. Thrombocytosis and thrombotic events distinguish this drug from other RA therapies.
Risk Management	Given the finding of serious thrombotic events, some fatal, which has not been observed with another JAK-inhibitor AND no obvious benefit over available RA therapies, approval with risk management is not recommended.	Applicant will need to better evaluate dose-response of baricitinib to identify a safe and effective dose or to

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		evaluate the current proposed doses more extensively to conclude a favorable benefit-risk in the setting of currently available therapies.

1. Further discussion to support regulatory action

Background

This new drug application (NDA) is for baricitinib, a Janus-Kinase (JAK) inhibitor, intended for the treatment of patients with moderately to severely active rheumatoid arthritis (RA). Rheumatoid arthritis is a chronic, progressive inflammatory autoimmune disease resulting in damage to multiple joints in the body. Inflammation of the joint synovium as a result of immune cell release of cytokines and their degradative mediators contribute to the joint damage. Treatments for RA have been divided into the conventional disease-modifying anti-rheumatic drugs (cDMARDs) and biologic DMARDs (bDMARDs). Of the cDMARDs, methotrexate (MTX) is considered first-line therapy; however, many patients require additional therapies. In the past two decades several drugs and biologics targeting immune pathways in the pathogenesis of RA have been approved. Please see Tables 1 and 2 in Dr. Badrul Chowdhury's Division Director's memo.

Cytokines are protein messengers that mediate communication between cells, including immune and inflammatory responses, hematopoiesis, and growth and development. A variety of cytokines play a role in RA pathogenesis and a subset of these bind to Type I or II cytokine receptors which lack intrinsic tyrosine kinase activity and rely on the intracellular kinase, JAK, of which there are four – JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) – to mediate intracellular signaling. Once bound, a cascade of events ensue including JAK-phosphorylation of tyrosine residues on the cytokine receptor which allows selective binding of Signal Transducer and Activator of Transcription (STAT) proteins, a group of DNA-binding proteins. These too, are phosphorylated, dimerize, and translocate to the cell nucleus to regulate gene transcription and the production of pro-inflammatory mediators, recruitment and activation of B cells, T cells and macrophages. JAK-inhibitors were developed to disrupt the intracellular signaling contributing to the inflammatory response in RA. Tofacitnib is currently the only JAK-inhibitor approved for the treatment of RA. Ruxolitinib is approved for myelofibrosis and polycythemia vera.

The development program for baricitinib is thoroughly discussed in multiple FDA reviews and I refer the reader to Dr. Janet Maynard's Cross-Discipline Team Leader (CDTL) memo and Dr. Chowdhury's Division Director memo for a complete history and discussion of the program submitted in support of this NDA.

The proposed indication as presented with the original submission is:

OLUMIANT is an inhibitor of Janus kinases (JAK1 and 2) indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis.

The proposed language under Dosage and Administration is:

Recommended dose of OLUMIANT is 4 mg once daily. For some patients, a dose of 2 mg once daily may be acceptable. Moderate renal impairment: reduce dose to 2 mg once daily.

There is agreement within FDA and with Eli Lilly that the two proposed doses for marketing, baricitinib 2 and 4 mg, are efficacious. However, there is not agreement on the benefit-risk assessment at the 4 mg dose and the limited exposure at the 2 mg dose has made a favorable benefit-risk conclusion for this dose challenging, particularly for the risk of thrombosis. The final recommendation of *Complete Response* (CR) has evolved over time within the Division. I am recommending a CR and this memo will outline the basis for my recommendation.

Clinical/Statistical – Efficacy

Phase 2 Program

There were three Phase 2 placebo-controlled dose-ranging studies that evaluated ACR20 at 12 weeks. Please see the clinical and clinical pharmacology reviews for details of these three Phase 2 trials. Table 1 below obtained from Dr. Chowdhury's memo, summarizes the results of these trials on ACR20.

Table 1 Phase 2 Dose-Ranging Studies

Study *	Time	Treatment †	ACR 20 %	p-value vs placebo
JADC	Week 12	Bar 4 mg	52	0.198
		Bar 7 mg	59	0.044
		Bar 10 mg	53	0.124
		Placebo	32	
JADA	Week 12	Bar 1 mg	57	0.045
		Bar 2 mg	54	0.088
		Bar 4 mg	75	<0.001
		Bar 8 mg	86	<0.001
		Placebo	41	
JADN	Week 12	Bar 1 mg	67	0.004
		Bar 2 mg	83	<0.001
		Bar 4 mg	67	0.004
		Bar 8 mg	88	<0.001
		Placebo	31	

* Study ID shown as Lilly's study number
† Bar = Baricitinib

JADA and JADN enrolled patients with active RA who had an inadequate response to MTX and evaluated the 1, 2, 4, and 8 mg doses of baricitinib versus placebo. Although JADN was conducted in Japan, global and Japanese Phase 1 studies did not identify PK differences due to ethnicity; hence, both JADA and JADN were informative on the efficacy of doses lower than 4 mg. In JADN, statistically significant efficacy was observed with the 1 and 2 mg daily doses which suggest that baricitinib 1 mg might have also been reasonable to evaluate further in Phase 3; however, due to timing of data availability, it was JADA that informed dose selection for Phase 3 trials with the primary focus on studying the 4 mg dose.

Phase 3 Program

There were four Phase 3 trials submitted in support of efficacy. All trials were randomized, double-blind, placebo and/or active-controlled trials in patients with moderately to severely active RA but with varying background therapies. The primary efficacy endpoint in all trials

was the proportion of patients experiencing response based on the American College of Rheumatology 20 (ACR20) criteria evaluated at Week 12 (JADV, JADW, and JADX) or Week 24 (JADZ) of randomized treatment period, before rescue therapy was allowed. Secondary endpoints included the Disease Activity Score 28 (DAS-28), the Health Assessment Questionnaire-Disability Index (HAQ-DI), and the van der Heijde modified Total Sharp Score (mTSS).

The following table summarizes the primary efficacy results in the Phase 3 trials.

Table 2. Summary of Primary Efficacy Results (ACR20) in Four Phase 3 Pivotal Trials

	% Responders			Odds Ratio (p-value)	
	B4	**B2**	**Pbo**	**B4 vs Pbo**	**B2 vs Pbo**
At Week 12					
JADW (bDMARD-IR)	55	49	27	3.4 (<0.001)	2.7 (<0.001)
JADX (cDMARD-IR)	62	66	39	2.5 (<0.001)	3 (<0.001)
JADV (MTX-IR)	70	--	40	3.6 (<0.001)	--
At Week 24					
	B4	**B4-MTX**	**MTX**	**B4-MTX vs MTX**	**B4 vs MTX**
JADZ (treatment-naïve)	78	77	62	2.2 (0.001)	2.0 (0.003)

From Table 2 above, baricitinib 4 mg was effective when compared to placebo in JADW, JADX, and JADV, and baricitinib 2 mg was effective when compared to placebo in JADW and JADX. Although both doses are effective, there was not a consistent finding of efficacy between these two doses in JADW and JADX, the only trials that randomized patients to both doses. Whereas JADW showed a numerically greater response to baricitinib 4 mg, JADX showed the converse with baricitinib 2 mg showing a greater numeric response than the 4 mg dose.

The secondary efficacy results generally aligned with the primary efficacy findings in the studies. In Figure 4.2 below, provided by the applicant in their March 17, 2017 response to an information request, several of the secondary efficacy components through Week 24 are shown side-by-side for JADW and JADX. In JADW where there was numerically greater response for baricitinib 4 mg over 2 mg on the primary endpoint, there was also a greater separation between the two doses on the secondary endpoints. This is to be expected since the secondary endpoints are components of the primary endpoint, ACR20. In JADX where the converse was observed for the 4 and 2 mg doses on the primary endpoint, there is less of a difference between the two doses for the secondary measures.

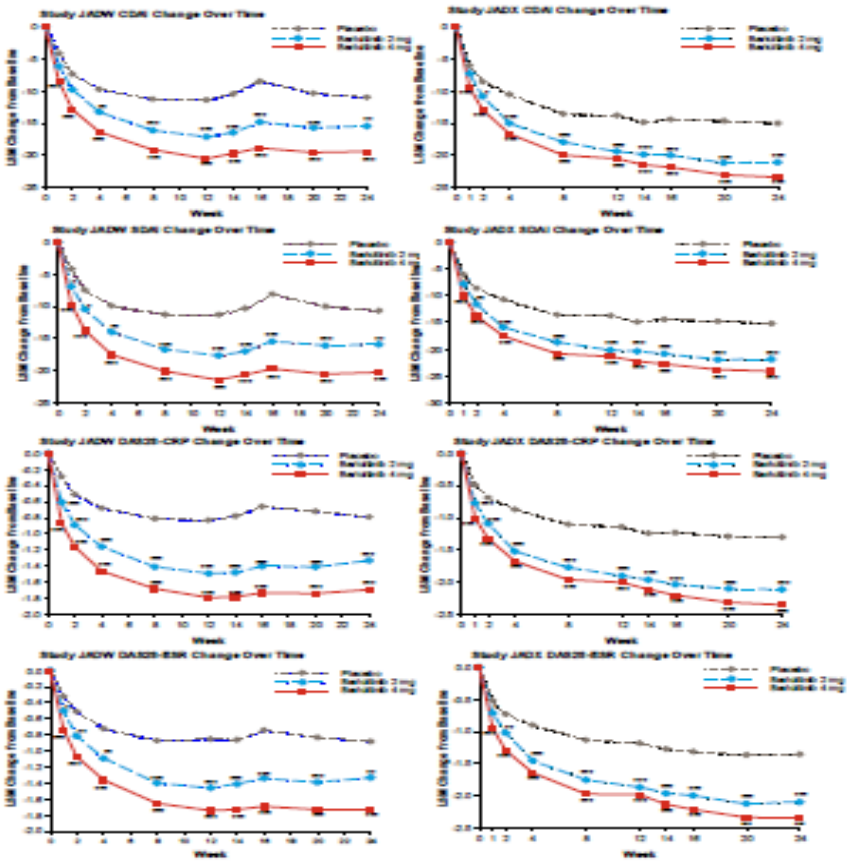


Figure 4.2. CDAI, SDAI, DAS28-hsCRP, and DAS28-ESR through Week 24 in Studies JADW and JADX.

A similar finding between the two doses in JADW and JADX for SF-36 PCS (physical component summary) and morning stiffness was also observed.

Study		Change from Baseline to Week 12		
		B4	B2	PBO
JADW (n=525)	SF-36 PCS	6.37	6.03	2.64
	Morning Stiffness (minutes)	-24	-21	-3.5
JADX (N=660)	SF-36 PCS	6.67	7.22	3.97
	Morning Stiffness (minutes)	-20	-30	-9

Presented by Dr. Janet Maynard at FDA Regulatory Briefing, March 17, 2017

These inconsistent findings between baricitinib 2 and 4 mg in JADW and JADX and also in the Phase 2 studies, JADA and JADN, has led the Division to conclude that there is little

difference in efficacy between these two doses, especially to justify dose-related safety concerns.

This concern was relayed to Eli Lilly during labeling negotiations as the Division was initially willing to consider the 2 mg dose as offering a more favorable benefit-risk profile for marketing. Eli Lilly disagreed with this position and maintained that the 4 mg dose offered a benefit over 2 mg based on the following arguments:

1. Baricitinib 4 mg has a more rapid onset of effect than the 2 mg dose
2. A planned randomized downward titration from 4 mg to 2 mg in a subset of patients from JADY support greater benefits with 4 mg due to worsening of symptoms with down-titration
3. In patients who had inadequate response to MTX, the addition of baricitinib 4 mg + MTX was superior to adalimumab + MTX. This was demonstrated in study JADV.
4. Baricitinib 4 mg monotherapy and its combined use with MTX were more efficacious than MTX alone in study JADZ, a population of RA patients who were treatment-naïve.

The rapidity of effect focused on the components of ACR 20 in JADW, which as I stated above is to be expected since this trial showed a numerically greater effect on ACR20 with baricitinib 4 mg. For JADX, Eli Lilly chose not to present rapidity of effect based on the components of ACR20 and from Figure 4.2 above one can see little difference between the two doses in this trial where baricitinib 2 mg demonstrated a greater numeric response on the primary endpoint. Instead, the applicant present patient reported outcomes (PRO) from daily diary assessments out to only 28 days. Evaluation of these PROs for the full 12-week controlled period shows a narrowing in the difference between the two doses with near identical changes for both doses by Week 12, except for morning joint stiffness. Evaluating subsets of secondary endpoints to counter the overall findings on the primary endpoint in JADX is an exploratory exercise.

In the initial submission, Eli Lilly provided data on step-down dosing in a subgroup of patients from JADY, an extension study of patients who completed Phase 2 study JADA, Phase 3 trials JADV, JADW, JADX, and JADZ, and also and ongoing safety trial JADG. In JADY, patients receiving baricitinib in their originating study continued into JADY at the baricitinib dose administered at the end of the originating study. Patients previously on placebo or an active comparator were treated with baricitinib 4 mg in JADY. The subgroup of patients who were eligible for a step-down dosing assessment had to meet the following criteria:

- Had received at least 15 months of treatment with baricitinib 4 mg without rescue
- Maintained low disease activity or remission for at least 3 months in Study JADY if previously in Study JADA, JADW, or JADY or sustained remission if previously in JADZ.

Upon meeting these criteria, patients would be re-randomized in a double-blinded manner to remain on baricitinib 4 mg or to step-down to baricitinib 2 mg. The objective was to determine if remission or low disease activity could be sustained with dose reduction.

With the initial NDA submission the following results were provided for approximately 300 patients who met criteria for randomization for step-down dosing.

Table JADY.7.1. Summary of CDAI Response Rates at Week 12 after Step-Down Re-randomization (Using Nonresponder Imputation)

	Combined Studies JADV/JADX/JADW		Combined Studies JADV/JADX		Study JADZ		Study JADW	
Endpoint	BARI 2-mg N=146	BARI 4-mg N=147	BARI 2-mg N=115	BARI 4-mg N=117	BARI 2-mg N=18	BARI 4-mg N=15	BARI 2-mg N=31	BARI 4-mg N=30
CDAI Week 12 Disease Activity (using NRI)								
CDAI ≤10 n (%)	123 (84.2)	136 (92.5)	99 (86.1)	109 (93.2)	16 (88.9)	15 (100)	24 (77.4)	27 (90.0)
CDAI ≤2.8 n (%)	54 (37.0)	57 (38.8)	46 (40.0)	49 (41.9)	13 (72.2)	13 (86.7)	8 (25.8)	8 (26.7)
CDAI BARI 4-mg vs BARI 2-mg percent difference in response rate at 12 weeks post-randomization (using NRI)								
CDAI ≤10 (%)	8.3		7.1		11.1		12.6	
p-Value	0.030		0.088		0.489		0.301	
CDAI ≤2.8 (%)	1.8		1.9		14.4		0.9	
p-Value	0.810		0.791		0.414		1.00	

Abbreviations: CDAI = Clinical Disease Activity Index; N = number of modified intent-to-treat patients; n = number of patients in the analysis; NRI = nonresponder imputation.

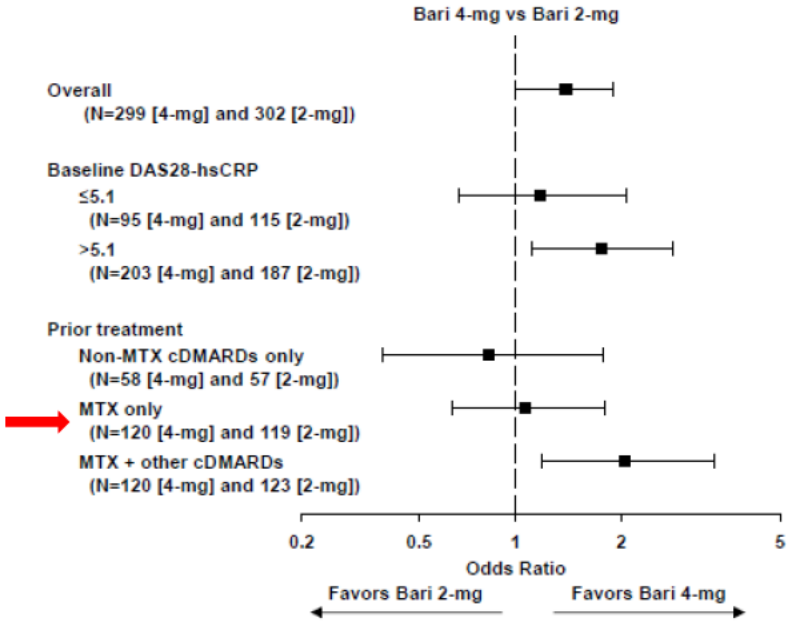
Sources: t_cdai_resp_jadvxwy_stepdown.rtf, t_cdai_resp_jadvxy_stepdown.rtf, t_cdai_resp_jadzy_stepdown.rtf, and t_cdai_resp_jadwy_stepdown.rtf.

In a recent submission to the NDA, the applicant provided updated data with approximately twice as many patients contributing to step-dosing re-randomization after 12 weeks. The results are similar to the original submission. In the combined studies cohort, a greater percentage of patients randomized to remain on the 4 mg dose achieved a CDAI score ≤ 10 that was statistically significant but not for a CDAI score ≤ 2.8, although there were numerically more patients maintaining disease control at the 4 mg dose. When evaluating by individual studies, there is not a consistent finding of significance in Studies JADZ and JADW. Although Eli Lilly emphasizes the randomized nature of this step-down dosing, the patients contributing to this analysis are a selected subset of responders to baricitinib 4 mg. There was no control for type 1 error in this analysis.

Of note, a randomized upward titration scheme from 2 mg to 4 mg for patients who had not achieved adequate disease control at 2 mg was not evaluated in this program.

In JADV, baricitinib 4 mg was superior to adalimumab in patients who have not achieved remission on MTX as evidence for it unique role in the RA armamentarium. These findings have been reviewed by the clinical and statistical reviewer and there is no disagreement on the conclusion of superiority of baricitinib 4 mg over adalimumab. However, this trial only compared the 4 mg dose to the active control and therefore we do not know if baricitinib 2 mg might also offer superior efficacy to adalimumab. Indeed, the applicant's submission included subgroup analyses of pooled studies where both the 2 mg and 4 mg doses were employed. These analyses by baseline patient disease severity show comparable efficacy between these two doses in patients with similar prior treatments as those studied in JADV (MTX-IR).

In Figure 4.7, the applicant pooled Studies JADA, JADN, and JADX which enrolled patients who were cDMARD-IR and compared the effects of the two doses on achievement of low disease activity (LDA) defined as DAS28-hsCRP≤3.2 at Week 12 (controlled period in all studies). To the applicant's figure I have highlighted the MTX-only subgroup (red arrow) where there is no difference in efficacy between the 4 mg and 2 mg doses. The MTX-only group corresponds to the patients enrolled in Study JADV where the applicant is seeking a superiority claim of baricitinib 4 mg over adalimumab.



Abbreviations: Bari = baricitinib; cDMARD = conventional disease-modifying anti-rheumatic drug; DAS28 = disease activity score modified to include the 28 diarthrodial joint count; hsCRP = high-sensitivity C-reactive protein; IR = inadequate responder; mLOCF = modified last observation carried forward; MTX = methotrexate; N = number of patients.

Figure 4.7. **DAS28-hsCRP ≤3.2 to Week 12 using mLOCF by baseline DAS28-hsCRP and prior treatment in the cDMARD-IR patient population.**

In Figure 4.8 below, also from the applicant's submission, a similar comparative analysis between the two doses was conducted by Eli Lilly but limited only to the Phase 3 trial, JADX which enrolled patients who were cDMARD-IR. Again, I have highlighted the MTX-only patients where there is no difference in efficacy between the 4 mg and 2 mg doses.

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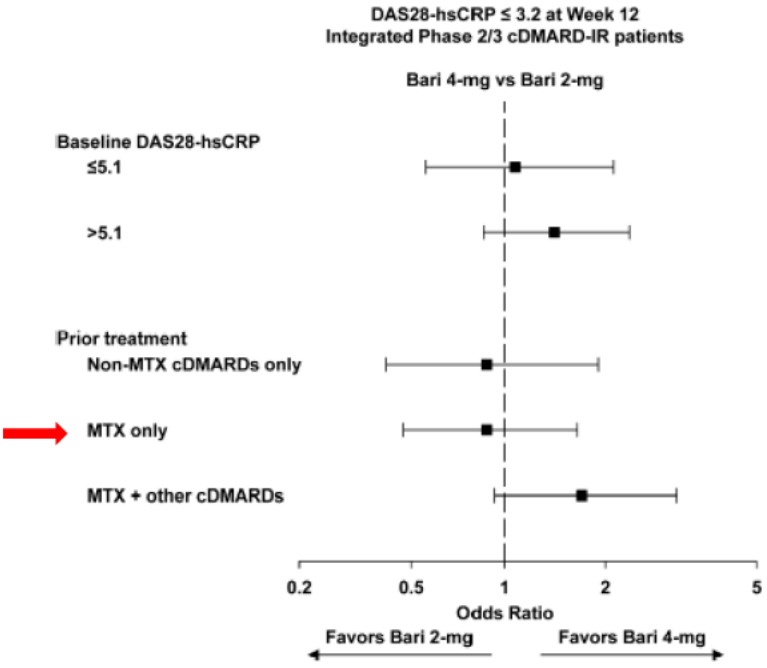
Figure 4.7 Study JADX – 4 vs 2 mg achieving LDA by Baseline Disease Severity and Prior RA Treatment



From their own analysis, it is difficult to conclude based on one study that ONLY baricitinib 4 mg is superior to adalimumab in patients who had an inadequate response to MTX. It is conceivable that a study which employed the baricitinib 2 mg dose might also show superiority over adalimumab.

Eli Lilly also claims superiority of baricitinib 4 mg over MTX in RA patients who are treatment-naïve based on Study JADZ. As in Study JADV, the clinical and statistical reviews confirm such a finding; however, baricitinib 2 mg was not employed in Study JADZ so again we do not know if the lower dose could have provided similar efficacy. These are patients with early RA with a mean time from diagnosis of disease of 1.4 years. In contrast, the range for mean time from diagnosis in the other Phase 3 trials was 6.3 years to 12.5 years. Given the earlier stage of disease in these patients, it is not unreasonable to evaluate whether baricitinib 2 mg is an option for these patients. It should also be noted that the tofacitinib program also conducted a similar study in patients with RA who had not previously received MTX or therapeutic doses of MTX. This study compared two doses of tofacitinib to MTX and showed less radiographic progression at Month 6 and 12 and greater improvements on ACR 20 at Month 6 for both tofacitinib doses versus placebo.[2,3] The results from this tofacitinib study make Lilly's argument of a unique benefit associated with baricitinib over MTX less compelling.

[2] See Table 8 Radiographic Changes at Months 6 and 12 in tofacitinib package insert at Drugs@FDA
[3] Lee, Eun Bong et al. Tofacitinib versus Methotrexate in Rheumatoid Arthritis. *NEJM* 2014;370:2377-2386.

Safety

The primary review, CDTL memo, and DD memos have extensively discussed the safety findings from this NDA. Overall, there are safety findings with baricitinib that have been observed with tofacitinib, another JAK-inhibitor approved for RA. Many of these drug-related AEs are also evident in the biologic DMARDs including risk of neutropenia, anemia, malignancy, immunosuppression, and opportunistic infections. Some of these findings appear dose-related although exposure at baricitinib 4 mg was much greater than the 2 mg dose and these risks may be underestimated at the lower dose.

The applicant has emphasized the greater selectivity of baricitinib for JAK 1 and 2 inhibition based on cell-free assays. Their position was that less affinity for JAK 3 inhibition would result in a lower risk of immunosuppression. However, cell-based assays and clinical safety findings do not support this assertion. Consequently, I agree with the Division that no unique safety benefit has been shown with baricitinib over tofacitinib. Instead, the converse may be the case as clinical imbalance of thrombosis and platelet elevations were observed with baricitinib over controls and these findings were not evident with tofacitinib.

For this section of my memo I will focus primarily on platelet elevations and thrombosis observed with baricitinib. Dr. Chowdhury has also highlighted hepatic safety concerns in his memo and a consult was recently received from FDA hepatologists. There were no cases of Hy's Law but there were patients who had symptoms and laboratory findings suggestive of drug-induced liver injury (DILI) although cases did not adequately capture information to allow for definitive analysis that DILI was the result of baricitinib treatment. The hepatology consult requested data from Phase 2 and 3 trials submitted in e-DISH format and that narratives be compiled by hepatologists with expertise in the diagnosis of DILI. These recommendations will be conveyed in the complete response action letter.

Platelet Elevation

Drs. Chowdhury, Maynard, and Nair have thoroughly described the platelet changes in this development program. Dr. Whittaker also provided an addendum to the pharmacology/toxicology review which further evaluated nonclinical evidence for treatment-induced thrombocytosis.

The following figure from Dr. Maynard's review summarizes the mean change in platelet counts over 52 weeks in the placebo-controlled datasets from JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY, and JADW/JADY.

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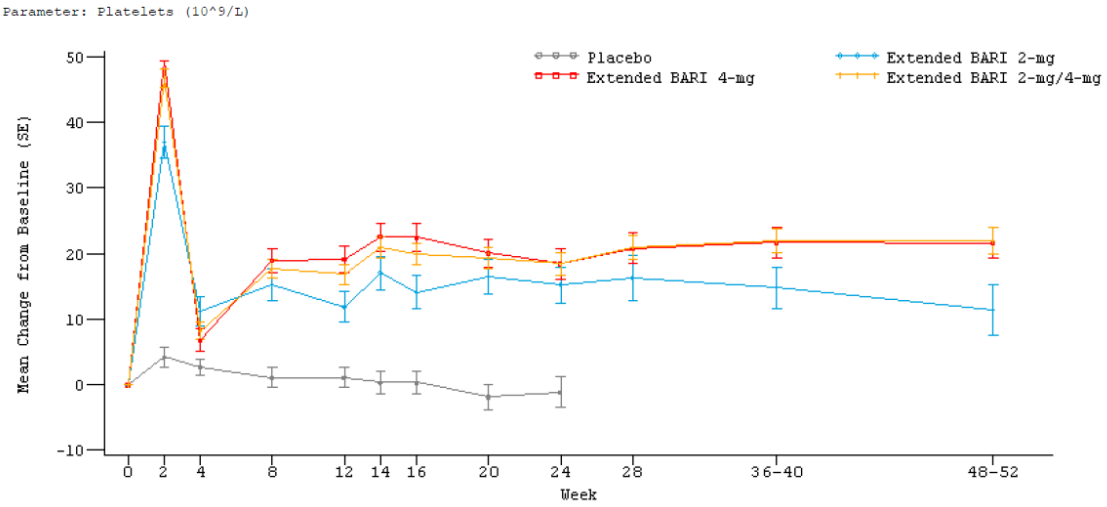
Figure 1. Mean Change in Platelets in Pooled Datasets for Placebo-controlled studies



Mean platelet counts increased shortly after administration of baricitinib 2 and 4 mg, peaking within 2 weeks and subsequently declined. This early increase did not coincide with the dates of onset for thrombotic events but overall mean levels after the increase did not return to baseline and remained higher than placebo. The proportion of patients experiencing a shift in platelet counts from ≤ 600 to > 600 was higher for the baricitinib 4 mg group (2%) compared to baricitinib 2 mg (1%), placebo (1%), and adalimumab (0.9%).

A comparison of mean platelet counts at baseline and throughout the study between the cohort of patients without and with thrombotic events showed little difference. The applicant was asked to provide a plot of platelet counts in the patients with thrombotic events. The following figure plots these data with platelet counts censored after the last available value before the thrombotic event. Only two patients have platelet counts prior to the event that would have been characterized as thrombocytosis; the remainder had platelet counts within the normal range.

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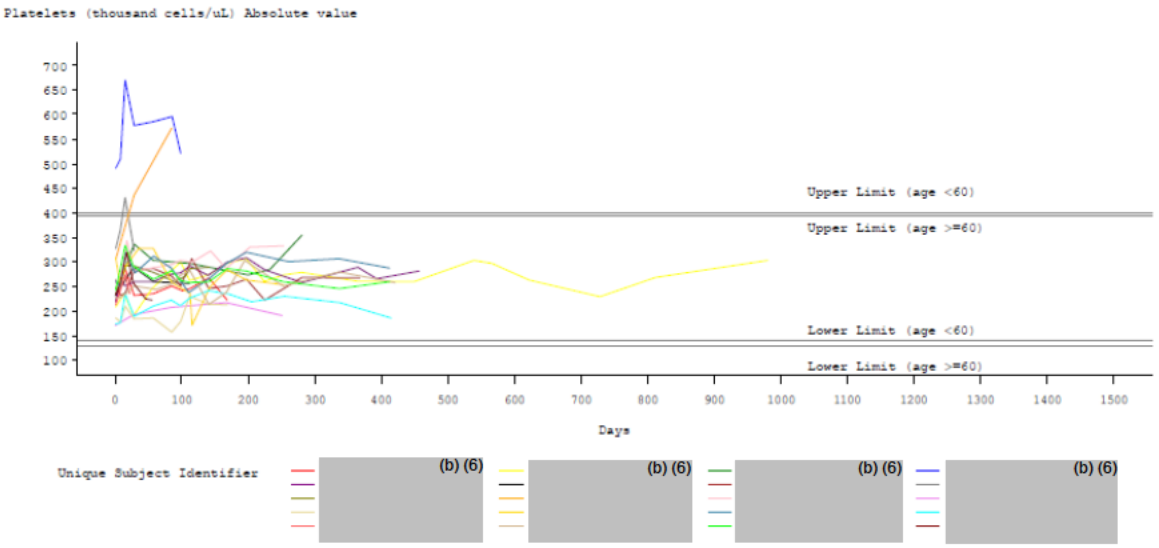

Thrombotic event is defined by treatment emergent deep vein thrombosis and/or pulmonary embolism.
The event day are: 37, 50, 66, 113, 142, 150, 169, 205, 225, 260, 295, 298, 330, 395, 431, 443, 466, 479, 523, 1063.

Program location: home/lillyce/prd/ly3009104/integrations/ra_reg_response/idb4/programs_nonsdd/f_platcn_bytime_withdvtpe_bypatient.sas
Data location: home/lillyce/prd/ly3009104/integrations/ra_submission/data/adam
Output location: home/lillyce/prd/ly3009104/integrations/ra_reg_response/idb4/programs_nonsdd/tfl_output/f_platcn_bytime_withdvtpe_bypatient.rtf

Figure 3. **Individual patient-level line plot by days since the initiation of baricitinib treatment, with data censored after the last available value before the thrombotic event.**

A clear temporal association of thrombocytosis and thrombotic event was not established. Regardless, thrombocytosis observed with baricitinib is a different finding from that in the tofacitinib program. Recent literature cited in Dr. Whittaker's review posits that thrombocytosis may be due to incomplete inhibition of JAK2; however, a definitive explanation for platelet elevations with some JAK-inhibitors remains to be elucidated.[4]

Similar to efficacy exploration in Phase 2, review of the hematologic changes in the Phase 2 study JADN suggests that baricitinib 1 mg may offer an acceptable benefit-risk profile for RA. The following table from the applicant's study report of JADN summarizes platelet counts for baricitinib doses of 1, 2, 4, and 8 mg from baseline to Week 2, where the peak elevation was observed in Phase 3. Although baricitinib 1 mg had a mean increase in platelet counts over placebo, this change was not statistically significant whereas there was a clear dose-dependent and significant increase from 2 mg through 8 mg.

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[4] Besancenot R et al. Jak2 and MPL protein levels determine TPO-induced megakaryocyte proliferation vs differentiation. *Blood*. 2014;124:2104-2115.

Laboratory Test: PLATELET COUNT (BILL/L)

		LY3009104					
	Placebo (N=49)	1 mg (N=24)	2 mg (N=24)	4 mg (N=24)	8 mg (N=24)	Combined LY (N=96)	P-value [1]
Week 0 (Baseline A)							
n	49	24	24	24	24	96	
Mean (SD)	264.3 (63.85)	271.0 (62.68)	268.8 (61.84)	268.1 (60.97)	255.3 (66.48)	265.8 (62.34)	0.773
Median	257.0	272.0	274.5	262.5	241.5	266.5	
Min, Max	159, 424	150, 398	187, 413	146, 381	116, 383	116, 413	
Week 2							
Raw Value							
n	49	24	24	24	24	96	
Mean (SD)	268.9 (70.67)	284.7 (53.05)	299.5 (92.01)	313.6 (71.61)	308.3 (79.62)	301.5 (75.02)	0.006
Median	271.0	301.5	303.0	305.0	310.5	305.0	
Min, Max	152, 437	163, 371	169, 556	163, 433	127, 461	127, 556	
Change from Baseline A to Week 2							
n	49	24	24	24	24	96	
Mean (SD)	4.6 (35.15)	13.6 (30.63)	30.7 (44.61)	45.5 (44.40)	53.0 (39.76)	35.7 (42.41)	<.001
Median	3.0	11.5	29.0	41.0	55.5	30.5	
Min, Max	-73, 98	-46, 87	-38, 143	-47, 143	-27, 152	-47, 152	
p-value [2]		0.287	0.008	<.001	<.001	<.001	

Thrombosis

In the pooled Phase 3 trials and the extension study, JADY, there was a numeric imbalance for venous thromboembolic (VTE) events not favoring baricitinib: 4 cases of DVT/PE were reported in the 4 mg, compared to none in the baricitinib 2 mg and placebo groups in the 0-16 week time period before rescue was allowed. As patients were allowed to switch to baricitinib 4 mg after week 16 and all placebo-treated patients were switched to active treatment after week 24, exposures across treatment groups were no longer comparable after week 16 to enable a comparison of risk across the treatment groups. From Table 3 below obtained from Dr. Chowdhury's review, it is evident that additional VTE events continued to accrue in the baricinitib 4 mg group and 2 cases were identified in the baricitinib 2 mg group.

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.

Eli Lilly argues that thrombosis is not a unique concern of baricitinib for the following reasons:

1. The events are rare and not statistically significantly different across treatment groups

2. Most of the cases of DVT/PE were reported during the uncontrolled periods of the trials and no cases have been reported in any of the completed or ongoing Phase 2 studies in non-RA patients. The rate of events is similar to population data in RA patients (i.e., RA, in itself, is a risk factor for thrombosis)
3. Cases of DVT/PE occurred in patients with predisposing risk factors for such events. Risk factors specifically mentioned by Eli Lilly included concomitant use of MTX and corticosteroids, obesity, preceding history of surgery, trauma, or decreased motility.
4. There is no plausible mechanism of action for baricitinib-induced thrombosis or for JAK-inhibition to contribute to this risk.

In this section, I will address each of the applicant's arguments and why they are inadequate to dismiss this signal as a concerning and unique risk of baricitinib that requires additional pre-market evaluation before consideration of approval.

For the 1st argument, it is highly unlikely to detect a statistically significant difference between the treatment groups in a typical NDA submission for rare adverse events. In consultation with FDA biostatisticians, if we are to assume a background thrombosis rate of 0.5 events per 100 pt-yrs and want to exclude a 2-fold increase in thrombotic risk between baricitinib and control, we would require a database of approximately 17,600 patients randomized 1:1 to have 90% power to exclude such a risk. Decreasing the power to 80% would only reduce the sample size necessary to exclude a 2-fold risk to 13,200. Hence, it would be unrealistic to expect a program such as the current baricitinib program which had a total of 3769 (from Table 2.7.4.5 of applicant's summary of clinical safety) patients randomized into the combined Phase 2 and 3 trials, to detect a statistically significant difference based on a total number of 20 DVT/PE events.

For the 2nd argument, I will refer to a recent submission from the applicant dated February 24, 2017. In this submission, Eli Lilly notes that the rarity of the events with exposure-adjusted incidence rates of 0.5 to 1.0 events per 100 pt-yrs for baricitinib 4 mg and 0.4 to 0.7 events per 100 pt-yrs for baricitinib 2 mg with few events occurring during the 16-week controlled periods of the Phase 3 trials. Consequently, the applicant performed a comparative analysis of the exposure-adjusted incidence rates observed in the baricitinib program to estimated incidence rates for venous thrombotic events obtained from published observational studies and summarized their analyses in the following Figure. Their conclusion is that the rates of VTE, PE, and DVT observed with baricitinib in their clinical development program are comparable to the rates observed across several published population studies in the RA population and that this risk is a disease-related risk, not a drug-related risk.

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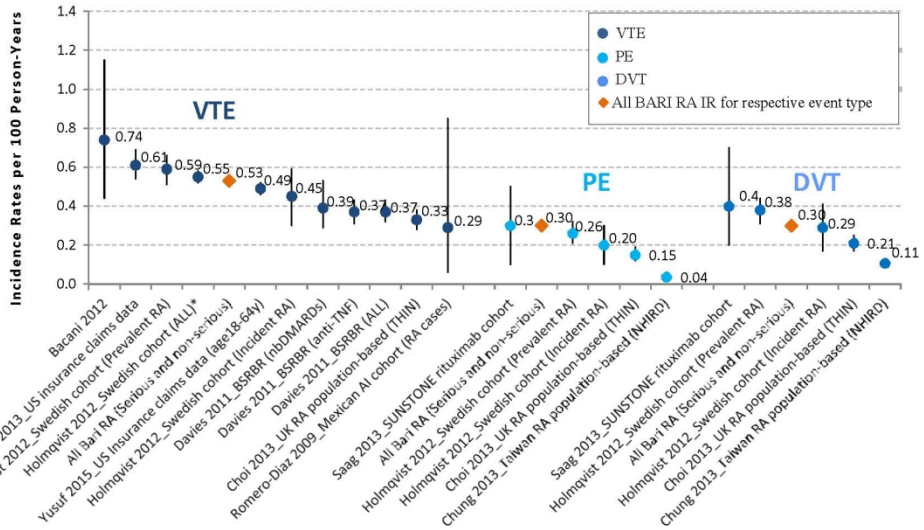

Abbreviations: BARI = baricitinib; DVT = deep vein thrombosis; IR = incidence rate; nbDMARDs = non-biologic disease-modifying anti-rheumatic drugs; PE = pulmonary embolism; RA = rheumatoid arthritis; TNF = tumor necrosis factor; UK = United Kingdom; US = United States; VTE = venous thromboembolic event; y = years.

* The incidence rate was calculated from information provided in the reference.

Figure 4.1. **Incidence rate of venous thromboembolic events among rheumatoid arthritis patients from observational studies and the baricitinib All BARI RA analysis set.**

The above comparative analysis is problematic in that these are not comparisons of randomized groups within a trial but are comparisons of disparate databases such as a retrospective cohort studies versus the randomized controlled trials in this NDA. Baseline patient characteristics and definitions for thrombotic events, collection, and adjudication of such events are unlikely uniform across these different databases.

The above analysis also ignores the fact that the thrombosis signal for baricitinib arises from a randomized controlled clinical trial database. Even if we limit ourselves to just the controlled portion of the program there is a clear numeric imbalance from Week 0-16 (before rescue was allowed) with 4 cases in baricitinib 4 mg, and none in baricitinib 2 mg or placebo. During this controlled period the incidence of VTE was 1.0 per 100 pt-yrs at the baricitinib 4 mg dose versus zero for barictinib 2 mg or placebo. Although the applicant argues that 12 additional cases in the 4 mg dose and two in the 2 mg dose groups occurred during the uncontrolled phase, this assumes that there would be cases in the control group to eliminate the imbalance observed in the controlled period. However, the absence of an adequate longer-term controlled period does not allow us to conclude an absence of thrombotic risk related to baricitinib treatment.

Finally, I am aware of one case of DVT/PE reported in a non-RA trial (psoriasis). Patient (b) (6) was a 30 year old Caucasian male who had a history of GERD,

nearsightedness, mild obesity and depression. He had no family or prior history of DVT or PE. There were no predisposing factors for PE including trauma, prolonged immobilization, recent surgery, varicose veins, dehydration, and/or family history of clotting factor disorders. The patient was receiving methotrexate. There were several plane trips in (b) (6) of two to three hours duration and one car trip of three to four hours duration. On (b) (6) the patient received his first dose of study drug (baricitinib 8 mg which was increased to 10 mg on (b) (6)). On (b) (6), the patient became dypsneic while walking his dog and collapsed. He was hospitalized where relevant labs included normal platelet count of 286, negative screen for anti-cardiolipin antibody and normal genotyping for Factor V Leiden and prothrombin mutations. CT scan showed extensive bilateral PE and Doppler revealed a DVT in the left leg. A request for the applicant to update their safety queries for non-RA programs to evaluate for thrombotic risk is warranted.

In their 3rd argument, Eli Lilly points to predisposing factors in the patients with VTEs. Again, this ignores the fact that the imbalance came from a database of 4 randomized controlled clinical trials. Review of the individual cases did identify some cases in which there is evidence that an inherent risk in the patient predisposed him/her to a VTE (e.g., lupus anti-coagulant, Factor V Leiden mutation, recent fracture). However, there were also cases in which no pro-coagulant or hypercoagulable state was identified. None of the four cases in the baricitinib 4 mg group that occurred during the 16-week controlled period reported the presence of a pro-coagulant.

The following table summarizes the VTE cases from the Phase 3 RA trials and the extension trial, JADY. With exception for (b) (6), all these cases contributed to the risk assessment summarized in Table 22 above. There were 10 PEs reported with baricitinib, 9 were serious and one was fatal. There were 10 DVTs reported with baricitinib, 6 were serious. Four cases occurred at the 4 mg dose in patients who were previously randomized to placebo but the thrombotic event occurred well into the crossover period (142, 169, 295, and 330 days). One fatal PE was reported in a patient treated with MTX monotherapy in Study JADZ. The narrative for this case reported the diagnosis as being made on clinical grounds without imaging studies and there was no report of treatment with anti-coagulation or thrombolytics.

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Table 4. Venous Thromboembolic Events reported in Phase 3 trials and extension JADY

Patient ID	Treatment Duration	Thrombosis Event	Imaging study for diagnosis
Baricitinib 4 mg (16 cases)			
(b) (6)	37 days	PE	Narrative states examination confirmed fresh embolism in PA
	50 days	PE (SAE, hosp)	CT-pulmonary angiography
	66 days	PE (SAE, hosp)	Chest CT and CT-angiography
	113 days	DVT	None reported. No treatment reported.
	142 days	DVT	
	150 days	DVT	None reported.
	169 days	PE (SAE, hosp)	CT-angiography. D-dimer increased.
	260 days	PE (SAE, hosp)	CT-angiography
	295 days	DVT/PE (SAE, hosp)	Peripheral vascular evaluation and CT scan.
	330 days	DVT (SAE, hosp)	Evaluated for left leg edema reported.
	395 days	DVT (SAE, hosp)	Ultrasound
	431 days	PE (SAE, hosp)	Angioscan
	443 days	DVT	None reported.
	466 days	PE (SAE, hosp)	V-Q scan
	479 days	DVT/PE (SAE, hosp)	None reported however mesh filter inserted.
	523 days	PE (SAE, hosp, fatal)	Chest CT
Baricitinib 2 mg (2 cases)			
(b) (6)	205 days	DVT	Duplex Doppler ultrasound, echo, cardiac cath
	298 days	DVT (SAE)	None reported
Control (1 case – MTX monotherapy)			
(b) (6)	235 days	PE (SAE, hosp, fatal)	None reported.

The applicant has emphasized MTX concomitant use as a predisposition to thrombosis in the cases reported in the baricitinib treatment arm. However, this ignores the fact that MTX was previously used in 99.4%, 71.3%, and 81.8% of patients in JADV, JADX, and JADW, respectively (Table 2.7.3 in Summary of Efficacy submission) and continuation was allowed into these studies; hence, the risk due to MTX was also present in the comparator group and yet there is only one case of VTE in the control arm.

Other predisposing factors leading to thrombosis in baricitinib treatment were raised by the applicant. In the table below, the applicant summarized selected characteristics at baseline and events that occurred during the trial which might contribute to a risk of thrombosis. There is not a striking imbalance for any of these events.

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Table 3. Baseline characteristic and events during trial possibly contributory to VTE (JADA/Y, JADC, JADN, JADV/Y, JADW/Y, and JADX/Y)

	Weeks 0-16			
	PBO N=1070	BARI 2-mg N=479	BARI 4-mg N=997	BARI 2/4-mg N=1476
Baseline BMI (kg/m^2)				
mean	27.75	28.99	28.0	28.32
median	26.64	27.61	26.95	27.05
≥30, n (%)	332 (31.1)	184 (38.6)	301 (30.2)	485 (32.9)
≥40, n (%)	61 (5.7)	38 (8.0)	60 (6.0)	98 (6.7)
Baseline history of DVT or PE, n (%)	13 (1.2)	4 (0.8)	11 (1.1)	15 (1.0)
Baseline use of oral contraceptive or SERM, n (%)	46 (4.3)	14 (2.9)	55 (5.5)	69 (4.7)
Initiation of oral contraceptive or SERM during the trial, n (%)	6 (0.6)	2 (0.4)	3 (0.3)	5 (0.3)
Adverse event of fracture reported during the trial, n (%)	18 (1.7)	13 (2.7)	11 (1.1)	24 (1.6)
Adverse event of cellulitis reported during the trial, n (%)	3 (0.3)	1 (0.2)	7 (0.7)	8 (0.5)
History of hypercoagulability or positive hypercoaguable workup during the trial, n (%)	4 (0.4)	0	1 (0.1)	1 (0.1)
Hospitalization for elective and non-elective surgery, n (%) [a]	21 (2.0)	13 (2.7)	26 (2.6)	39 (2.6)

In addition to the VTEs reported in the Phase 3 trials and extension trial, JADY, there was one report of DVT/PE on baricitinib 4 mg in JADN (JADN-035-03504) and PE/lung abscess on baricitinib 8mg/4mg in JADA/JADY-965-02351.

Arterial occlusive events were reported in three patients treated with baricitinib.

- (b) (6) was a 77-year old woman who developed pancytopenia and an infected leg ulcer 11 days after receiving the last dose of baricitinib 2 mg. Treatment for the ulcer was complicated by peripheral arterial occlusive disease in lower leg requiring heparin treatment.
- (b) (6) was a 47-year old man who was originally on placebo but received baricitinib 4 mg in JADY. Two hundred-eighty days into JADY he developed right lower extremity rest pain and claudication and arterial occlusive disease was diagnosed resulting in placement of a right superficial femoral artery popliteal artery stent.
- (b) (6) was a 56-year old woman who had received baricitinib 4 mg for 22 weeks. She was hospitalized for MTX-induced interstitial lung disease and experienced brachial artery thrombosis while hospitalized.

Finally, Eli Lilly argues that there is no plausible mechanism for baricitinib-induced thrombosis and states a signal has not been observed with other inhibitors of the JAK signaling pathway. The absence of a plausible mechanism is an inadequate defense for ignoring the

clinical imbalance of thrombotic events in this program. In addition, their assertion that a signal has not been observed with other JAK-inhibitors should raise concern that baricitinib carries a unique safety finding.

Advisory Committee Meeting
No advisory committee meeting was convened during this review cycle. Consideration should be given to taking this application to an advisory committee upon receipt of a response to the *Complete Response* letter.

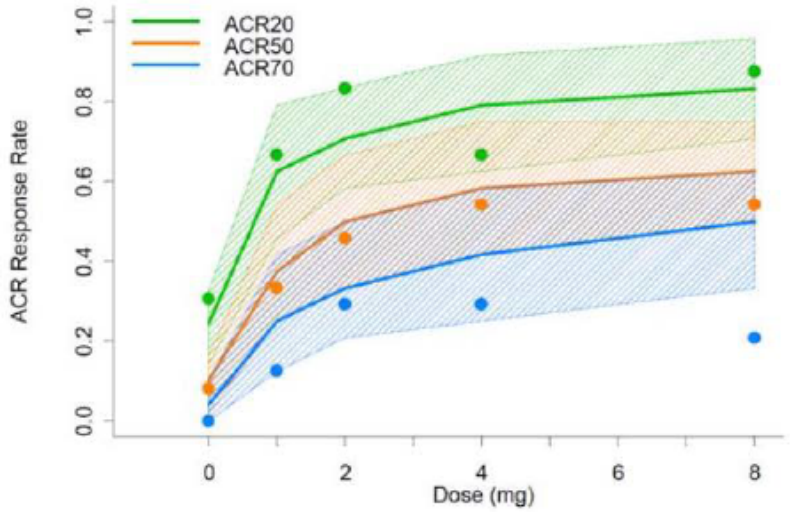
This application was discussed at a CDER Regulatory Briefing on March 17, 2017.

Conclusions/Recommendations
Baricitinib 2 and 4 mg daily dosing achieved statistically significant improvements in signs and symptoms of RA relative to placebo. However, imbalance in thrombotic events, most coded as serious adverse events including a fatal pulmonary embolism, distinguishes baricitinib from other available RA therapies. There were 18 events in the baricitinib group (16 at 4 mg, 2 at 2 mg) and none in the placebo group. Four of the events occurred during the first 16 weeks of treatment in the Phase 3 trials, 12 occurred after 6 months where all placebo patients were switched to baricitinib 4 mg. The diminishing exposure in the 2 mg dose group and the lack of a placebo arm after 6 months challenges our ability to determine if the risk is limited only to the 4 mg dose or if the risk is similar to background risk in RA patients, although the numeric imbalance of 4 vs 0 in the 16-wk controlled period is of concern. Overall, the risk for VTE was estimated to be 0.5 to 1.0 for the 4 mg dose group and 0.4 for the 2 mg dose group; however, inadequate exposure at the 2 mg dose may underestimate this risk. Except for a few cases, most narratives provide evidence that a thrombotic event did occur (e.g., diagnosis by pulmonary angiogram and/or anti-coagulant therapy initiated) and while some cases did have compelling explanations for a hypercoagulable state (e.g., lupus anticoagulant), the majority did not and assertions made by the applicant for other predisposing factors, such as obesity or concomitant MTX therapy, were also present in the control groups.

As efficacy was established with the proposed doses, one might argue that the number of thrombotic events was small and labeling for such rare and serious events could be considered to permit an informed benefit-risk decision by prescribers and patients. Members of the review team and I did consider potential paths for approval with the data in hand but ultimately my conclusion was that Eli Lilly had not fully evaluated a safe and effective dose of baricitinib for the treatment of RA and a complete response would be issued. Several factors influenced this decision.

First, Phase 2 dose-ranging studies suggested that lower doses may have been effective and possibly safer. For example, the following dose-response curve from JADN could justify further evaluation of the 1 mg dose which also showed no statistically significant increase in platelet elevation compared to placebo, assuming that is a biomarker for thrombotic risk. The 2 mg dose might have been a viable safe and effective dose, had it been evaluated as extensively as the 4 mg dose in the Phase 3 program.

Figure 3: Dose-response in Phase 2 Study, JADN



Not having fully evaluated the dose-response of baricitinib, it would be imprudent to carve out a population in labeling, especially given that all populations studied in this program have also been studied with tofacitinib. Based on Section 14 Clinical Studies of the most recent product label for tofacitinib, the following table summarizes the population studied and the efficacy measures in the confirmatory trials for tofacitinib.

Table 4 Confirmatory Trials for Tofacitinib

Study No. and Population	**Duration of Trial**	**Treatments (N)**	**Efficacy Endpoints**
Study 1 cDMARD-IR bDMARD-IR	6 months	Tofa 5 bid Tofa 10 bid Placebo	ACR 20 at Month 3 HAQ-DI DAS-28
Study 2 cDMARD-IR	12 months	Tofa 5 bid Tofa 10 bid Placebo	ACR 20 at Month 6 HAQ-DI DAS-28
Study 3 MTX-IR	12 months	Tofa 5 bid Tofa 10 bid Adalimumab Placebo	ACR 20 at Month 6 HAQ-DI DAS-28
Study 4 MTX-IR	2 yrs	Tofa 5 bid Tofa 10 bid Placebo	ACR 20 at Month 6 mTSS at Month 6 HAQ-DI DAS-28
Study 5 TNF-blocker-IR	6 months	Tofa 5 bid Tofa 10 bid Placebo	ACR 20 at Month 3 HAQ-DI DAS-28
Study 6 MTX-naïve	2 yrs	Tofa 5 bid Tofa 10 bid MTX	mTSS at Month 6 ACR70 at Month 6

Tofacitinib, at both doses studied, was superior to comparators in these trials on the primary endpoint of ACR20 and many of the secondary endpoints including radiographic progression of joint disease in Study 4. Given that tofacitinib has established efficacy in the same RA populations baricitinib is seeking but lacks the potential risk for serious thrombotic events, one cannot make an argument that baricitinib might address an unmet need without first providing a better assessment of a lower dose.

Several possible paths can be outlined to address the deficiency in this program and further discussions should be encouraged at an End-of-Review meeting. Although a benefit over an existing therapy is not a requirement for approval if a safe and effective dose of baricitinib can be identified, such a benefit might justify tolerating a unique risk of baricitinib if that risk continues to be observed with additional studies.

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/s/

MARY T THANH HAI
04/12/2017